Quality of care in incident type 2 diabetes and initial presentation of vascular complications: Prospective cohort study using linked electronic health records from CALIBER research platform

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I, Nur Hafidha Hikmayani, confirm that the work presented in this thesis is my own.
Where information has been derived from other sources, I confirm that this has been indicated in this thesis.

Abstract

Background. Numbers of new cases of type 2 diabetes (T2D) are increasing rapidly. Early and continuing intervention after T2D presentation is crucial for best possible outcomes, ensuring that the existing high burden of T2D will not be aggravated. Identification of patterns of continuous care and predictors for meeting key targets for T2D management can improve quality of care. Glycaemic control is particularly important for primary prevention of vascular complications but its relationship with contemporary cardiovascular diseases (CVDs) has been less explored. More importantly, long-term glycaemic control can be assessed from routine monitoring, potentially providing new insight into T2D management to prevent vascular complications. Linked electronic health records are invaluable data resources for investigating these issues.

Objective. To examine the quality of care in an incident T2D cohort through assessment of temporal trends of care, predictors of glycaemic, blood pressure and lipid control, and associations of short-term and long-term glycaemic control with chronic vascular complications.

Methods. The data source for studies in this thesis was CALIBER which links electronic health records from primary care, hospitalisation, myocardial infarction and mortality registries. Patients newly diagnosed with T2D between 1998 and 2010 were followed-up until a censoring administrative date or initial occurrence of vascular complications. Trends in receipt of care and attainment of glycaemic, blood pressure and total cholesterol targets were examined. Predictors for meeting the targets were explored using multinomial logistic regressions. Association of early glycaemic control with a range of specific cardiovascular complications were investigated using Cox regressions. A longitudinal metric for glycaemic control was developed by quantifying time spent at target during follow-up and was tested for its association with cardiovascular and microvascular outcomes using mixed logistic regressions.

Results. A total of 52,379 incident T2D patients were identified with a median follow-up of over 4 years. Positive trends were observed for blood pressure and total cholesterol control, but not for glycaemic control, whilst attainment of HbA1c and blood pressure targets over time consistently fell short. Older age at diagnosis was an important predictor for meeting the key targets. In 36,149 patients free from prior CVD, early glycaemic and blood pressure control was associated with lower risk for heart failure and peripheral arterial disease, whereas cholesterol control with myocardial infarction and transient ischaemic attack. Shorter duration at glycaemic target was associated with higher risk of major adverse cardiovascular events, cardiovascular death and diabetic retinopathy.

Conclusions. This thesis highlights missed opportunities and inequality in T2D care. Both short-term and long-term glycaemic control are important for reducing risk of vascular complications. Limitations and implications of the findings for clinical practice and research were discussed.

Impact Statement

Harnessing the UK's big health data which spans from GP and hospitalisation records to heart disease and death registries – all linked under the CALIBER research platform, this thesis has captured patients' journey from being initially diagnosed with T2D, through receiving recommended care and achieving intermediate care outcomes (i.e. targeted biomarkers), to the point they develop hard outcomes (i.e. diabetes chronic complications affecting blood vessels). The findings of this thesis have provided insights into the quality of care in patients newly diagnosed with T2D as it investigated the trends over time in both receipt of care and target achievement, their contributing factors, how the quality of care subsequently contributed to the development of diabetes chronic complications and how repeat HbA1c records can be used to measure the care effectiveness. The evidence presented in this thesis lend further support for improving early and long-term T2D care alike, and for leveraging electronic health data to support public health research and policy.

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Abbreviations

4D	*German Diabetes and Dialysis Study*
ACCORD	*Action to Control Cardiovascular Risk in Diabetes*
ACEI	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
ADA	American Diabetes Association
ADVANCE	*Action in the Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation*
AGE	Advanced glycation end-product
AHA	American Heart Association
ALLHAT-LLT	*Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial – Lipid Lowering Trial*
ALTITUDE	*Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints*
ARB	Angiotensin II receptor blocker
ARQ	Acceptable research quality
ARV	Average real variability
ASPEN	*Atorvastatin Study for Prevention of coronary heart disease Endpoints in Non-insulin dependent diabetes mellitus*
AVS	Ankle vibration sense
BARI 2D	*Bypass Angioplasty Revascularization Investigation 2 Diabetes*
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CALIBER	*ClinicAl research using LInked Bespoke studies and Electronic health Records*
CAN	Cardiovascular autonomic neuropathy
CARDS	*Collaborative Atorvastatin Diabetes Study*
CHD	Coronary heart disease
CI	Confidence interval
CIF	Cumulative incidence function
CKD	Chronic kidney disease
CPRD	Clinical Practice Research Datalink
CV	Coefficient of variation
CVD	Cardiovascular disease
DAN	Diabetic autonomic neuropathy
DAPT	Dual antiplatelet therapy
DED	Diabetic eye disease
DIABHYCAR	*Non-insulin dependent Diabetes, Hypertension, microalbuminuria or proteinuria, Cardiovascular events and Ramipril*
DIGAMI 2	*Diabetes mellitus and Acute Myocardial Infarction 2*
DIN-LINK	Doctor Independent Network Link

DIRECT-Protect 2	*Diabetic Retinopathy Candesartan Trials – Protect 2*
DPN	Diabetic peripheral neuropathy
DPP-4	Dipeptidyl peptidase 4
DQIP	Diabetes Quality Improvement Project
EASD	European Association for the Study of Diabetes
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
ELIXA	*Evaluation of Lixisenatide in Acute Coronary Syndrome*
EMPA-REG OUTCOME	*Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients – Removing Excess Glucose*
EMR	Electronic medical record
ESRD	End stage renal disease
ESC	European Society of Cardiology
EXAMINE	*Examination of cardiovascular outcomes with Alogliptin versus standard of care*
FIELD	*Fenofibrate Intervention and Event Lowering in Diabetes*
FFA	Free fatty acid
GFR	Glomerular filtration rate
GLP-1	Glucagon-like peptide 1
GP	General practitioner
GPRD	General Practice Research Database
HDL	High density lipoprotein
HEART 2D	*Hyperglycemia and its Effects after Acute myocardial infarction on cardiovasculaR outcomes in patients with Type 2 Diabetes mellitus*
HES	Hospital Episodes Statistics
HOPE	*Heart Outcomes Prevention Evaluation*
HPS	*MRC/BHF Heart Protection Study*
HR	Hazard ratio
HSCIC	Health and Social Care Information Centre
ICD-10	International Classification of Disease tenth revision
IDNT	*Irbesartan Diabetic Nephropathy Trial*
IQR	Interquartile range
IRR	Incidence rate ratio
LDL	Low density lipoprotein
LEADER	*Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results*
MACE	Major adverse cardiovascular event
MICRO-HOPE	*Microalbuminuria, Cardiovascular and Renal Outcomes – HOPE*
MINAP	Myocardial Ischaemia National Audit Project
MVD	Microvascular disease
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIDDM	Non-insulin dependent diabetes mellitus

NOS	Not otherwise specified
NPDR	Non-proliferative diabetic retinopathy
NPV	Negative predictive value
NSF	National Service Framework
NSTEMI	Non ST-elevation myocardial infarction
OHA	Oral hypoglycaemic agent
ONS	Office of National Statistics
OPCS-4	Office of Population, Censuses and Surveys Classification of Interventions and Procedures fourth revision
OR	Odds ratio
ORIGIN	*Outcome Reduction with an Initial Glargine Intervention*
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PDR	Proliferative diabetic retinopathy
PPAR	Peroxisome proliferator-activated receptor
PPV	Positive predictive value
PROactive	*Prospective pioglitAzone Clinical Trial In macroVascular Events*
QOF	Quality and Outcomes Framework
RAAS	Renin–angiotensin–aldosterone system
RAS	Renin–angiotensin system
RCT	Randomised controlled trial
RECORD	*Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes*
RENAAL	*Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan*
ROS	Reactive oxygen species
RR	Relative risk
RRR	Relative risk ratio
RSD	Residual standard deviation
SAVOR-TIMI 53	*Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus – Thrombolysis In Myocardial Infarction 53*
SGLT2	Sodium-glucose co-transporter 2
SIGN	Scottish Intercollegiate Guidelines Network
SD	Standard deviation
SU	Sulphonylurea
SUSTAIN-6	*Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes*
SV	Successive variation
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TECOS	*Trial Evaluating Cardiovascular Outcomes with Sitagliptin*
THIN	The Health Improvement Network
TIA	Transient ischaemic attack

TITRE	TIme at TaRgEt
TNF	Tumour necrosis factor
TRAIL	TNF-related apoptosis inducing ligand
TZD	Thiazolidinedione
UKPDS	*UK Prospective Diabetes Study*
UTS	Up to standard
VADT	*Veteran Affairs Diabetes Trial*
VEGF	Vascular endothelial growth factor
VIM	Variation independent of mean
VLDL	Very low density lipoprotein

*Italicised abbreviations are names of study

Chapter 1

Introduction

Sugar is now more dangerous than gunpowder.
— Yuval Noah Harari, *Homo Deus: A Brief History of Tomorrow*

1.1 Type 2 diabetes (T2D)

Diabetes mellitus is a chronic metabolic disease, characterised by elevated glucose levels circulating in the blood due to lack of insulin secretion or insulin resistance. Insulin – a hormone produced by beta cells of the pancreatic islets – is responsible for stimulating the cellular uptake of glucose from the blood. Under conditions of insulin resistance, the cells fail to respond adequately to insulin, leaving excessive glucose in the blood. The classic symptoms of diabetes include the triad of polyuria (excessive urination), polydipsia (increased thirst) and polyphagia (increased hunger), and unexplained weight loss.

Diabetes mellitus is now at pandemic level with over 400 million cases worldwide in 2013, projected to increase by 55% within the next two decades.[1] Type 2 diabetes (T2D) – a state of long-standing insulin resistance with compensatory hyperinsulinemia – accounts for over 90% of cases, the burden of which is considered enormous globally.

1.1.1 The growing burden of T2D

Although some people are more genetically susceptible, the escalating prevalence of T2D reflects the growing ageing population, increasing obesity and sedentary lifestyles, and – applied to the United Kingdom (UK) – changes in ethnic make-up. In 2013, there were an estimated 3.2 million people in the UK with a diagnosis of T2D which gives an average prevalence in adults of 6.0%, rising to around 7.2% if additional undetected cases are taken into account.[2]

T2D chronicity presents major challenges to healthcare due, principally, to its association with cardiovascular diseases (CVD) and small vessel diseases affecting the eyes, kidneys and nerves. A meta-analysis of 102 prospective studies involving nearly 700,000 adults estimated that diabetes doubled the risk of coronary heart disease (CHD) and ischemic stroke.[3] However, a recent longitudinal study incorporating over 1.9 million individuals with a median follow-up of 5.5 years, showed that T2D produced a similar increase in the risk of heart failure and peripheral arterial disease (PAD), which were the most common initial cardiovascular manifestations, more common than CHD or stroke.[4] Microvascular disease adds further to the healthcare challenge, renal failure leading to dialysis or kidney transplant occurring in about a quarter of patients with diabetic nephropathy.[5] Yet more disabling is diabetic retinopathy which accounts for one-third of all cases of blindness,[6] whilst diabetic foot ulcer, most commonly associated with diabetic neuropathy and PAD, accounts for approximately 80% of non-traumatic lower limb amputations.[7] Patients with diabetes are also two to six times more likely to be admitted to hospital,[8,9] with over 12,000 hospitalisations per 100,000 individuals[9] and an average length of stay twice that of patients without diabetes.[8] Among individuals diagnosed with diabetes in middle age, premature death is common with an estimated 6 years of life lost.[10] CVD and renal failure contribute to 52% and 11% of diabetes mortality, respectively.[11]

T2D and type 1 diabetes (T1D) altogether consume a considerable share of healthcare costs, accounting for £9.8 billion of National Health Service (NHS) expenditure in 2010/11, which is 10% of the total NHS budget.[12] Of these direct costs, 78% was spent on treating complications, particularly CVD (34%), excess inpatient days (19%), renal diseases (10%), and foot ulcer and amputation (10%). Prescriptions only accounted for 9% of diabetes expenditure, yet this has risen by 56% over the last 8 years.[13] The estimated indirect costs of premature mortality, absenteeism, reduced productivity and informal care were considerably higher at £13.9 billion.[12] Another study estimated yet higher direct costs of £13.8 billion for diabetes in 2010, of which hospitalisation complications accounted for the largest fraction at over 65%, followed by the cost of medication to manage complications (15%) which doubled the overall cost of diabetes medication. On an individual level, the annual cost of inpatient care to treat diabetes complications was estimated at between £1,800 and £2,500, 6-7 times higher than the annual outpatient costs.[14] The cost burden of diabetes is projected to rise within the next 25 years by £39.8 billion in total if no changes are made to the way diabetes is managed.[12]

1.1.2 Pathomechanisms of diabetic vascular complications

Development of diabetes vascular complications implicates a range of metabolic and haemodynamic factors. Metabolic factors include glucose and its metabolites such as advanced glycation end-products (AGEs), whereas hemodynamic factors include the renin angiotensin system (RAS) and vasoactive components such as the endothelin and urotensin systems.[15] Atherosclerosis is the underlying mechanism in the development of macrovascular disease, whereas glucotoxicity appears to relate more to microvascular disease. The pathophysiology of macrovascular and microvascular diseases in T2D is briefly revisited below:

1.1.2.1 Macrovascular (cardiovascular) complication

Role of hyperglycaemia. Hyperglycaemia has either a direct or indirect toxic effect on macrovasculature. High glucose levels entering the polyol pathway at an increased flux rate raise diacylglycerol formation, whereas increased glucose flux into the hexosamine pathway can mediate vascular injury. The atherothrombotic risk is increased by accumulation of AGEs which exert pro-inflammatory and pro-fibrotic effects on the vascular cells. Insulin resistance towards glucose regulation adds resistance to the antiproliferative effects of insulin.[15]

More recently, the role of novel factors such as tumour necrosis factor (TNF) related ligand and the complement system on macrovascular complications has also been suggested. It is proposed that TNF-related apoptosis inducing ligand (TRAIL) has a pro-apoptotic effect on cells damaged by hyperglycaemia, thus hastening the progression towards macrovascular diseases.[16] The hyperglycaemia-induced complement system possibly stimulates AGE receptor activation or enhances mitochondrial reactive oxygen species (ROS) production which, in turn, induces apoptosis.[17]

Role of hypertension, dyslipidemia and platelet hypercoagulability. Hypertension commonly arises in hyperglycaemic milieu and subsequently complicates diabetes through accelerated development and progression of atherosclerosis. The pathological mechanism involves a constellation of insulin resistance, hyperinsulinemia, elevated renal reabsorption of sodium, sympathetic tone hyperactivity and RAS stimulation by accumulating AGEs. The accumulation of AGEs induces upregulation of certain components of the RAS, leading to promotion of endothelial dysfunction. Predisposition of endothelium towards atherogenic milieu is caused by imbalance in the release of vasoconstrictors (e.g. angiotensin-II and endothelin-I) and vasodilators (e.g. nitric oxide), the dysfunctional endothelium further promoting vasoconstriction, inflammation, cellular growth and atherosclerosis. Similarly, activation of the endothelin system induces vasoconstriction, proliferation of vascular smooth muscle cells, wall thickening, inflammation and tissue remodelling, resulting in atherosclerosis and, consequently, cardiovascular events.[18,19]

Dyslipidaemia is also common in diabetes, characterised by low levels of high density lipoprotein (HDL) and high levels of low density lipoprotein (LDL) and triglyceride. Formation of AGEs in diabetic milieu can trigger the formation of modified albumin which inhibits cholesterol efflux to HDL. Insulin resistance increases free fatty acid (FFA) flux to the liver which results in over-

production of triglyceride-rich very low-density lipoprotein (VLDL), leading to exchange of triglyceride for cholesterol between VLDL and LDL-HDL particles. Subsequent hydrolysis of triglyceride-enriched HDL and LDL catalysed by hepatic lipase results in the formation of small, cholesterol-poor HDL and LDL particles. Being more prone to oxidation, the dense LDL particles are a major contributor to premature atherogenesis.[20]

Platelets tend to aggregate in diabetic milieu and its hypercoagulability is thought to play a pivotal role in accelerated atherosclerosis through early atherothrombosis (i.e. thrombus formation on eroded or ruptured atherosclerotic plaques).[21]

1.1.2.2 Microvascular complication

Role of hyperglycaemia. Prolonged hyperglycaemia selectively damages vulnerable microcirculation. Major targets include capillary endothelial cells in the retina, mesangial cells in the renal glomerulus, and neurons and Schwann cells in peripheral nerves, in which down-regulation of glucose transport fails to occur when extracellular glucose levels are elevated, eventually causing intracellular hyperglycaemia. This state is followed by increased vascular permeability which enables extravasation of accumulating plasma proteins in the vessel walls. Changes in the extracellular matrix as well as hypertrophy and hyperplasia of endothelial, mesangial and arteriolar smooth muscle cells contribute further to vessel wall thickening, resulting in progressive narrowing and occlusion of microvascular lumina.[22]

Hyperglycaemia also alters afferent and efferent arteriolar tone, leading to glomerular hypertension. This hemodynamic change is followed by albumin leakage from glomerular capillaries and structural changes such as membrane thickening, hypertrophy, glomerulosclerosis, and podocyte injury and loss. Decline in glomerular filtration rate (GFR) and increased urinary albumin excretion occur in response to widespread glomerular capillary occlusion.[23] In the retina, hyperglycaemia induces apoptosis of Müller cells, ganglion cells, pericytes and endothelial cells.[24] Degeneration of pericytes and endothelial cells also occurs in diabetic vasa nervorum which precedes dysfunctionality of peripheral nerves.[25]

Role of hypertension, dyslipidemia and platelet hypercoagulability. Hypertension accelerates the onset and progression of nephropathy through upregulation of glucose transporter proteins and activation of inflammatory mediators.[26]

Elevated VLDL and triglyceride levels are associated with retinopathy and albuminuria. Lipoprotein lipase – a key enzyme in triglyceride hydrolysis – generates natural peroxisome proliferator-activated receptor (PPAR) ligands, dysfunction of which promotes microangiopathy following a loss of endogenous PPAR agonists.[27] PPAR-α agonists were shown to inhibit angiogenesis, inflammation and cell migration through vascular endothelial growth factor (VEGF) pathway,[28] as well as regulating endothelial cell survival and limiting apoptosis through AMP-activated protein kinase signal transduction pathway.[29]

Blood hypercoagulability and adhesion of platelets and leukocytes to the endothelial surface promote microthrombus formation and luminal occlusion, eventually causing impaired perfusion, ischemia and dysfunction of the affected tissues.[22]

1.1.2.3 Oxidative stress: The unifying mechanism for vascular complications

In addition to increases in glucose flux via the polyol pathway, intracellular formation of AGEs, expression of the AGE receptor, and hexosamine pathway flux, another common pathway mediating hyperglycaemic-induced vascular and tissue damage is the excessive activation of protein kinase C isoforms. The isoform activation particularly mediates retinal and renal blood flow decrease in diabetes, possibly by depressing nitric oxide production and/or increasing endothelin. All these known biochemical mechanisms, however, are not supported by findings from clinical studies which attempt to block one of the pathways, leading to a unifying hypothesis that all varying mechanisms for the pathogenesis of vascular damage stem from oxidative stress, activated by overproduction of mitochondrial ROS superoxide resulting from intracellular hyperglycaemia.[30] It is suggested that persistent production of these free radicals may explain the continuing progression of vascular and tissue damage even after glucose normalisation (known as 'metabolic memory').

1.1.3 Preventive management for T2D vascular complications: Evidence and recommendations

Strategies for managing diabetes that impact on the burden of complications are urgently needed. These strategies need to be centred around behavioural and pharmacological interventions that have been shown in epidemiological studies to be effective for primary or secondary prevention of cardiovascular and microvascular disease in T2D. Importantly, the accumulating evidence base has led to a shift away from a glucocentric approach for protecting against vascular complications towards a more comprehensive, target-driven approach which encompasses the full range of risk factors while taking age and cardiovascular risk assessment into account.[31-34] A body of evidence on the benefits of controlling risk factors which underpin current recommendations for T2D management is discussed below, while more detailed comparison of the current guidelines for the prevention of vascular complications is summarised in **Appendix A on pages 322-325**.

1.1.3.1 Lifestyle modification

Physical activity. Insulin-glucose dynamics, lipid profile, blood pressure and other cardiovascular risks are all amenable to improvement by regular physical activity or exercise training. A meta-analysis of 23 randomised trials concluded that >150 minutes of structured weekly aerobic or resistance training for at least 12 weeks was associated with a greater HbA1c decline than shorter training programmes. Simple physical activity advice, however, only improved glycaemic control when combined with dietary advice.[35] The type of exercise is also important, HDL and triglycerides responding to aerobic exercise programmes, while blood pressure control requires endurance

exercise.[36] Regular physical activity may also reduce the risk of CVD due to antiinflammatory and antithrombotic mechanisms.[36]

Weight control. Weight control by diet and exercise is a key component of lifestyle intervention. A multicentre randomised trial investigating the effects of long-term weight control on cardiovascular events reported that such intensive lifestyle intervention was more effective than a support and education programme for improving HbA1c, systolic blood pressure and HDL in obese participants with T2D, although no difference in cardiovascular events was observed between the groups.[37]

Long-term weight loss (attributed to lower energy intake and improved physical activity) and reduced T2D incidence were also documented after bariatric surgery, as compared with conventional therapy, among Swedish obese individuals.[38] A more recent meta-analysis of eight RCTs (N=619 obese T2D patients) reported greater weight loss (mean difference [in kg] = -16.9, 95% CI -19.8 to -14.1) and BMI reduction (mean difference = -5.8, 95% CI -6.9 to -4.6) as well as improved glycaemic and lipid control and higher rate of T2D remission, confirming the superiority of bariatric surgery over non-surgical treatment.[39]

Weight loss following bariatric surgery is thought to 'reverse' diabetes (i.e. restoring glycaemic control without the need for diabetes medication) by enhancing insulin secretion and sesitivity, reducing lipotoxicity and inflammation which impair glucose regulation, and altering the levels of secreted gut hormones in response to food.[40] Bariatric procedures also appear to have different roles on severe obesity in T2D: gastric restrictive procedures (e.g. gastric banding, gastrectomy, gastroplasty) limit gastric volume, induce satiety, and subsequently reduce the body weight, whereas intestinal bypass procedures (e.g. Roux-en-Y gastric bypass, biliopancreatic diversion) result in fat and nutrients malabsorption as well as caloric intake restriction. In a meta-analysis of 621 studies with 135,246 T2D patients,[41] greater effects on long-term weight reduction (maintained for at least two years) were reported in 63.3% (mean difference of weight [kg] = -43.5, 95% CI -47.5 to -39.5) and 59.7% (mean difference = -44.7, 95% CI s48.4 to -41.0) of morbidly obese patients undergoing biliopancreatic diversion/duodenal switch and gastric bypass, respectively, relative to banding procedures (46.2%, mean difference = -32.0, 95% CI -35.1 to -28.8). The respective patient proportions by procedures for T2D remission outcome were 95.1%, 80.3% and 56.7% and these appeared to be proportionately associated with the weight loss.

Smoking cessation. A prospective study among smokers newly diagnosed with T2D revealed that, compared to continued smokers, those who quit had a significant reduction at one year in metabolic parameters (fasting blood glucose and HbA1c), lipid profiles (LDL and total cholesterol), blood pressure and albuminuria. Smoking cessation also significantly reduced the prevalence of neuropathy, PAD and microalbuminuria.[42]

Current recommendations. Lifestyle management should be the main focus of the initial consultation in T2D, before consideration of medical treatment. While rarely sufficient on its own, it remains the cornerstone strategy for cardiovascular risk reduction. This is particularly important

in the contemporary calorie-rich environment and current recommendations are for appropriate intake of total energy with a balanced diet based primarily on vegetables, fruits, wholegrain cereals and low-fat protein sources.[31-34] Moderate to vigorous physical activity performed regularly is also recommended for contributing to diabetic control and prevention of CVD.[31,32,34] These dietary and exercise measures combine to facilitate weight control which is of huge importance in T2D, weight reduction (or stabilisation at best) being central to the management of overweight or obese patients, with assessment for bariatric surgery being considered for obese, newly diagnosed patients.[31-34] Smoking cessation should be guided by the five A principles (i.e. Ask, Advise, Assess, Assist, Arrange) and backed up with pharmacological support as necessary.[31-34]

1.1.3.2 Glucose and glycaemic control

The terms glucose control and glycaemic control are often used interchangeably. In this thesis, I chose to discriminate between the two terms by attributing glycaemic control to HbA1c and glucose control to other assays. Blood glucose control (as with T2D diagnosis) can be determined by several functional parameters. Fasting plasma and 2-hour postprandial blood glucose levels have been the most common parameters used to measure short-term glucose control. In contemporary practice, however, HbA1c (short for glycated haemoglobin A1c) is considered the gold-standard assay for glycaemic control. HbA1c measures glucose molecules that cling to haemoglobin in the erythrocytes; thus, given an erythrocyte's lifespan of around 120 days, it can indirectly reveal the average of blood glucose levels over the prior four months.[43] Percentage of haemoglobin that has glucose molecules bound is proportional to the length of hyperglycaemia.

Glucose control. A meta-analysis of 102 prospective studies (including nearly 700,000 individuals with and without diabetes) reported twofold excess risk for CHD (HR 2.36, 95% CI 2.02-2.76) in individuals who had prior diabetes with a baseline fasting blood glucose concentration of ≥7 mmol/L. An average fasting blood glucose concentration of 8.5 mmol/L conferred similar excess risk for CHD (HR 2.0) and ischaemic stroke (HR 2.5).[44]

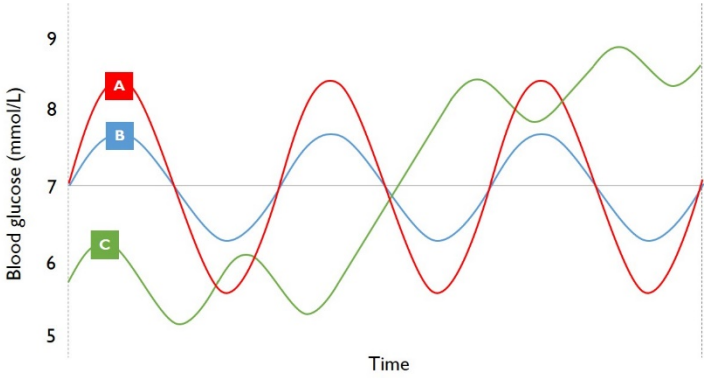
Glycaemic control. Data from a prospective cohort study of over 48,000 T2D patients in New Zealand without known CVD reported that each 1% increase of HbA1c was associated with an 8% increase in hazard for myocardial infarction and a 9% increase for stroke over 2.4 years of follow-up.[45] In a prospective study using the UK General Practice Research Database (GPRD) with nearly 28,000 T2D patients receiving intensified treatment (median follow-up 3.9 years), higher or lower mean HbA1c levels than 7.5% were associated with increased all-cause mortality and initial cardiac events.[46] A similar U-shaped association of mean HbA1c levels with all-cause mortality was documented by another retrospective study involving 1,447 T2D patients with incident heart failure; during a median follow-up of 2.8 years, the risk was higher amongst those with HbA1c levels of <6.0% (HR 2.5) and >9.0% (HR 1.8).[47] The U-shaped relationship was also seen between latest HbA1c levels and myocardial infarction in a GPRD study with over 101,000 T2D patients (median follow up 5.4 years).[48]

The UK Prospective Diabetes Study (UKPDS) trial documented a significant 25% risk reduction for microvascular outcomes, but not for myocardial infarction, stroke and all-cause mor-

tality following tight glucose control with sulphonylureas and insulin.[49] However, the post-trial analysis revealed risk reduction of 15% for myocardial infarction and 13% for all-cause mortality 10 years later, despite a vanishing difference in HbA1c after the first year.[50] These findings were corroborated by another post-trial analysis reporting similar effects with greater reduction of microvascular risk by 37% and additional risk reduction for PAD by 43% for every 1% reduction in mean updated HbA1c, although no specific HbA1c threshold was observed for any outcomes.[51] The modest benefits of intensive glucose control were nevertheless revealed from the Action in Diabetes and Vascular Disease (ADVANCE) trial with 14% risk reduction for major microvascular events (HR 0.86, 95% CI 0.77 to 0.97) and 6% for major macrovascular events (HR 0.94, 95% CI 0.84 to 1.06).[52] Further, the microvascular benefit from intensive glycaemic therapy has been reportedly lost in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) post-trial analysis (HR 0.95, 95% CI 0.85 to 1.07).[53]

Glucose and glycaemic variability. There is an emerging concern about the deleterious effect of glucose or glycaemic variability from one measure to the next, where higher fluctuation of blood glucose or HbA1c levels may indicate poorer control. Glucose variability refers to the changes from hyperglycaemia (either fasting or postprandial) and hypoglycaemia over a given period of time. Accumulating studies have documented that the onset and progression of T2D complications are attributed not only to hyperglycaemia but also hypoglycaemia (commonly drug-induced),[52,54-58] suggesting that fluctuating blood glucose levels over the diabetes course can be as harmful as the stable, chronic hyperglycaemia or a single episode of an acute one. Growing evidence indicates that glucose variability is predictive of microvascular complications and coronary artery disease (CAD)[59] as well as of non-severe hypoglycaemia in T2D.[60] The high variability could even be harmful to nondiabetic patients treated in intensive care units,[61] making glucose variability a more complex physiological phenomenon than glucose control.

Figure 1.1 Visualisation of simplified glycaemic variability



Mean blood glucose and area under the curve are identical in A and B; mean blood glucose is roughly identical in A, B and C. Reproduced from DeVries (*Diabetes*, 2013)[62] and Suh and Kim (*Diabetes Metab J*, 2015).[63]

Figure 1.1 above visualises the concept of glucose variability. Individuals with normal or moderate blood glucose values (calculated as mean) can have high glucose variability (depicted by A). The clinical implication is that improving glucose control can be harder among these indi-

viduals – more intensive treatment to lower blood glucose levels can increase the risk of hypoglycaemia as glucose fluctuations can be deepened to the low end. If glucose variability is mainly skewed towards high values, a more intense treatment is still appropriate. Conversely, if the variability is only skewed towards low values, a less intense treatment should be considered to avoid hypoglycaemia. Clinicians should therefore look at, if at all possible, both patients' glucose control and variability so the harmful effect of glucose swings can be averted.

Unlike T1D where alternating hyper-, normo- and hypoglycaemia are linked to absolute insulin deficiency, glucose variability in T2D patients is subject to the disease heterogeneity. In non-insulin-treated T2D, increase of postprandial blood glucose plays a major role in glucose variability, while hypoglycaemia only having a minor, yet not negligible, contribution.[64]

A range of variability metrics have been developed. However, glucose variability metrics are perhaps most useful for T1D due to data availability from more intense measures taken to monitor the insulin- induced hypoglycaemias. The most widely use metrics for glucose variability are standard deviation (SD), coefficient variation (CV), mean of daily differences (MODD), mean amplitude of glycaemic excursions (MAGE), continuous overlapping net glycaemic action (CONGA) and area under the curve (AUC). SD refers to spread of mean (thus assuming that glucose measures are normally distributed, which is typically not the case), while CV is the percentage of SD to mean ratio. MAGE evaluates the mean glucose values greater than 1 SD of all values in a series and correlates with the overall and intraday SD. MODD calculates the difference between glucose values at the same time on two consecutive days only. CONGA measures intraday glucose variability and is adaptable for varying time intervals thus providing short- and long-term variability measures. AUC provides an indicator of overall glycemia through calculation of the 24-hour cumulative exposure to glucose levels using the trapezoidal rule.[63-65]

For T2D where close monitoring of blood glucose may not be as frequent, glycaemic (HbA1c) variability appears to be more relevant, although some glucose variability metrics such as SD and CV can still be applied for between blood glucose measures with longer interval (i.e. non-daily). As a measure of averaged blood glucose levels over the last 2-3 months, HbA1c is not capable of capturing hypoglycaemia episodes, thus its variability – unlike glucose's – is not a strong predictor of hypoglycaemia risk.[66,67] In addition to SD and CV, other glycaemic variability metrics are less commonly used which include variability independent of mean (VIM, a transformation of SD uncorrelated with mean), residual standard deviation (RSD, the square root of residual mean square from a linear mixed effect model fit), average real variability (ARV, mean absolute difference between successive measures), successive variation (SV, square root of mean squared difference between successive measures), mean absolute change (difference between index value and last value), and mean absolute residual (around the line connecting index value with last value).[65,68] Computation of these metrics is presented in **Appendix B on page 325**.

In a small cross-sectional study, glucose and HbA1c excursion exhibited a triggering effect on oxidative stress and endothelial dysfunction.[69] Post-hoc analysis from the ADVANCE trial further showed that blood glucose and HbA1c excursion had a predictive function for T2D com-

plications. Among 4,399 T2D patients in an intensive glucose treatment arm with at least three fasting blood glucose or HbA1c measurements, those with the highest HbA1c-SD decile had 1.6 and 3.3 times the risk for combined macro-/microvascular events and all-cause mortality, respectively, than those with the lowest decile. The highest decile of fasting blood glucose SD was only associated with risk excess for vascular events (HR 2.70).[70] A Danish prospective study involving over 11,200 T2D patients (median follow-up 6 years) reported that in those with an index HbA1c of ≤8% both mean absolute residual and mean absolute change of HbA1c were associated with increased mortality, whereas in patients with an index HbA1c of >8%, only mean absolute change had an association with mortality.[68]

Current recommendations. Guidelines mostly call for a target HbA1c level of ≤7.0% (≤53 mmol/mol) while recognising that a less rigorous goal may be more realistic in many cases. The National Institute for Health and Clinical Excellence (NICE) has, however, set a yet tighter initial target of ≤6.5% with a more relaxed target of <7.5% in the subsequent evaluation; further relaxing the HbA1c target should be considered in particular cases and older or frail patients to avoid the harmful effects of hypoglycaemia and other adverse events from intensive medication treatments.[33] Of note, none of the guidelines specifies a concatenated value from repeated measurements over time for the recommended target, suggesting that the current approach still embraces 'snapshot' target achievement on a single occasion, not taking historical glycaemic control or between-measure fluctuation into account. Whilst being poised to become a future target parameter for optimum control, glucose/glycaemic variability remains a challenge due to the lack of consensus on the gold standard metric and the most optimal clinical approach to target it.

With regard to diabetes medications, metformin is the first-line therapy but combination with other hypoglycaemic agents or insulin may be needed to achieve guideline recommended HbA1c targets. A list of currently approved T2D medications and their mechanisms and effects is summarised in **Table 1.1 below**.

Table 1.1 Pharmacological agents for managing T2D[32,71,72]

Drug class	Representative agent	Route of administration	Mechanism of action	Adverse effects
Biguanides	Metformin	Oral	▪ Directly increases insulin sensitivity in muscle, adipose tissue and liver ▪ Increases glucose uptake ▪ Decreases hepatic gluconeogenesis	▪ Weight loss (anorectic effect) ▪ Bloating, flatulence, diarrhea, abdominal discomfort ▪ Lactic acidosis (in those with impaired kidney or liver function)
Sulphonylureas	Glipizide Glimepiride Glyburide Gliclazide	Oral	Stimulates insulin secretion through binding to K-channel in pancreatic β-cells	▪ Weight gain ▪ Hypoglycaemia ▪ Skin rash
Meglitinides (glinides)	Repaglinide Nateglinide	Oral	Stimulates insulin secretion by closing K-channel in β-cells	▪ Potential hypoglycaemia ▪ Allergic skin reaction ▪ Nausea ▪ Diarrhea, constipation, abdominal discomfort

Thiazolidinediones (glitazones)	Pioglitazone Rosiglitazone*	Oral	▪ Increases insulin sensitivity in muscle, adipose tissue and liver through activation of PPAR-γ receptor ▪ Increases glucose uptake ▪ Decreases hepatic gluconeogenesis ▪ Helps decrease blood pressure & triglyceride, and helps increase HDL	▪ Weight gain ▪ Fluid retention ▪ Congestive heart failure (in those at risk) ▪ Osteopenia, fracture ▪ Anemia ▪ Macular oedema ▪ Hepatic failure ▪ Bladder cancer
Dipeptidyl peptidase 4 (DPP-4) inhibitors (gliptins)	Sitagliptin Saxagliptin Vidagliptin Linagliptin Alogliptin	Oral	Inhibits DPP-4 from hydrolysing incretin, resulting in increased insulin secretion from β-cells and decreased glucagon secretion from α-cells	▪ Diarrhea, abdominal discomfort ▪ Upper respiratory tract infection ▪ Hepatic failure
α-glucosidase inhibitors	Acarbose Miglitol	Oral	Blocks intestinal enzymes which break down carbohydrates, thereby delaying carbohydrate digestion and attenuating postprandial blood glucose excursion	Flatulence, diarrhea, abdominal discomfort
Amylin analogue	Pramlintide	Injection	▪ Suppresses glucagon secretion ▪ Delays gastric emptying and increases satiety	▪ Hypoglycaemia ▪ Weight loss ▪ Nausea, vomiting ▪ Headache
Glucagon-like peptide 1 (GLP-1) agonists	Liraglutide Exenatide Dulaglutide Lixisenatide Albiglutide	Injection	▪ Activates GLP-1 receptor, resulting in increased insulin secretion from β-cells and decreased glucagon secretion from α-cells ▪ Delays gastric emptying and increases satiety	▪ Weight loss ▪ Nausea, vomiting, diarrhea, abdominal discomfort ▪ Biliary disease, gallstone ▪ Headache ▪ Nervousness ▪ Hypoglycaemia
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	Dapagliflozin Empagliflozin Canaglifozin	Injection	Lowers renal threshold for glucose and decreases glucose reabsorption from tubular lumen, thereby increasing urinary glucose excretion (glucosuria)	▪ Hypotension ▪ Genital mycosis ▪ Urinary tract infection ▪ Acute kidney injury ▪ Dehydration, hyperkalemia ▪ Increased LDL ▪ Ketoacidosis ▪ Fracture
Insulin	▪ Rapid acting (aspart/ glulisine/ lispro) ▪ Short acting (regular) ▪ Intermediate acting (NPH, lente) ▪ Long acting (detemir/ gargline/ degludec) ▪ Inhaled	Injection	▪ Increases glucose uptake ▪ Decreases hepatic gluconeogenesis ▪ Inhibits lipolysis and proteolysis, and enhances protein synthesis	▪ Hypoglycaemia ▪ Weight gain ▪ Lipoatrophy and lipohypertrophy at injection sites ▪ Allergic reaction

*Banned in Europe

It is important to emphasise the potential severe hypoglycaemic effect of insulin and sulphonylureas. Studies have documented significant benefits of intensive glycaemic control on reducing the risk of vascular complications, at the cost of a higher risk of severe hypoglycaemia which was shown to be capable of – interestingly bidirectionally – provoking serious cardio- and cerebrovascular events.[55,57,73] In a meta-analysis of 33 studies with over 1.3 million patients in total, sulphonylurea use was linked to a significantly increased risk of cardiovascular death (RR 1.27, 95% CI 1.18 to1.34).[74] Among the plausible biological mechanisms for this phenomenon are inflammation,[75] endothelial function,[76] cardiac autonomic neuropathy (CAN),[77] and cardiac ischemia or fatal arrhythmia.[78-80] Severe hypoglycaemia may also have a role in aggravating cognitive decline in older patients.[81-83] In the population-based matched cohort study, 225,045 elderly people with newly diagnosed diabetes had 16% increased risk of dementia (HR 1.16, 95% CI 1.15 to 1.18) as compared to 668,070 non-diabetic controls, and the risk was greater in those with prior stroke, PAD and CKD.[83] In chronic diabetes, changes in hippocampal synaptic plasticity and so-called diabetes encephalopathy appear to lead to cognitive and behavioural deficits.[84,85] As a corollary to these, current guidelines do not recommend intensive treatment with insulin and/or multiple oral antidiabetes agents in older, frail patients and other cases where hypoglycaemic effect may outweigh the attributable cardiovascular benefits.[31-34]

1.1.3.3 Blood pressure control

Blood pressure control. Hypertension has been shown to increase the risk of CVD fourfold.[86] The positive effects of lowering blood pressure below 150/85 mmHg were shown in the UKPDS trial. During an 8.4 year median follow-up, tight control with an angiotensin converting enzyme inhibitor (ACEI) or a β-blocker conferred significant reductions in diabetes-related death (32%), stroke (44%) and microvascular events (37%) compared with patients treated for higher blood pressure targets.[87] A post-hoc analysis of the trial demonstrated that every 10 mmHg decrease of systolic blood pressure reduced the risk of diabetes-related death by 15%, myocardial infarction by 11% and microvascular complications by 13%, with those in <120 mmHg category being at lowest risk.[88] In the more recent ACCORD trial, patients assigned to intensive therapy achieved significantly lower systolic blood pressure (mean 119 mmHg, compared to 134 mmHg in standard therapy) but cardiovascular risk reduction was only observed for stroke by 40%.[89] Results from a meta-analysis of 13 randomised trials in diabetes patients concluded that targeting a systolic blood pressure of 130-135 mmHg is acceptable, whereas a lower target of <130 mmHg, while further lowering stroke risk, offered no benefits for cardiac or microvascular events and tended to increase serious adverse events.[90] In the multinational ADVANCE trial, hypertensive T2D patients assigned to combination of ACEI and diuretic showed a greater mean reduction in blood pressure, a 9% risk reduction in major macro- or microvascular event, an 18% risk reduction in cardiovascular death and a 14% risk reduction in all-cause death over 4.3 years of follow-up.[91]

Current recommendations. The optimal blood pressure threshold in diabetes continues to be debated, current guideline recommendations ranging from <130/80[34] to <140/85 mmHg.[31] Along with lifestyle advice, an ACEI (or alternatively an angiotensin II receptor blocker [ARB]) is the

drug class of choice in hypertensive diabetic patients, particularly in the presence of proteinuria or microalbuminuria. However, combination with other antihypertensive drug classes is usually needed to achieve blood pressure goals.

1.1.3.4 Lipid control

Lipid control. A meta-analysis of 14 randomised trials enrolling over 18,000 diabetic participants with a follow-up of 4.3 years provides evidence on the efficacy of statins in the prevention of cardiovascular events in T2D.[92] In diabetic participants, each 1 mmol/L reduction of LDL was associated with at least 20% reductions in myocardial infarction or coronary death, coronary revascularisation and stroke. The benefit was seen at LDL starting as low as 2.6 mmol/L, highlighting a positive relationship between LDL and cardiovascular risk. Contrary to these findings, the cardiovascular benefits of statins appear to be ineffective in patients with chronic kidney disease (CKD).[93,94] Statins do not attenuate development of nephropathy nor do affect retinopathy or neuropathy.

Interestingly, fibrates were shown to reduce the microvascular risks through antiinflammatory actions.[95] In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, statin-naïve patients randomly assigned to fenofibrate had less albuminuria progression and less retinopathy requiring laser therapy.[96] A subsequent retrospective cohort study similarly reported a 22% risk reduction (HR 0.78, 95% CI 0.69 to 0.90) in progression to diabetic retinopathy with fibrate treatment.[97] However, results from the ACCORD trial showed that fibrate offers no cardiovascular benefits when added to simvastatin.[98] Addition of ezetimibe to statins, on the other hand, resulted in LDL cholesterol levels lowering and improved cardiovascular outcomes[99] and appears to be safely prescribed to patients with advanced CKD.[100]

Current recommendations. Guidelines agree on statin therapy in diabetes, with an LDL target of 2.6 mmol/L (100 mg/dL) in patients without cardiovascular risk factors or target organ damage.[31-34] A lower LDL target of 1.8 mmol/L (70 mg/dL) is advised for patients with high cardiovascular risk, overt CVD or aged over 40 with at least one cardiovascular risk factor. Strategies for increasing HDL should be lifestyle-based, not pharmacological.

1.1.3.5 Platelet function stabilisation

Platelet function control. A meta-analysis of 287 randomised trials involving a total of 212,000 patients conducted by the Antithrombotic Trialists' Collaboration revealed that risk reduction in vascular events (myocardial infarction, stroke and death) following antiplatelet therapy was not significant in diabetic patients.[101] However, the Collaboration had previously shown that the effects of antiplatelet therapy on vascular diseases were similar in people with and without diabetes, suggesting a beneficial effect of treatment for primary prevention in diabetes.[102] Gastrotoxicity has been reported, but antiplatelet therapy is not associated with vitreous nor retinal bleeding in diabetic patients.[103]

Current recommendations. For secondary prevention of CVD in T2D, low-dose aspirin (75-150 mg daily) is recommended or clopidogrel in cases of aspirin intolerance. Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel gives additive cardioprotective effects and is recom-

mended for a full 12 months in all patients following acute coronary syndrome (ACS), regardless of diabetes status. Guidelines also support the use of newer P2Y12 receptor blockers (prasugrel or ticagrelor) which have more potent antiplatelet activity than clopidogrel in diabetic patients and other high risk groups with ACS treated with percutaneous coronary intervention (PCI). Indications for antiplatelet therapy for primary prevention of CVD are less well defined in patients with diabetes but are usually recommended only for those at particularly high cardiovascular risk taking into account the risks of treatment.[31-34]

1.1.3.6 Intensive, multitarget treatment

The multifactorial nature of T2D implies that targeting a single parameter only to manage the disease is unlikely sufficient in reducing the risks of vascular complications. The Denmark's Steno trial (N=160, mean follow-up 3.8 years) documented the lower rates of progression to nephropathy (OR 0.27, 95% CI 0.10 to 0.75), retinopathy (OR 0.45, 95% CI 0.21 to 0.95) and autonomic neuropathy (OR 0.32, 95% CI 0.12 to 0.78) in microalbuminuric T2D patients assigned to intensified multifactorial treatment with lifestyle modification and pharmacological multitherapy (targeting hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria altogether).[104] Greater declines in HbA1c, blood pressure, lipid profiles and albumin excretion rate in the intensive treatment group were reported in the sequential Steno-2 trial (mean treatment period 7.8 years, N=130 at the end of trial), as well as lower risks of CVD (HR 0.47, 95% CI 0.24 to 0.73) and nephropathy (HR 0.39, 95% 0.17 to 0.87).[105] The benefits were sustained for another 5.5 years after the trial ended (N=93), indicated by lower risks of CV-cause death (HR 0.43, 95% CI 0.19 to 0.94) and all-cause death (HR 0.41, 95% CI 0.25 to 0.67), and fewer patients needing retinal photocoagulation (RR 0.45, 95% CI 0.23 to 0.86).[106] After a total of 21.2 years of observation (mean post-trial follow-up 13.4 years, N=34), the risk of hospitalisation for heart failure was reduced by 70% (HR 0.30, 95% CI 0.14 to 0.64).[107]

1.2 Quality of diabetes care

1.2.1 Definition, aims and measurements

Quality of care is defined as "the degree to which health services to individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge".[108] High quality of care aims to deliver safe, effective, timely, efficient, patient-centred and equitable care, and can be measured by examining the structure of the care setting, measuring the process of care and assessing the outcomes of care.[108] Structure of care refers to health providers' characteristics, personnel and care policies. Process of care assesses whether patients receive what is known to be good care which, applied to diabetes, might include blood glucose measurement, foot examination, renal function test, antihypertensive prescribing or cardiac procedures in high risk patients. Outcomes of care refers to patients' health status following treatment which, applied to diabetes, might include intermediate outcomes (e.g. HbA1c and LDL levels achieved) or hard outcomes (e.g. stroke, 10-year survival, death).

1.2.2 Why is quality of diabetes care important?

There is a growing recognition of the need for high quality care for diabetes in order to protect against cardio- and microvascular complications and improve prognosis. Diabetes is undeniably a complex disease which requires a multifaceted approach to healthcare. Among chronic diseases, diabetes is perhaps the most psychologically and behaviourally challenging one to manage since the management also relies considerably on patients' self-care efforts. Quality of care is, therefore, an interest shared by patients with diabetes and those who deliver and pay for their care. Patients and their families have a vested interest in receiving the best evidence-based care, particularly from their primary care provider, through whom most ambulatory treatment takes place. Healthcare providers are under pressure to deliver best, cost-effective practices, but are confronted with a variety of guidelines that may be difficult to contextualise within their own setting. For this, and other reasons, guideline implementation is variable and this has become a major preoccupation of policy makers seeking to avoid suboptimal care and waste of resource. Health insurers too have justifiable reason to take an interest in diabetes care on financial grounds in order that the services they are covering can be both of high quality and cost-effective.[109]

1.2.3 Quality indicators for diabetes care

In recognition of the need to stem the global epidemic of diabetes, the United Nations passed a resolution in 2006, encouraging member states "to develop national policies for the prevention, treatment and care of diabetes in line with the sustainable development of the healthcare systems, taking into account the internationally agreed upon development goals, including the Millennium Development Goals".[110] This call emphasises that implementation of high quality interventions for diabetes – while reckoning on different health care structures and resource availability – will restrain the growth of health expenditures through reduction of costly complications and unnecessary procedures.

A comprehensive set of measures for evaluation and quality improvement for diabetes has been previously developed and implemented in the United States under the Diabetes Quality Improvement Project (DQIP), aiming to gain efficiency in care through translation of key diabetes care recommendations into feasible, comparable and accountable measures within and across healthcare settings.[111] As a precondition for evidence-based health policy reforms, European countries have also arranged standardised indicators for diabetes care in order to measure and benchmark the performance of their different healthcare systems.[112] Such efforts allow more consistent and reliable assessment of quality of care as well as enhancing research uptake into practice, ultimately leading to improvements in diabetes care and clinical outcomes.

In the United Kingdom, an action has been taken to that effect by the launch of the Quality and Outcomes Framework (QOF) in 2004. The QOF is a voluntary incentive scheme for GP practices as an integral component of their contracts with the NHS.[113] Under the QOF, several process and outcome indicators of care for key chronic diseases are incorporated and regularly updated to adapt to changes in guidelines, against which practices score points and get achievement-based

financial rewards for the provision of quality care across a range of clinical areas. The final reward is adjusted to account for clinical workload, local demographics and prevalence of chronic conditions in the practice's locality. To promote knowledge, efficiency and transparency about how well a GP practice is measuring up against the national average, an online database has been developed (http://content.digital.nhs.uk/qof) by NHS Digital (formerly the Health and Social Care Information Centre, HSCIC) where annual level performance on various clinical indicators for 15 key chronic conditions (including diabetes) are made relevant and accessible to patients, the public, health professionals and policy makers.

Despite the similarity of selected care indicators, the QOF for diabetes – as for other diseases – is distinct from the US's DQIP in that it is intended more for resourcing and rewarding good practices rather than for performance management. The QOF reward essentially helps fund further improvements in care delivery. When first introduced in 2004, the QOF for diabetes consisted of 13 process and 4 intermediate outcome indicators.[113] Quality indicators for process of care include measurements or records of:

- BMI
- smoking status
- smoking cessation advice
- HbA1c
- retinal screening
- peripheral pulse check
- neuropathy testing
- blood pressure
- serum creatinine
- microalbuminuria testing
- treated protein- or microalbuminuria
- total cholesterol
- influenza immunisation

whilst quality indicators for care outcomes include attainment of:

- HbA1c targets of 7.4% and 10%
- blood pressure target of 145/85 mmHg
- total cholesterol target of 5 mmol/L

The standards for the QOF for diabetes have undergone several revisions since its inception which include introduction of new indicators, replacement or removal of ineffective indicators, and changes to indicator wording, indicator timeframe, coding/business logic, and point values or thresholds. The revised QOF standards continue to measure achievement against a set of evidence-based indicators. In 2013, the indicator codes have all been reset and re-ordered – altered to a 5-digit alpha-numeric code DM001 after previously starting with DM1 – to reflect the flow of care processes.[114,115] **Appendix C on pages 326-330** summarises changes to the QOF indicators for diabetes from 2004 to the latest in 2014.

In addition to the QOF data, the prevalence and effectiveness of diabetes care against NICE guidelines and quality standards are also scrutinised annually by the National Diabetes Audit (NDA). The audit is however less complete as participation of practices in the NDA is voluntary or highly selective. The NDA measures nine key processes and three treatment targets for diabetes care monitoring as well as the rates of acute and chronic diabetes complications. The key processes include five risk factors (HbA1c levels, blood pressure, cholesterol levels, BMI and weight, and smoking review) and four screening tests for complications (foot exam, urinary albumin or protein test, blood creatinine test and retinopathy screening), whereas treatment targets include HbA1c, blood pressure and cholesterol control.[116]

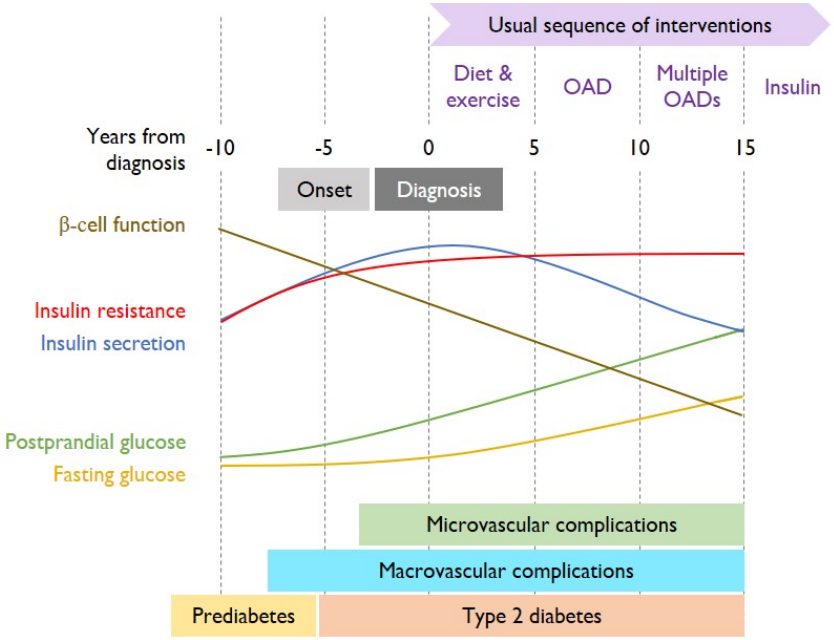
1.2.4 Quality of care in newly diagnosed T2D

Findings from the UKPDS analysis suggest what is known as 'legacy effect' – the similar concept to glycaemic memory – which refers to sustained or improved vascular benefits after a decade following intensive treatment for hyperglycaemia.[50] The clinical message of the UKPDS is clear enough that T2D should be diagnosed early and aggressively managed in order to optimally gain the long-term vascular benefits. In fact, with somewhat high prevalence of patients found to have vascular complications at screening or the time of T2D diagnosis,[117,118] the concept of legacy effect may hold true; diabetic individuals may have been exposed to the harmful effects of hyperglycaemia during their pre-diabetes state or even years before diagnosis of T2D, suggesting that late diagnosis or slow intervention will fail to prevent the complications in the first place.

In the context of quality of care, it is crucial to explore the extent to which high quality care has been delivered in the natural history of T2D and how this may relate to the initial presentation of T2D complications. Efforts to prevent T2D complications and ensure optimal management can be assessed more accurately by observation using administrative and/or clinical data in newly diagnosed patients rather than the established T2D patients, provided the partial loss of information on continual care in the latter population despite feasible attempt to control for duration of diabetes analytically. That said, if a quality of care study uses a prevalent cohort where the observation period is generally set within the same range across all patients (e.g. identified as having T2D in a defined year), historical data on diabetes care in the established patients – despite their availability – will be 'left truncated' or unknowingly disregarded at study entry for the sake of fair comparison with the new patients having no previous care data, hence causing substantial bias. Likewise, the assessment of care will be overestimated (and biased) should such historical data are used. On the other hand, studies that capture patients from their respective time of initial T2D diagnosis have the advantage of allowing a 'pure' T2D cohort such that a mechanistic study of process of care may be undertaken. Smaller study size is yet an offset; by definition, prevalent studies take both old and new cases into account, whereas incident studies only include the new ones which may be harder to discover. Still studies with incident cohort are not necessarily subject to shorter duration of follow-up in comparison with prevalent cohort, even when the cohorts are drawn from the same data source(s) with similar temporal span for follow-up. This is because old cases could have 'exited' earlier for some reasons (e.g. no longer adherent to care plans, deteriorating condition, death).

Confining to incident cohort has another drawback in that ascertainment cannot be made as to whether they are indeed new cases given the fact that vascular complications can be present at the time of or even prior to T2D diagnosis (**Figure 1.2 below**).[117-121] Similar to other diseases where their subclinical processes are frequently subtly occurring, it is otherwise difficult to establish the exact onset of T2D in a patient.

Figure 1.2 Natural history of T2D and typical sequence of interventions



Reproduced from: Holman RR, *Diabetes Res Clin Pract*, 1998;[119] Ramlo-Halsted BA and Edelman SV, *Clin Diabetes*, 2000;[120] and Nathan DM, *N Eng J Med*, 2002.[121]

Importantly, though, newly diagnosed cases represent a particularly interesting clinical window of getting the disease management right at the beginning. Insights from T2D care studies using incident population can be applied to primary care where the disease often first presents and is potentially most effective to manage. The natural history of T2D can potentially be modified through early and continual interventions that the progression of hyperglycaemia as well as the development of vascular complications can be prevented or attenuated.

1.3 Electronic health records (EHRs) for quality of care research

Electronic health records (EHRs) are defined as "a longitudinal electronic record of patient health information generated by one or more encounters in any care delivery setting".[122] This definition suggests a broader coverage than electronic medical records (EMRs) which refer to a digital version of a patient's paper chart in a single practice. EHRs are generated by patients' healthcare providers in a number of formats (e.g. dictionary-guided codes, free-text, scanned notes) and typically contain detailed information about patient demographics, medical history, symptoms, diag-

noses, examination results, laboratory test results, radiology images, immunisation, prescriptions, and progress notes.

Despite high capital costs for its initial implementation, the EHR system offers several advantages over a manual system and it has, indeed, transformed healthcare delivery. By having patient records electronically available and continually updated, clinicians can track patients' information more easily and quickly, thus allowing for more accurate in-depth evaluation as well as avoidance of duplicative testing, imaging procedures and ineffective treatment. EHR also facilitates preventive care by computerised alerts, averts lost prescriptions, and potentially reduces medical errors caused by indecipherable manual prescriptions. With these advantages, EHR can improve clinical efficiency as well as patient outcomes.[123]

There has been increasing interest in optimising EHRs by re-using real-time information collected for secondary purposes, beyond patient care. The richness and instant availability of EHR data has made it an invaluable source for clinical, epidemiological, health outcomes and health economics studies particularly those that aim to further improve healthcare delivery.[124,125]

1.3.1 EHR *versus* bespoke cohort studies

Many large epidemiological findings have been historically based on bespoke cohort studies to obtain reliable follow-up data but such studies are generally geographically isolated to facilitate recruitment and follow-up of participants. EHR-based studies have the advantages of being larger in size and having a wider coverage with lower cost, being less prone to selection bias with higher representativeness of the general population, holding more comprehensive information on more (contemporary) diseases, and having an opportunity for linkage with other clinical care as well as conducting a trial within EHR. EHR studies, however, have some disadvantages, such as requiring consent from patients that their data will be used for research, and varying levels of data completeness and granularity. An absence of HbA1c record, for instance, could mean several possibilities: the patient has no diabetes, the patient has diabetes but not tested nor recorded, or clinicians are unaware that the patient has diabetes.[125]

1.3.2 EHR studies versus randomised clinical trials (RCTs)

While findings from randomised controlled trials (RCTs) are admittedly superior to any observational studies that are more prone to biases, EHR studies offer a different perspective on the treatment evaluation. Translation of RCT findings into real-world practice is limited by the fact that investigation of the efficacy (and safety) of treatment modality is conducted in a highly controlled environment where real-world patient populations are largely excluded. In contrast, EHR studies evaluate the treatment effectiveness in usual clinical care settings and generally apply broader eligibility criteria than RCTs, thus representing general patient population and clinical practice. Furthermore, EHR studies can examine factors that influence treatment effectiveness in real-life (such as treatment adherence, healthcare utilisation, and psychological and financial burden) which otherwise cannot be addressed by RCTs.[126]

1.3.3 Linked EHR and quality of T2D care

Different EHRs can be linked for research purposes since using a single EHR alone may not be adequate to answer all research questions. Linked EHRs have the advantage of providing richer data or variables of interest as well as enabling data validation. Data linkage to determine which records from different sources belong to the same person is made possible by the use of unique identifiers such as health identifier numbers.

The United Kingdom is unique in being the only country with a CVD registry, primary care data, hospitalisation data and census data available on a national scale for research, linkage between which is made possible by the implementation of a universal healthcare system under the NHS. Moreover, the high participation and representativeness of GP practices in primary care databases and their vital role in gatekeeping patients from the next level of care[127] imply that a patient's journey can be easily and largely tracked due to registration with a practice, thus enabling evaluation of care delivery.[128] This great opportunity has driven the government to place EHR research as a central part of the strategy to enhance and accelerate national health research. To that effect, four new centres of EHR research have been launched, one of which is in London where the CALIBER (ClinicAl research using LInked Bespoke studies and Electronic health Records) platform is set up.[129]

The CALIBER research platform links four major UK health databases for primary care (Clinical Practice Research Datalink, CPRD), secondary care (Hospital Episode Statistics, HES), the acute coronary syndrome registry (Myocardial Ischaemia National Audit Project, MINAP) and the mortality and social deprivation registry (Office for National Statistics, ONS), covering over two million adult patients.[128] CALIBER's data sources provide a unique opportunity to investigate quality of diabetes care from diagnosis through continual investigations to chronic vascular complications and even death. Data from CPRD – being clinically and longitudinally recorded – particularly provide a sufficient timeframe to capture trends in real-world care since general practitioners (GPs) look after patients over a long period. The large number of patients covered by CALIBER also enables specification of risk factors and capture of multiple disease presentations. CALIBER data will, therefore, be the ideal analytic substrate for this thesis. Data sources, disease phenotyping and validation studies for CALIBER will be described in more detail in **Chapter 3**.

1.4 Potentials and missed opportunities in quality of care in newly diagnosed T2D

1.4.1 Continuity of care

One of the core principles of effective healthcare organisation is continuity of care. Quality of care parameters can provide a time-to-time benchmark against which to evaluate diabetes care and identify areas and periods needing improvement. Evidence is for general improvement in the processes of T2D care across different healthcare settings although worrying variations persist.[130,131] However, this evidence is founded almost entirely on prevalent cases and whether it applies to

newly diagnosed patients with T2D has received little attention. The distinction is relevant because numbers of new cases of T2D in contemporary practice are increasing rapidly and early and continuing interventions to protect against disease progression and cardiovascular complications early after presentation are important for achieving the best possible outcomes.

1.4.2 Equality of care and relationship of care processes and outcomes

A line of research has identified a range of different factors contributing to meeting diabetes treatment targets but has largely ignored patients newly diagnosed with T2D, early intervention in whom has proven to be vital to reduce the disease burden.[50] Re-identification of risk factors for meeting the targets in incident cases will help develop strategies for optimal diabetic care. Studies in a population with prevalent T2D suggest that there remains inequality of care across different patient groups with a commonality of older age, white ethnicity and lower BMI being the significant factors for meeting HbA1c, blood pressure and lipid targets,[132,133] whereas gender was inconsistently found as a predictor for meeting blood pressure target.[132,134] In particular, duration of diabetes was inversely related to meeting glycaemic and blood pressure targets,[132] suggesting that opportunities for improving outcomes are likely to be greatest in newly diagnosed cases. However, it is a common pitfall of quality measures for chronic disease that they lack strong associations with outcomes.[135] It needs confirmation, therefore, that process measures for quality among patients with newly diagnosed T2D are predictive for meeting intermediate outcome targets.

1.4.3 Specific CVDs following attainment of intermediate outcome targets

Most studies on the quality of diabetes care have limited their outcome assessment to intermediate measures and have shown that patients generally fall short of achieving targets for glycaemic, lipid and blood pressure control, even in well-developed and resourced settings.[130-132,136] Nevertheless, these studies have often stopped short of exploring the long-term vascular consequences of care and it remains unclear whether achievement of intermediate outcome targets can predict downstream outcomes. The question is crucial as highlighted by a recent study that reported higher risk of cardiovascular events among T2D patients with poor quality of care scores.[137] This study, however, excluded newly diagnosed patients and used a composite quality of care metric and aggregate cardiovascular endpoints, making it hard to identify which individual component of care affects the cardiovascular events. Additionally, how specific CVDs beyond just myocardial infarction or stroke as a broad disease entity – which are now more recognisable in contemporary practice – are influenced by the quality of diabetes care is worthy of exploration. Further research is, therefore, needed to address issues not answered by the previous study, which is ideally conducted using a linkage of large EHRs such as the CALIBER platform to allow measurements of care from T2D diagnosis and detailed CVD phenotyping.

1.4.4 Long-term glycaemic control and vascular outcomes

The study of glycaemic control effect on vascular complications has been dominated by adoption of a single snapshot of HbA1c value, mostly measured at the baseline period of study. More recently, a number of metrics generated from available repeated measures of HbA1c are increasingly used to define long-term glycaemic control. Prospective studies in the incident T2D population, drawn from CPRD, documented a linear association between the updated mean of HbA1c category and myocardial infarction and heart failure.[48,138] The excess risk for diabetic retinopathy by fourfold in the T2D patient group with a mean HbA1c of >9% (and by twofold in the 7-9% group compared with <7% group) was also shown by a South Korean study.[139] While averaged HbA1c reflects a longitudinal measure, it ignores – unless time-weighted – the potential varying interval between measures in real-world settings. A follow-up analysis of the ADVANCE trial reported a significant association between one unit increase of HbA1c variability measured using various metrics and the risks of major adverse cardiovascular event (MACE), major microvascular events and all-cause mortality.[70] HbA1c variability metrics may be capable of longitudinally measuring both the amplitude and time element of glycaemic control at a time, but still cannot explain whether achievement of HbA1c target over time is fully taken into account. Lower variability does not necessarily indicate good glycaemic control if the HbA1c values are all above target, likewise higher variability may still be considered a good control if all values are below the recommended target. The drawbacks of available longitudinal glycaemic control metrics argue the importance of developing a new metric which also proportionally estimates the overall period under glycaemic control, and, importantly, how it may be predictive of chronic vascular events. Within the quality of care context, such examination in the newly diagnosed T2D population will generate a more accurate estimate provided that no HbA1c measures taken prior to the start of the study (i.e. initial diagnosis) are overlooked – as if it was conducted in a population with established T2D where the study start may be arbitrarily chosen at the same time point for all cases.

1.5 Aim and objectives

The existing research into quality of care and outcomes in patients with T2D has been briefly discussed, although a formal literature search to capture more relevant studies is still needed. Most studies identified at this stage typically enrolled prevalent T2D; therefore, the evidence base is incomplete and there remain important knowledge gaps whether the findings also apply to patients with newly diagnosed T2D. Linkage of primary and secondary care records with myocardial infarction and death registries offers the potential to define the patient journey from T2D diagnosis through intermediate outcomes to development of vascular complications.

Taking advantage of the unique opportunities offered by available linkage of national EHRs within the CALIBER research platform, the overarching aim of this thesis is, therefore, to investigate the associations between quality of care and vascular outcomes in a newly diagnosed T2D population. The specific objectives of this thesis are:

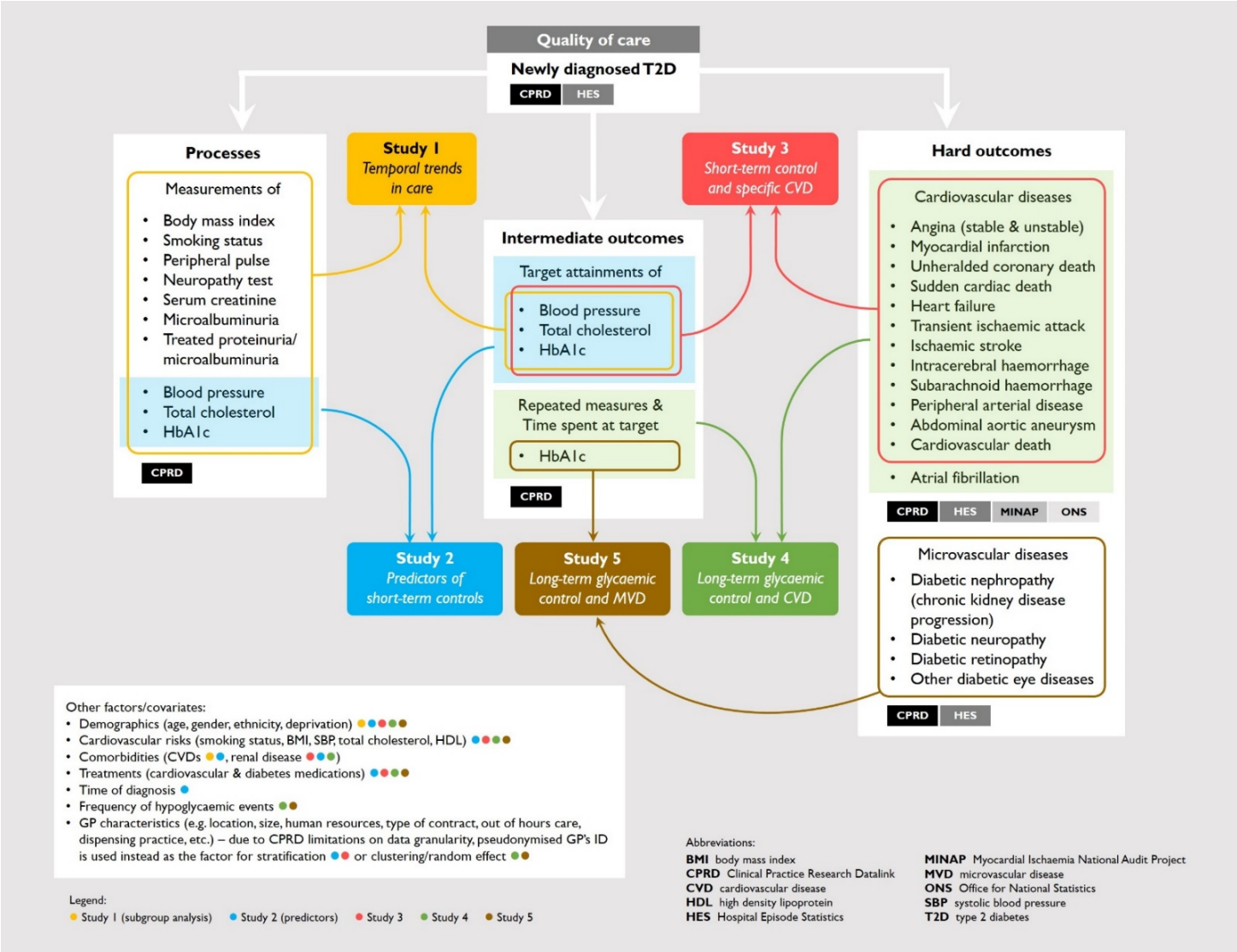
1. To describe temporal trends in quality of T2D care (Study 1)
2. To identify factors associated with achievement of intermediate outcome targets for glycaemia, blood pressure and lipids (Study 2)
3. To examine the associations between achievement of intermediate outcome targets and initial presentations of a wide range of cardiovascular outcomes (Study 3)
4. To investigate the associations between duration at glycaemic control and cardiovascular outcomes (Study 4)
5. To investigate the associations between duration at glycaemic control and microvascular outcomes (Study 5)

Clarity of these issues in a population newly diagnosed with T2D can fill the knowledge gaps as well as add value to the significance of early and continual intervention after diagnosis, thereby providing further insights for clinicians, public health and policy makers to set priorities and reconsider strategies for care optimisation in order to reduce the disease burden. An overview of studies to be carried out along with the intertwined data sources and key variables to use for addressing the thesis objectives is depicted in **Figure 1.3 on page 47.**

1.6 Thesis structure

I begin my thesis by presenting in more detail the literature review on studies relevant to the thesis objectives (**Chapter 2**). I go on to describe the linked EHRs of the CALIBER research platform in **Chapter 3**, where the methods used to identify incident T2D cases, vascular diseases and variables of interest can also be found. In **Chapter 4**, I present derivation of the main incident T2D cohort from CALIBER and findings from Study 1 about achievement, over time, of care processes and intermediate outcomes targets since initial diagnosis. This is followed by a presentation of Study 2 in **Chapter 5** where, among other conventional factors, I particularly explore how key care processes in T2D may relate to their respective intermediate outcomes. **Chapter 6** reports the findings of Study 3 about the relationships between achieving intermediate outcome targets and the onset of a wide array of contemporary CVDs. **Chapter 7** describes the development of TITRE, a longitudinal glycaemic control metric, which will be used to measure the main exposure variable in the two chapters which follow. Exploration of the association between duration at glycaemic control measured using TITRE and cardiovascular outcomes (Study 4) is reported in **Chapter 8**. In **Chapter 9**, I redefine and validate microvascular endpoints from the CALIBER before reporting their associations with duration at glycaemic control (Study 5) in **Chapter 10**. Finally, **Chapter 11** brings together the overall findings and recommendations of my thesis for improving the quality of T2D care.

Figure 1.3 Conceptual framework of PhD study



Chapter 2

Literature review

> Do what you have to do until you can do what you want to do.
> — Oprah Winfrey

2.1 Chapter outline

To address the objectives of this thesis, I firstly carried out a literature review on the quality of T2D care studies which aimed to identify (a) trends over time in quality of care, (b) factors associated with attainment of key intermediate outcome targets, (c) cardiovascular outcomes attributable to short-term attainment of key intermediate outcome targets, (d) cardiovascular outcomes attributable to long-term glycaemic control, and (e) microvascular outcomes attributable to long-term glycaemic control. This chapter describes the methods used in the literature search and summarises the key findings, highlighting gaps in the knowledge base on which this thesis will build.

2.2 Abstract

Background. Early and continuing care delivery is crucial to mitigate vascular complications from T2D. Information is lacking on trends in care delivery and outcomes as well as predictors and vascular consequences of the triad control: HbA1c, blood pressure and lipid since onset of T2D. This literature review aimed to identify existing studies which have investigated these issues in order to guide further research.

Methods. I used MEDLINE and Embase through the Ovid® database to identify large population-based studies with follow-up of at least one year which evaluated temporal trends in T2D care and explored predictors and cardio- or microvascular complications for meeting targets for key intermediate outcomes, particularly HbA1c.

Results. Two stages of literature search were carried out. The first stage identified six relevant studies which assessed temporal trends in care; five explored predictors for achieving HbA1c, blood pressure or lipid targets and two investigated the effect of meeting the targets on cardiovascular outcomes. The second stage found a total of 23 studies investigating the effect of long-term glycaemic control on the development of cardio- and microvascular outcomes. Most studies retrieved had been conducted amongst prevalent T2D populations. The proportion of patients in receipt of care from time to time was generally higher than the proportion meeting key targets. Predictors for meeting intermediate outcome targets were found to be inconsistent. There was some evidence of a significant association between meeting key targets and conventional or composite cardiovascular outcomes, but such association with contemporary cardiovascular outcomes is unknown. Averaged HbA1c levels or HbA1c excursion between measures over each follow-up period was also found to be positively associated with cardio- and microvascular outcomes, but the time factor was generally not considered in the measurement of long-term glycaemic control.

Discussion. There were limited studies conducted among newly diagnosed T2D populations which investigated the trajectory of care and predictors for meeting intermediate outcome targets. Association of glycaemic, blood pressure and lipid control with disaggregated, contemporary cardiovascular outcomes is unclear. In particular, long-term glycaemic control suffered temporal shortfall in the measurement despite its positive association with many vascular complications. All these knowledge gaps suggest the need for further research.

2.3 Introduction

Most studies investigating the quality of care for T2D have focused on prevalent cases, and information about continuing management amongst the incident population is limited. Factors associated with achieving intermediate outcome targets for HbA1c, blood pressure and lipids are also poorly defined in this population and still less is known about how meeting these targets influences vascular outcomes. In particular, maintaining the recommended target for HbA1c is indispensable in the management of T2D; however, glycaemic control has been generally deter-

mined, in either clinical practice or most studies, from HbA1c level measured on a single occasion, potentially leading to underestimation of its importance and impact on vascular outcomes.

This literature review focuses on studies investigating the following issues amongst the T2D population: (i) temporal trends in quality of care, (ii) factors contributing to attainment of key intermediate outcome targets, (iii) cardiovascular outcomes following short-term attainment of key intermediate outcome targets, (iv) cardiovascular outcomes following long-term glycaemic control, and (v) microvascular outcomes following long-term glycaemic control.

Two stages of literature search were performed. The first stage aimed to identify studies addressing temporal trends, contributing factors, and cardiovascular outcomes in the quality of T2D care (**Section 2.4 below**), whilst the second aimed to find studies addressing vascular complications following long-term glycaemic control (**Section 2.8 on page 77**).

2.4 Methods and results (Part I)

2.4.1 Search strategy

A systematic literature search using MEDLINE and Embase through Ovid® was carried out to identify epidemiological studies on temporal trends in the quality of care for T2D, factors determining attainment of quality of care indicators and the implications of quality of care for cardiovascular outcomes. Combined searches using terms or keywords and truncation (denoted by '?' or '*') to identify terms with similar syntax are reproduced in **Table 2.1 on page 51**. I limited the search to articles published in the English language since 2000. Additional sources for studies assessing contributing factors for target attainment and cardiovascular outcomes were sought using backward and forward citation methods. Key papers identified beforehand but missed in this literature search were also added.

2.4.2 Inclusion criteria

Titles and abstracts of studies initially identified were then screened for relevance. Studies were eligible for review if they fulfilled the following criteria:

- Observational design
- Adequate sample size (≥1,000 individuals)
- Full-text available
- Involved individuals with T2D (with a dedicated T2D analysis if all diabetes types were included) regardless of timing of diagnosis
- Assessed temporal trends in quality of diabetes care
- Assessed factors associated with attainment of intermediate outcome targets
- Assessed association between attainment of intermediate outcome targets and cardiovascular outcomes

Table 2.1 Search strategy for systematic literature review on temporal trends, contributing factors and cardiovascular outcomes for quality of T2D care

Search number	Search terms or keywords[†] and search strategy	∑ articles retrieved[‡]
1	type 2 diabetes mellitus OR non insulin dependent diabetes mellitus OR NIDDM OR adult onset diabetes mellitus OR maturity onset diabetes mellitus	205,437
2	inciden* OR newly diagnosed	1,840,379
3	1 AND 2	21,219
4	quality of healthcare OR healthcare quality OR healthcare quality assessment OR healthcare quality indicator OR *quality of care* OR *process* of care* OR *care outcome** OR *intermediate outcome**	97,978
5	1 AND 4	834
6	3 AND 4	57
7	blood glucose OR hba1c OR *glycosylated h?emoglobin*	302,523
8	blood pressure OR *systolic blood pressure* OR *diastolic blood pressure*	891,986
9	cholesterol OR low density lipoprotein OR high density lipoprotein OR triglyceride OR *lipid* OR *total cholesterol*	1,407,383
10	7 OR 8 OR 9	2,415,084
11	trends OR temporal trends	299,278
12	5 AND 10 AND 11	15
13	6 AND 10 AND 11	1
14	*diabetes control* OR *target attainment* OR *target achievement*	16,875
15	risk factor OR *factor* OR determinant	4,462,998
16	5 AND 10 AND 14 AND 15	12
17	6 AND 10 AND 14 AND 15	3
18	ischemic heart disease OR angina pectoris OR stable angina OR unstable angina OR acute coronary syndrome OR myocardial infarct OR *acute infarct** OR *cardiac infarct** OR *coronary infarct** OR *heart infarct** OR *heart attack** OR STEMI OR STEAMI OR AMI	596,351
19	heart failure OR congestive heart failure OR arrhythmia OR cardiac arrhythmia OR *ventricular arrhythmia** OR sudden cardiac death OR *sudden coronary death OR cardiovascular mortality OR cardiovascular death*	672,678
20	*cardiovascular disease** OR *cardiovascular complication**	467,543
21	18 OR 19 OR 20	1,530,852
22	stroke OR cerebrovascular stroke OR acute stroke OR transient ischemic attack OR *isch?emic stroke* OR basilar artery ischemia OR basilar artery insufficiency	513,603
23	brain haemorrhage OR cerebral haemorrhage OR subarachnoid hemorrhage OR intracranial hemorrhage OR *h?emorrhagic stroke* OR aneurysmal subarachnoid haemorrhage	86,039
24	*cerebrovascular disease** OR *cerebrovascular complication** OR *cerebrovascular accident**	198,733
25	22 OR 23 OR 24	671,605
26	peripheral arterial disease OR peripheral vascular disease	49,784
27	abdominal aortic aneurysm OR *abdominal aorta rupture* OR *abdominal aorta leak*	24,536
28	*macrovascular disease** OR *macrovascular complication**	6,929
29	*cardiovascular outcome* OR *cardiovascular endpoint* OR *cardiovascular prognosis OR cardiovascular event*	11,045
30	21 OR 25 OR 26 OR 27 OR 28 OR 29	2,115,046
31	5 AND 10 AND 14 AND 30	17
32	6 AND 10 AND 14 AND 30	3
33	12 OR 16 OR 31	35
34	13 OR 17 OR 32	6
35	*cohort stud** OR *longitudinal stud** OR *prognosis stud**	599,127
36	33 AND 35	3
37	electronic health record OR computerized medical record OR computerized patient record OR *electronic medical record** OR *electronic health database* OR *routine data collection*	47,215
38	33 AND 37	4
39	remove duplicates from 33	32

[†]Search terms are MeSH or EMTREE heading, or otherwise keywords (italics).
[‡]As of 7 July 2015.

Observational studies were favoured since these are more representative of real-world practice, with preference given to cohort or longitudinal studies in order to provide comparability with studies to be performed in this thesis. Unless serially analysed (>2 time points), cross-sectional studies of quality of care indicators only that did not report contributing factors or cardiovascular outcomes were discarded. Also discarded were review articles, surveys relying on self-reported data (prone to subjectivity and recall bias), interventional studies and randomised trials (e.g. to test whether particular or novel strategies could improve quality of diabetes care).

2.4.3 Results

The initial search combining the terms 'incident' with 'type 2 diabetes mellitus' (or similar keywords) generated 21,219 citations. Further combination with the term 'quality of care' narrowed the citations down to 57. Inclusion of the terms 'trends', 'risk factor' or 'determinant', and 'cardiovascular outcome' to accommodate the multiple objectives of this thesis further restricted the retrieval to six citations only none of which, by inspection of the title and abstract, were relevant to the objectives of this research. Narrowing the search by keywords for study type (e.g. longitudinal or retrospective cohort) returned four citations only. Likewise, using the term 'electronic health record' limited the retrieval to one citation only. Specific terms for incidence, study type and electronic health record were ignored accordingly to ensure that the number of articles was adequate for the purpose of this literature review. Overall, 32 citations were retrieved after de-duplication (**Table 2.1 on page 51**).

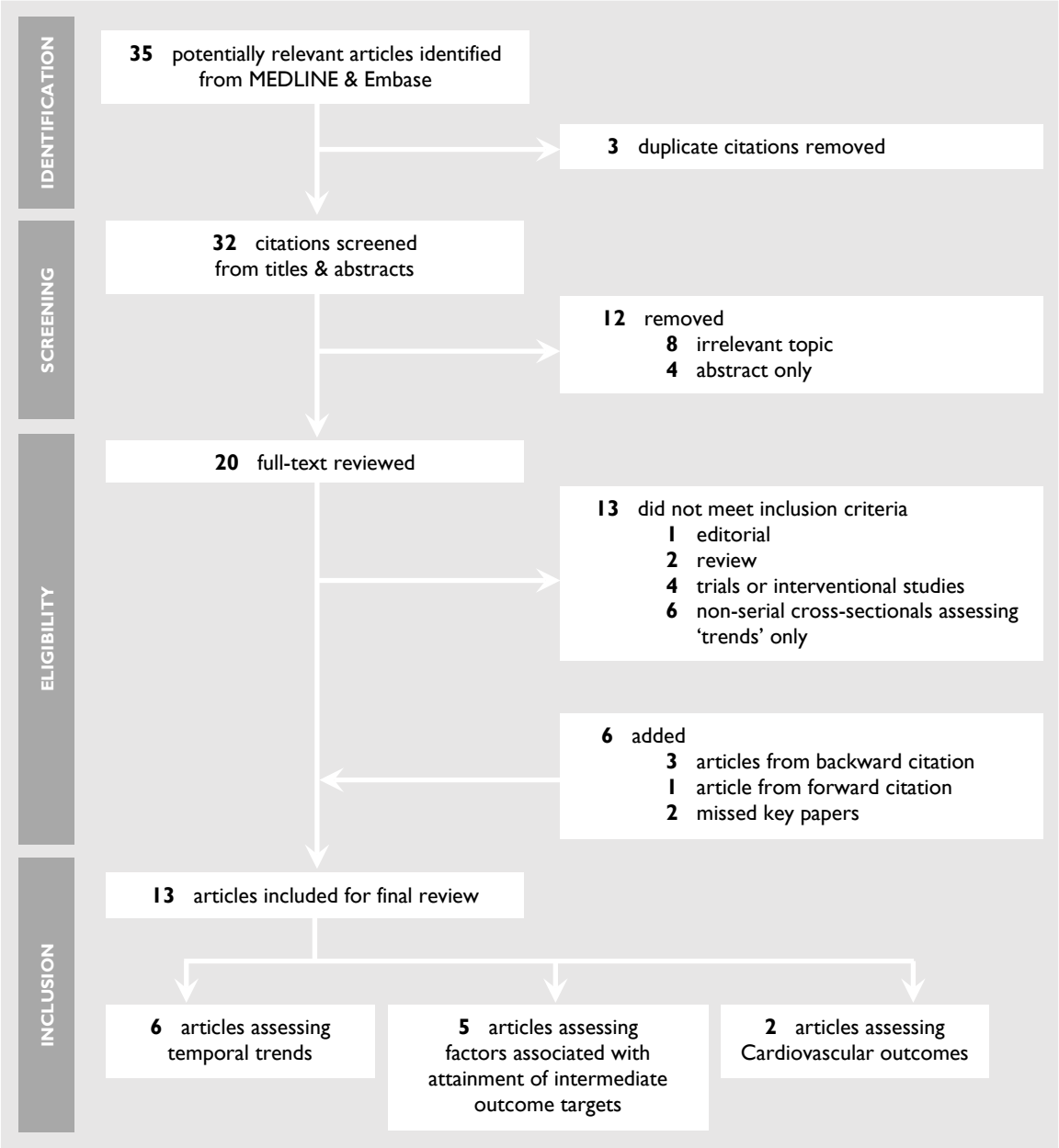
Of the 32 abstracts screened, eight discussed irrelevant topics and four could not be obtained in full text. Of the remaining 20 articles, 13 did not fulfil the inclusion criteria. Three articles referenced by the remaining eligible studies, one article citing eligible studies and two key articles previously identified were added, providing a total of 13 articles extracted for this review (**Figure 2.1 on page 53**). Of these, six articles assessed temporal trends in the quality of diabetes care, five examined factors associated with the attainment of intermediate outcome targets and two explored cardiovascular outcomes following attainment of intermediate outcome targets.

2.5 Temporal trends for quality of care in newly diagnosed T2D

2.5.1 Findings of literature search

The six studies on temporal trends for quality of diabetes care were from developed countries, four European. Most were an open retrospective cohort design and there was one serial cross-sectional study that reported only trends in outcomes of care.

Figure 2.1 Flow chart of article inclusion (Part I)



Processes of care. Despite selecting somewhat different indicators, the six studies were consistent in reporting improved T2D care over time. Blood pressure measurement in 85-94% of cases was the best recorded quality indicator across all studies.[130,140,141] Next was total cholesterol measurement (68-90%), overtaking HbA1c measurement after 2005 (72-87%).[130] However, there was variation between studies and, in one Italian study, HbA1c measurement in approximately 90% of cases was the best recorded quality indicator, followed by blood pressure (76%) and lipid profile (67%).[142] Conversely, the same Italian study reported low rates of foot (13%) and eye examination (30%) compared with rates of >80% in a New Zealand study.[143] In the UK, marked improvements were reported in the documentation of microalbuminuria, neuropathy and peripheral pulse check which, over a five-year period, increased from less than 20% to over 75% of

patients.[130] Another UK study reported improved measurements of HbA1c, blood pressure, cholesterol and BMI from 1994 to 2001 in T2D patients and claimed that the trends in incident cases were identical (detailed results not presented).[96] A more recent and larger study using the same data source documented continuing improvements in these quality indicators over the next six-year period (2001-2007).[130]

Intermediate outcome targets. HbA1c targets varied across the six studies. In the earlier UK study, the proportion of high risk patients achieving their 6.5% HbA1c target showed a small reduction over time, whereas the proportion of low risk patients achieving their 7.5% HbA1c target tended to increase. The overall trajectory was U-shaped, similar to the findings from a New Zealand study,[143] with approximately 48-55% of patients meeting their targets.[140] In the more recent UK study, however, the trajectory was consistently positive, with 60% meeting their HbA1c target at the final assessment.[130] Positive trends were also reported in the Dutch and Italian studies with 61% and 43% of patients, respectively, meeting their HbA1c targets.[141,143] Positive temporal trends for blood pressure and cholesterol target achievement were also reported for all except the Australian study,[144] with >70% of patients achieving the blood pressure target and nearly 90% the cholesterol target in the UK studies compared with 44%, 42% and 23% (blood pressure) and 62%, 48% and 30% (cholesterol) in the Dutch, Italian and New Zealand studies, respectively. Only one study from Australia reported a temporal decline in targets met for HbA1c, blood pressure, and cholesterol.[144] Across all studies, the proportion of patients meeting intermediate outcome targets fell short of the proportion of patients receiving related processes of care.

Cardiovascular outcomes. Only the New Zealand study that used linked EHRs captured trends in hard outcomes, reporting temporal declines in hospital admission rates for macrovascular complications but increases in admissions for microvascular complications.[143]

Treatment. Four studies extended their interest in quality of T2D care to prescribed medications.[140-143] The UK study observed temporal increases in the proportions of patients on insulin and long-acting oral hypoglycaemic agents (sulphonylureas and metformin).[140] No significant trends for diabetes and blood pressure treatment were observed in any study, despite increasing proportions of patients with inadequate control in the Dutch study.[141] For lipid lowering drugs, prescribing trends were variable across studies, negative in the Dutch study[141] and positive in the New Zealand study.[143]

2.5.2 Discussion

A summary of reviewed articles is mapped in **Table 2.2 on pages 55-56**. Definitions of quality indicators varied across different studies making comparisons difficult. Overall, though, processes of care for patients with T2D and attainment of intermediate outcome targets showed positive trends over time although trajectories showed considerable variation and, in two studies, were U-shaped. A consistent finding was that temporal increases in the proportions of patients achieving intermediate outcome targets consistently fell short of the proportions receiving relevant processes of care.

Table 2.2 Literature reviews on studies assessing temporal trends in quality of care for T2D

First author (Year)	Country	Design (Conv./EHR)	Inclusion criteria	Study period	N patients	Data source	Trends in quality of care
deLusignan (2005)[140]	UK (England & Wales)	Longitudinal (EHR)	▪ T2D (prevalent & ***incident***)	1994-2001	13,173 patients in 2001 (number varied over time) from 74 practices	Primary care	▪ ***Processes*** – Positive trends (increased proportions) in HbA1c, blood pressure, cholesterol & BMI measures ▪ ***Intermediate outcomes*** – Significant positive trends in blood pressure & cholesterol control, significant negative trends in glycaemic (6.5%) & BMI control ▪ ***Intermediate outcome targets*** – Depending on coronary event risk: HbA1c <6.5 or <7.5%, blood pressure <140/80 or 160/100 mmHg, total cholesterol <5.0 mmol/L ▪ ***Treatment*** – Increased insulin & oral agents prescribing ▪ ***Newly diagnosed patients*** – Identical trends (not presented in details)
Taggart (2008)[144]	Australia	Serial cross-sectional (EHR)	▪ T2D (prevalent)	1995-2004	3,358 patients in 2004 (number varied over time) from 134 practices	Diabetes registry	▪ ***Processes*** – Not reported ▪ ***Intermediate outcomes*** – Significant mean reductions in HbA1c, blood pressure & total cholesterol, but failed to achieve targets ▪ ***Intermediate outcome targets*** – HbA1c ≤7%, blood pressure <130/80 mmHg, total cholesterol <4.0 mmol/L
Calvert (2009)[130]	UK (England & Wales)	Longitudinal (EHR)	▪ T1D & T2D (prevalent)	2001-2007	42,032 T2D patients in 2007 (number varied over time) from 147 practices	Primary care	▪ ***Processes*** – Significant positive trends in all 14 measures ▪ ***Intermediate outcomes*** – Significant positive trends in HbA1c, blood pressure & cholesterol control ▪ ***Intermediate outcome targets*** – HbA1c ≤7.5 and ≤10%, blood pressure ≤145/85 mmHg, total cholesterol ≤5.0 mmol/L
Voorham (2010)[141]	Netherlands	Longitudinal (EHR)	▪ T2D (prevalent)	2004-2007	2,929 patients in 2007 (number varied over time) from 95 practices	Primary care	▪ ***Processes*** – Positive trends in HbA1c, blood pressure & lipid measures ▪ ***Intermediate outcomes*** – No significant mean change in HbA1c, but significant mean reductions in blood pressure & cholesterol; Significant positive trends in HbA1c, blood pressure & cholesterol control ▪ ***Intermediate outcome targets*** – HbA1c <7%, systolic blood pressure <140 mmHg, total cholesterol <5.0 mmol/L ▪ ***Treatment*** – No significant changes in diabetes & blood pressure treatment, significant negative trends in lipid treatment
Tomlin (2013)[143]	New Zealand	Longitudinal (EHR)	▪ T1D & T2D (prevalent)	2001-2010	11,757 T2D patients in 2010 (number varied over time) from 170 practices	Diabetes registry, secondary care & mortality data (linked)	▪ ***Processes*** – Improved HbA1c, blood pressure & lipid measures ▪ ***Intermediate outcomes*** – Significant mean reductions in HbA1c, blood pressure & total cholesterol, significant mean increase in BMI; Significant positive trends in HbA1c, blood pressure, cholesterol, triglycerides & BMI control, significant negative trends in obesity

							▪ ***Intermediate outcome targets*** – HbA1c ≤7.2%, blood pressure <130/80 mmHg, total cholesterol <4.0 mmol/L, triglycerides <1.7 mmol/L ▪ ***Cardiovascular outcomes*** – Significant reduced hospital admission rates for macrovascular complications, increased rates for microvascular complications in all diabetes (not related to quality of care attainments) ▪ ***Treatment*** – Significant positive trends in diabetes, blood pressure and lipid treatment
Rossi (2014)[142]	Italy	Longitudinal (EHR)	▪ T2D (prevalent)	2004-2011	532,651 patients in 2011 (number varied over time) from 300 diabetes clinics	Secondary care	▪ ***Processes*** – Positive trends in HbA1c, blood pressure, lipid, renal function, eye and foot examination measures ▪ ***Intermediate outcomes*** – Mean reductions in HbA1c, blood pressure & lipid profiles, mean increase in BMI; Positive trends in HbA1c, blood pressure & LDL-C control; Negative trends in unfavourable outcomes (poor glycaemic, blood pressure and lipid control) despite treatment ▪ ***Intermediate outcome targets*** – HbA1c ≤7%, blood pressure <130/80 mmHg, LDL-C <100 mg/dL ▪ ***Treatment*** – Positive trends in diabetes, blood pressure, lipid and aspirin treatment; Positive trends in treatment for higher risk patients ▪ ***Quality of care summary score*** – Positive trends in achievement of high score (good quality of care)

Abbreviations: BMI, body mass index; EHR, electronic health record; LDL-C, low density lipoprotein cholesterol; T1D, type 1 diabetes; T2D, type 2 diabetes.

The introduction of QOF in the UK appears to have successfully driven up the quality of diabetes care. It is worth noting that both UK based studies used the Doctor Independent Network Link (DIN-LINK) database, which overrepresents primary care with dispensing practices in the south of England and likely captures higher quality of care data than elsewhere in the country while under-representing deprived patients amongst whom low therapy uptake and compliance are often more common.[145] This may limit the generalisability of these studies, particularly as the analyses were not weighted or stratified by practice. Similar issues likely apply to the Italian study which, despite being the largest study reviewed, drew its patients from the specialist care setting,[142] setting it apart from the other studies in which the majority of patients may not have had access to specialist care unless a referral had been made.

It is important to bear in mind that the studies included in this literature review all recruited prevalent T2D cases, and despite the overall positive trends in processes of care and attainment of intermediate outcome targets, they may not be directly applicable to newly diagnosed patients. Improved care in incident cases was only alluded to in one study. The prevalence estimates from all reviewed studies were derived at practice level and the findings cannot reflect true quality of care over time because numbers of patients varied over the study period, and continual observation of a single group was not undertaken. Therefore, findings from this literature review suggest that the processes and intermediate outcomes of care need to be re-assessed amongst the newly diagnosed T2D population.

2.5.3 Limitation of this review

The strategy used for this review restricted the search to large, recent studies published in the English language which explicitly stated relevant terms for quality of care in the titles and abstracts. Combined terms were iteratively included to generate a search with high specificity but low sensitivity. Thus, there is the possibility that potentially relevant T2D studies were missed.

2.5.4 Conclusion

The existing studies on temporal trends in quality of care have generally reported improved care in populations with established T2D. The trajectory of T2D care is ideally evaluated by continuous observation from onset of the disease, but studies addressing the issue in newly diagnosed cases are sparse indicating that research to fill the literature gap is needed. Knowledge of such trends from diagnosis of T2D will help to identify which element or time period of care necessitates improvement, thereby enabling care optimisation through early as well as sustained interventions.

2.6 Predictors of glycaemic, blood pressure and lipid controls in newly diagnosed T2D

2.6.1 Findings of literature search

Five studies, only two of which were longitudinal, investigated factors affecting the attainment of intermediate outcome targets (**Table 2.3 on pages 59-60**). The two longitudinal studies reported on factors associated with long-term glycaemic and blood pressure control and the remaining cross-sectional studies reported on factors associated with meeting intermediate outcomes either individually or in aggregate.

Glycaemic control. Gender, BMI and age were identified as being associated with glycaemic control; target attainment tended to be lower in women and patients with a high BMI, [132,146-148] but higher with increasing age.[132] Thus two studies reported that patients aged over 85 were more likely than younger age groups to meet HbA1c targets, [146,147] but another study was contradictory and reported the opposite.[148] Reduced likelihood of achieving glycaemic targets was also more common as diabetes progressed,[132,147,148] but the effects of treatment were inconsistent with pharmacological treatment emerging as a negative predictor in one cross-sectional study.[132,148] Absence of microvascular complications and being a non-smoker, on the other hand, were positive predictors of glycaemic control.[132]

Blood pressure control. Age and gender were associated with blood pressure control, women and older patients being more likely to achieve blood pressure targets.[146] However, the picture was complex and, in one study, younger patients were more likely to achieve long-term control.[105] High BMI, absence of macrovascular complications and antihypertensive treatment all showed negative associations with achieving blood pressure targets.[132,146,149]

Lipid control. Increasing age, male sex and being overweight were all associated with total cholesterol or LDL target attainment.[132,146,147] Lipid lowering drug also increased the odds of LDL control threefold.[132] Other positive yet modest associations were documented for macrovascular complications, blood glucose monitoring and longer duration of diabetes.[132]

Composite outcomes. A Scottish study reported composite outcomes defined as joint attainment of glycaemic (HbA1c ≤7.5%), blood pressure (<140/ 80 mmHg), cholesterol (≤5 mmol/L) and not-smoking targets.[146] In older patients, the odds of achieving this composite outcome was increased threefold. Being female and overweight or obese, on the other hand, reduced the odds by 25%, 14% and 31%, respectively. In the multisite cross-sectional study, BMI and duration of diabetes were linearly associated with reduced odds of achieving composite targets of HbA1c <7%, blood pressure <130/80 mmHg and LDL <2.6 mmol/L.[132] Blood pressure treatment also significantly reduced the likelihood of meeting the composite target by 25%, while lipid lowering treatment and macrovascular complications increased the likelihood by 70% and 31%, respectively.

Table 2.3 Literature reviews on studies assessing factors associated with attainment of glycaemic, blood pressure and total cholesterol targets in T2D population

First author (Year)	Country	Design (Conv./EHR)	Inclusion criteria	Study period	N patients	Data source	Variables adjusted	Significant positive predictors for target attainment
Nilsson (2005)[149]	Sweden	Longitudinal study (EHR)	▪ T2D (prevalent) ▪ ≥40 years old ▪ Blood pressure data available	1997-2003	1,759 patients	Diabetes registry	▪ Demographics (age, sex) ▪ Cardiovascular risks (BMI, smoking, HbA1c, diabetes duration, microalbuminuria)	▪ ***Blood pressure target (<135/85 mmHg)*** – younger age, lower BMI, lower frequency of microalbuminuria
Tomlin (2007)[148]	New Zealand	Longitudinal study (EHR)	▪ T1D & T2D (prevalent)	2000-2005	9,988 T2D patients	Diabetes registry	▪ Demographics (age, sex) ▪ Cardiovascular risks (BMI, smoking, diabetes duration) ▪ Diabetes treatment	▪ ***Glycaemic target (HbA1c <7%)*** – younger age, shorter duration of diabetes, decreased BMI, diabetes treatment
Guthrie (2009)[146]	UK (Scotland)	Cross-sectional (EHR)	▪ T2D (prevalent) ▪ ≥35 years old	2006 (12 months)	10,161 patients from 59 practices	Diabetes registry	▪ Demographics (age, sex, deprivation) ▪ Cardiovascular risks (BMI, diabetes duration)	▪ ***Glycaemic target (HbA1c ≤7.4%)*** – older age, lower BMI ▪ ***Blood pressure target (<140/80 mmHg)*** – older age, lower BMI ▪ ***Total cholesterol target (≤5 mmol/L)*** – older age, male ▪ ***Not smoking target*** – older age, least deprived ▪ ***Composite targets*** – older age, male, lower BMI
Wong (2012)[147]	Hong Kong	Cross-sectional (EHR)	▪ T2D (prevalent)	2009 (4 months)	1,970 patients from 3 practices	Primary care	▪ Demographics (age, sex) ▪ Cardiovascular risks (BMI, diabetes duration) ▪ Payment status ▪ Provider type	▪ ***Glycaemic target (HbA1c ≤7%)*** – older age, male, lower BMI, shorter duration of diabetes, clinic as training centre ▪ ***Blood pressure target (<130/80 mmHg)*** – fee payer ▪ ***LDL-C target (≤2.6 mmol/L)*** – overweight
Stone (2013)[132]	Multicountry (8 European countries)	Cross-sectional (Mixed)	▪ T2D (prevalent) ▪ ≥18 years old ▪ Depression ▪ Pregnant ▪ Consent not provided ▪ Participation in interventional study	2009/2010 (21 months)	7,597 patients	Primary care, secondary care & survey data	▪ Demographics (age, sex) ▪ Cardiovascular risks (BMI, smoking, diabetes duration, glucose monitoring) ▪ Vascular complications ▪ Provider type ▪ Treatment	▪ ***Glycaemic control (HbA1c <7%)*** – older age, no diabetes treatment, non-smoker, lower BMI, shorter duration of diabetes, no glucose monitoring, no microvascular complication ▪ ***Blood pressure target (<130/80 mmHg) –*** female, lower BMI, no blood pressure treatment, macrovascular complication ▪ ***LDL-C target (<2.6 mmol/L)*** – older age, male, longer duration of diabetes, lipid treatment, glucose monitoring, macrovascular complication

	▪ ***Composite targets*** – lower BMI, shorter duration of diabetes, no blood pressure treatment, lipid treatment, macrovascular complication

Abbreviations: BMI, body mass index; EHR, electronic health record; LDL-C, low density lipoprotein cholesterol; T1D, type 1 diabetes; T2D, type 2 diabetes

2.6.2 Discussion

The studies included in this systematic review of T2D provided variable, often conflicting, associations between basic demographic and clinical factors and achievement of intermediate outcome targets. This no doubt reflects differences between study settings, analytical methodology and data quality. Nevertheless, it was possible to identify some consistency in the associations between male gender, lower BMI, and shorter duration of T2D with achievement of intermediate outcome targets. The effects of age appear to be more complex but it is possible to conclude from this review that short-term achievement of glycaemic and blood pressure targets is associated with older age groups while long-term achievement is associated with younger age groups.

The studies included in this review were variable in the predictors they included in their analysis of intermediate outcomes. Some potentially important factors, such as physical activity and ethnicity, were ignored altogether while comorbidities were included in only one study. The influence of treatment factors was explored in only two studies, one of which came to the wholly counterintuitive conclusion that prescription of specific diabetic and hypertensive treatment was associated with a lower likelihood of meeting the relevant intermediate outcome targets.[132] This study, however, was somewhat biased in its selection of healthier patients and many recruiting physicians had a particular interest in diabetes with considerable between-country variation. The cross-sectional nature of some studies makes estimates of the associations of factors affecting intermediate outcomes less robust and, where applicable, demands caution in interpreting associations between treatment and outcomes.

A further limitation of the studies included in this review was that none of them explored how processes of care (e.g. HbA1c test frequency) influenced achievement of the relevant intermediate outcome target (e.g. glycaemic target). This is an important omission that tends to diminish their clinical relevance. Clinical relevance is further diminished by the inclusion of only prevalent cases in nearly all the studies with no attempt to track care delivery from initial diagnosis of T2D to intermediate outcomes. This makes the true impact of baseline effects and treatment on the chosen outcomes hard to interpret, justifying further research in the newly diagnosed T2D population.

Despite the limitations, all studies included in this systematic review used EHRs to develop large populations of patients with T2D. They were geographically diverse and utilised a variety of data sources and sampling schedules for documentation of intermediate outcome targets. They provide, therefore, a reasonable basis for identifying relevant demographic and clinical risk factors for comparison with the study in this thesis.

2.6.3 Limitation of this review

Similarly to the previous review on temporal trends, this literature review may have missed some relevant publications due to application of somewhat specific terms used in the construction of

the search, the screening method through title and abstract only, and omission of small and obsolete studies.

2.6.4 Conclusion

The reviewed studies were variable in terms of documenting factors associated with meeting key intermediate outcome targets in T2D; they were limited by recruitment of prevalent T2D patients and study design which are not truly longitudinal, making the true associations hard to justify. Importantly, no identified studies have previously attempted to explore processes of care as determinants of intermediate outcomes. Large EHR data resources can be used to avoid these shortcomings by establishment of a population cohort with incident T2D, from which continuous observation of patients from the onset of disease through care delivery to meeting intermediate outcomes is made possible to allow identification of the related factors.

2.7 Glycaemic, blood pressure and lipid controls and CVDs

2.7.1 Findings of literature search

Two longitudinal studies that specifically evaluated the effects of meeting intermediate outcome targets on CVDs within the context of quality of diabetes care were identified (**Table 2.4 on page 64**). Both were Italian studies employing the same quality of care scoring system which was based on four indicators related to vascular complications: HbA1c, blood pressure, LDL and microalbuminuria. In essence, the lowest score is assigned to patients with elevated values who are not treated, or patients with unsatisfactory values despite being treated. When the desired goals are attained (HbA1c <8.0%, blood pressure <140/90 mmHg, LDL <3.37 mmol/L and/or treated microalbuminuria), the highest score is assigned. The summary score ranges from 0 to 40, with a lower score indicating poor quality of care.[150]

The scoring system developed was validated in primary and secondary care settings. During a median follow-up of 5 years, 15.2% of the recruited patients developed a cardiovascular event, the incidence rate being inversely related to the summary score. Compared to patients with a score of >20, those with a score of ≤10 were found to have higher risks of total cardiovascular events (adjusted relative risk [RR] 1.89), MACE (a composite of myocardial infarction, stroke and cardiovascular death, 2.04), myocardial infarction (2.47), cardiac revascularisation (2.24) and lower limb complications (1.86). An increased risk of total cardiovascular events (1.43) and MACE (1.56) was also seen in patients with a moderate score of 10-20.[150]

The more recent study drew its population from specialist clinics and modified the score threshold defining poor quality of care as a score ≤15.[137] During a median follow-up of 28 months, cardiovascular events occurred in 9.2% patients, lower cardiovascular event-free survival being observed in patients with a lower score. Patients scoring ≤15 had the greatest risk of MACE (adjusted incident rate ratio [IRR] 1.84) and lower limb complications (2.48) relative to those with scores >25. Perhaps because a higher cut-off was chosen in this study compared with the other

Italian study, increased risks for MACE and cardiac revascularisation were not seen in patients with poor quality care (score ≤15).

2.7.2 Discussion

Both studies showed how evaluation of quality of care can be used to predict the development of cardiovascular events in T2D. However, the score chosen to measure quality of care has several limitations, most importantly because not all determinants of cardiovascular outcomes were included. For example, foot examination was not incorporated for prediction of lower limb complications. Conversely, inclusion of microalbuminuria might be seen as less pertinent for a score designed to predict cardiovascular events. Certainly, the score offers some practicality for identification of high risk patients but, being a summary measure, it tends to obscure the effects of individual factors on cardiovascular risk. In short, the scoring system is perhaps more useful as a measure of clinical performance than as a model for predicting an individual's risk of cardiovascular events.

The representativeness of the patients included in these studies also merits scrutiny, particularly the patients in the more recent of the two studies who were recruited from specialist diabetic clinics, not primary care. Neither study included newly diagnosed patients and provided little useful information, therefore, on the timing of relationships between baseline factors, intermediate outcomes and cardiovascular outcomes.

Finally, the estimates for cardiovascular events reported in these two studies may not reflect the true risk. Thus, the studies did not exclude patients with previous cardiovascular events when calculating the incidence rates. Moreover, follow-up was short in the more recent study ensuring that estimates of the impact of the score were less robust in not allowing the risk for myocardial infarction and stroke to be individually estimated. All other endpoints analysed in both studies were aggregated, providing no information about the wider range of CVDs (e.g. heart failure or AAA) to which patients with T2D are susceptible. How individual attainment of intermediate outcome targets might differentially influence presentation with specific CVDs merits further exploration.

Table 2.4 Literature review on studies assessing the associations between attainment of intermediate outcome targets in T2D population and cardiovascular outcomes

First author (Year)	Country	Design (Conv./EHR)	Inclusion criteria	Study period	N patients	Data source	Variables adjusted	Cardiovascular endpoints
Berardis (2008)[150]	Italy	Longitudinal (EHR)	▪ T2D (prevalent)	1998-2004 (median follow-up 5 years, IQR 3.3–5.4)	3,235 patients	Primary care, secondary care	▪ Demographics (age, sex) ▪ Cardiovascular risks (BMI, smoking, diabetes duration, history of cardiovascular event) ▪ Diabetes complications ▪ Comorbidities ▪ Provider type	▪ ***Incident cardiovascular events*** – 492 (15.2%) patients ▪ ***Quality of care summary score ≤10 (poor)*** – significantly associated with higher risks of total cardiovascular events (RR 1.89), major cardiovascular events (2.04), myocardial infarction (2.47), cardiac revascularisation (2.24), stroke (2.00), lower limb complications (1.86) ▪ ***Score 10-20 (moderate)*** – significantly associated with higher risks of total cardiovascular events (RR 1.43), major cardiovascular events (1.56), myocardial infarction (1.55)
Rossi (2011)[137]	Italy	Longitudinal (EHR)	▪ T2D (prevalent) ▪ ≥18 years old	2006-2009 (median follow-up 28 months, IQR 24-31)	5,181 patients	Secondary care	▪ Demographics (age, sex) ▪ Cardiovascular risks (BMI, smoking, diabetes duration, history of cardiovascular event)	▪ ***Incident cardiovascular events*** – 477 (9.2%) patients ▪ ***Quality of care summary score ≤15 (poor)*** – significantly associated with higher risks of total cardiovascular events (IRR 1.84) and lower limb complications (2.48)

Abbreviations: BMI, body mass index; EHR, electronic health record; LDL-C, low density lipoprotein cholesterol; IRR, incidence rate ratio; RR, relative risk; T1D, type 1 diabetes; T2D, type 2 diabetes.

2.7.3 Additional literature review: Cardiovascular outcome trials of T2D-related treatment

2.7.3.1 Search strategy

In addition to the observational studies reviewed above, I summarised RCTs of related treatment in T2D populations addressing intermediate and cardiovascular outcomes. This additional review specifically aimed to look at intermediate outcome targets achieved and cardiovascular endpoints used in trials in order to allow indirect comparison with selected target levels and endpoints in the study of this thesis.

2.7.3.2 Inclusion criteria

Relevant RCTs were identified backwardly from current guidelines[31-34] and high quality meta-analyses.[151-153] Trials were included in review if they met the following criteria:

- Conducted exclusively in T2D or diabetes population (with a dedicated analysis for T2D if all diabetes types were included) regardless of timing of diagnosis, otherwise subgroup analysis for T2D must be sufficiently presented if trial was conducted in other high risk population
- Adequate sample size for T2D cases (≥1,000 individuals)
- ≥1 year of follow-up
- Assessed cardiovascular outcomes following treatments to control glycaemic, blood pressure or lipid levels, preferably with clear information on intermediate outcome targets achieved

This review excluded trials with a multifactorial intensive treatment approach, on-going trials and observational, unplanned post-hoc analysis from trials.

2.7.3.3 Cardiovascular outcome trials of pharmacological interventions targeting glycaemic levels

Cardiovascular outcomes. Fourteen relevant trials were identified by initial search conducted in July 2015, and four recent trials completed in 2016 were later added through a search in the Cochrane Library (**Table 2.5 on pages 67-71**). The UKPDS is the longest trial, and the only trial enrolling incident T2D, to examine the efficacy of diabetes treatment. Using patients on diet as comparators, this non double-blind trial documented a significant reduction for all diabetes-related endpoints (RR 0.88) in the intensive treatment arm assigned to OHA or insulin.[49] In addition to myocardial infarction and stroke, further analyses showed no significant risk reductions for other specific cardiovascular endpoints (heart failure, PAD, angina and sudden death). Subanalysis in overweight patients showed the protective effects of intensive treatment with metformin on cardiovascular death (0.64), diabetes-related death (0.58) and a diabetes-related endpoint (0.68).[154] These beneficial effects were not observed in the intensive treatment arm with sulphonylureas or insulin. A more recent trial of add-on gliclazide – a sulphonylurea – also used

specific PAD and heart failure among other endpoints yet did not observe any significant cardiovascular benefits.[52]

Other recent trials of OHA classes generally used classical cardiovascular endpoints, often as aggregates. Of the three RCTs of thiazolidinediones (TZDs), only one included TIA.[155] Unstable angina was included as a specific endpoint in one trial of DPP-4 inhibitors.[156] None of these trials documented significant cardiovascular benefits.

Unstable angina and heart failure (or related hospitalisation) were included as study endpoints in four recently completed trials designed to test that treatment with novel GLP-1 agonist and SGLT2 inhibitor agents is no less efficacious than active treatment already in use.[157-160] TIA was added as a specific endpoint in two of these non-inferiority trials.[158,160] The addition of empaliflozin – an SGLT2 inhibitor – to standard treatment was demonstrated to be superior than placebo in reducing risk for MACE, cardiovascular mortality and hospitalisation for heart failure.[160] Superiority of GLP-1 agonists over placebo was also documented; the addition of liraglutide reduced the risk for MACE, cardiovascular mortality and non-fatal myocardial infarction,[158] while the addition of semaglutide conferred similar benefit for MACE, non-fatal stroke and revascularisation procedures.[159] However, no additional cardiovascular protection was seen by adding lixisenatide.[157]

Four trials investigating insulin's efficacy yielded no significant risk reductions for cardiovascular events.[161-164] Heart failure is of endpoints in two trials of insulin[161,162] while unstable angina is only included in the largest trial.[161]

The ACCORD trial investigated the effect of intensive treatment with any diabetes regimens with 90% of patients in the intensive treatment arm receiving TZD.[165] Increased risks of all-cause and cardiovascular mortality were reported despite risk reduction for non-fatal myocardial infarction, leading to premature termination of the trial.

HbA1c levels achieved. Achievement of HbA1c ≤7% at final visits is only documented in three large trials of intensive treatment[52,155,165] and one trial of insulin.[161] Four other trials reported achievement of HbA1c levels between 7 to 7.5%.[49,154,156,163,166]

Discussion. Most cardiovascular outcome trials of diabetes medications enrolled patients with established T2D. More recent trials used TIA and unstable angina as specific endpoints, recognising the importance of identifying intervention effects on less severe cardiovascular events, which has implications for early prevention strategy. Despite a stringent HbA1c target set, the interventions given generally failed to meet the predefined goal, explaining in part the unobserved cardiovascular benefits in most typical trials. It should be noted that the more recent non-inferiority trials[156-160,166-169] targeted high risk patients (whose HbA1c levels tended to remain high at the end of trial) and the incremental benefits of newly developed treatments shown could have only been equipoised or marginal *vis-à-vis* the existing agents, not placebo.

Table 2.5 Randomised controlled, cardiovascular outcome trials of medical interventions targeting glycaemic control in T2D population

Study (year)	Setting	Population	N patients	Follow-up	Intervention (N patients)	HbA1c (%) achieved	Cardiovascular endpoints*	Effect sizes (95% CI)**
UKPDS 33 (1998)[49]	UK	T2D (incident)	3,867	Median 10 years	Intensive blood glucose control with SU/insulin (2,729) *vs* conventional (diet with stepwise treatment if needed) (1,138)	Median 7.0 (6.2–8.2) *vs* 7.9 (6.9–8.8)	▪ **DM-related endpoint (563 *vs* 438)** ▪ DM-related death (285 *vs* 129) ▪ All-cause death (489 *vs* 213) ▪ *Fatal MI (207 vs 90)* ▪ *Non-fatal MI (197 vs 101)* ▪ *Fatal sudden death (24 vs 18)* ▪ *Heart failure (80 vs 36)* ▪ *Angina (177 vs 72)* ▪ *Fatal stroke (43 vs 15)* ▪ *Non-fatal stroke (114 vs 44)* ▪ *Death from PAD (2 vs 3)*	▪ **RR 0.88 (0.79–0.99**) ▪ RR 0.90 (0.73–1.11) ▪ RR 0.94 (0.80–1.10) ▪ *RR 0.94 (0.68–1.30)* ▪ *RR 0.79 (0.58–1.09)* ▪ *RR 0.54 (0.24–1.21)* ▪ *RR 0.91 (0.54–1.52)* ▪ *RR 1.02 (0.71–1.46)* ▪ *RR 1.17 (0.54–2.54)* ▪ *RR 1.07 (0.68–1.69)* ▪ *RR 0.26 (0.03–2.77)*
UKPDS 34 (1998)[154]	UK	▪ T2D (incident) ▪ Overweight	1,704	Median 10.7 years	Intensive blood glucose control with metformin (342) *vs* conventional (411)	Median 7.4 *vs* 8.0	▪ **DM-related endpoint (98 *vs* 160)** ▪ **DM-related death (28 *vs* 55)** ▪ **All-cause death (50 *vs* 89)** ▪ *Fatal MI (16 vs 36)* ▪ *Non-fatal MI (24 vs 40)* ▪ *Fatal sudden death (3 vs 6)* ▪ *Heart failure (11 vs 17)* ▪ *Angina (21 vs 22)* ▪ *Fatal stroke (6 vs 9)* ▪ *Non-fatal stroke (6 vs 16)* ▪ *PAD (6 vs 9)*	▪ **RR 0.68 (0.53–0.87)** ▪ **RR 0.58 (0.37–0.91)** ▪ **RR 0.64 (0.45–0.91)** ▪ *RR 0.50 (0.23–1.09)* ▪ *RR 0.69 (0.35–1.34)* ▪ *RR 0.58 (0.09–3.61)* ▪ *RR 0.73 (0.27–1.97)* ▪ *RR 1.12 (0.51–2.46)* ▪ *RR 0.75 (0.19–2.93)* ▪ *RR 0.42 (0.12–1.45)* ▪ *RR 0.74 (0.26–2.09)*
					Intensive blood glucose control with SU/insulin (951) *vs* conventional (411)	Median 7.4 *vs* 8.0	▪ DM-related endpoint (350 *vs* 160) ▪ DM-related death (103 *vs* 55) ▪ All-cause death (190 *vs* 89) ▪ *Composite MI (139 vs 73)* ▪ *Composite stroke (60 vs 23)* ▪ *PAD (12 vs 9)*	▪ RR 0.93 (0.77–1.12) ▪ RR 0.80 (0.58–1.11) ▪ RR 0.92 (0.71–1.18) ▪ *RR 0.79 (0.60–1.05)* ▪ *RR 1.14 (0.70–1.84)* ▪ *RR 0.56 (0.24–1.33)*
DIGAMI 2 (2005)[164]	Sweden, Finland, Norway, Denmark, Netherlands, UK	▪ T2D (established) ▪ Acute MI	1,253	Median 2.1 years	Intensive treatment with short-term + long-term insulin (474) *vs* short-term insulin + standard glucose control (473) *vs* standard glucose control (306) after MI	Mean (24h) 7.2 *vs* 7.2 *vs* 7.3, Mean (end of trial) ~6.8 across groups	▪ All-cause death, group 1 *vs* 2 (23.4% *vs* 21.2%) ▪ *All-cause death, group 2 vs 3 (21.2% vs 17.9%)* ▪ *All-cause death, group 1 vs 3 (23.4% vs 17.9%)*	▪ HR 1.03 (0.79–1.34) ▪ *HR 1.23 (0.89–1.69)* ▪ *HR 1.26 (0.92–1.72)*

PROactive† (2005)[166]	19 European countries	▪ T2D (established) ▪ With macro-vascular disease	5,238	Mean 34.5 months	Addition of pioglitazone (2,605) *vs* placebo (2,633) to usual treatment	Median 7.0 (5.4–8.8) *vs* 7.6 (6.0–9.3)	▪ All-cause death (177 *vs* 186) ▪ Non-fatal MI (119 *vs* 144) ▪ Stroke (86 *vs* 107) ▪ ACS (56 *vs* 72) ▪ ***MACE (301 vs 358)***	▪ HR 0.96 (0.78–1.18) ▪ HR 0.83 (0.65–1.06) ▪ HR 0.81 (0.61–1.07) ▪ HR 0.78 (0.55–1.11) ▪ ***HR 0.84 (0.72–0.98)***
ADVANCE (2008)154[52]	20 countries (Asia, Australasia, Europe, N. America)	▪ T2D (established) ▪ ≥55 years old ▪ History of macro/ microvascular disease or ≥1 cardiovascular risk factor	11,140	Median 5 years	Intensive glucose control with gliclazide plus other drugs (5,571) *vs* standard (5,569)	Mean 6.5 (±0.9) *vs* 7.3 (±1.3)	▪ MACE (557 *vs* 590) ▪ *All-cause death (498 vs 533)* ▪ *Cardiovascular death (253 vs 289)* ▪ *Major coronary events (310 vs 337)* ▪ *Major cerebrovascular events (238 vs 246)* ▪ *Heart failure (220 vs 231)* ▪ *PAD (343 vs 366)*	▪ RR reduction 6% (-6–16) ▪ *RR reduction 7% (-6–17)* ▪ *RR reduction 12% (-4–26)* ▪ *RR reduction 8% (-7–21)* ▪ *RR reduction 3% (-16–19)* ▪ *RR reduction 5% (-14–21)* ▪ *RR reduction 6% (-9–19)*
ACCORD (2008)[165]	USA & Canadas	▪ T2D (established) ▪ With established CVD or additional cardiovascular risk factors ▪ HbA1c ≥7.5%	10,251	Mean 3.5 years	Intensive (any glucose-lowering agents) (5,128) *vs* standard treatment (5,123)	Median 6.4 (6.1–7.0) *vs* 7.5 (7.0–8.1)	▪ MACE (352 *vs* 371) ▪ ***All-cause death (257 vs 203)*** ▪ ***Cardiovascular death (135 vs 94)*** ▪ ***Non-fatal MI (186 vs 235)*** ▪ *Non-fatal stroke (67 vs 61)* ▪ *Fatal & non-fatal HF (152 vs 124)*	▪ HR 0.90 (0.78–1.04) ▪ ***HR 1.22 (1.01–1.46)*** ▪ ***HR 1.35 (1.04–1.76)*** ▪ ***HR 0.76 (0.62–0.92)*** ▪ *HR 1.06 (0.75–1.50)* ▪ *HR 1.18 (0.93–1.49)*
VADT (2009)[155]	USA	▪ T2D (established) ▪ With suboptimal response to therapy	1,791	Median 5.6 years	Intensive treatment with rosiglitazone & metformin/SU on maximal doses (899) *vs* standard treatment on half of maximal doses (892)	Median 6.9 *vs* 8.4	▪ Composite of MI, stroke, cardio-vascular death, congestive HF, revascularisation, inoperable CAD, amputation (264 *vs* 235) ▪ *Angina (163 vs 139)* ▪ *TIA (19 vs 13)* ▪ *Limb ischaemia (15 vs 19)* ▪ *Intermittent claudication (13 vs 17)*	▪ HR 0.88 (0.74–1.05) ▪ *HR 1.20 (0.96–1.51)* ▪ *HR 1.48 (0.73–2.99)* ▪ *HR 0.80 (0.40–1.56)* ▪ *HR 0.78 (0.38–1.60)*
RECORD† (2009)[167]	25 countries (Europe & Australasia)	▪ T2D ▪ On maximum tolerated dose of metformin/SU	4,447	Mean 5.5 years	Addition of rosiglitazone to metformin/SU (2,220) *vs* usual treatment with metformin & SU (2,227)	Mean 7.5 *vs* 7.9 (background metformin), 7.6 *vs* 7.8 (background SU)	▪ Composite of cardiovascular death and hospitalisation (321 *vs* 323) ▪ *All-cause death (136 vs 157)* ▪ *Cardiovascular death (60 vs 71)* ▪ *Composite MI (64 vs 56)* ▪ *Composite stroke (46 vs 63)* ▪ *MACE (154 vs 165)* ▪ ***Fatal & non-fatal HF (61 vs 29)***	▪ HR 0.99 (0.85–1.16) ▪ *HR 0.86 (0.68–1.08)* ▪ *HR 0.84 (0.59–1.18)* ▪ *HR 1.14 (0.80–1.63)* ▪ *HR 0.72 (0.49–1.06)* ▪ *HR 0.93 (0.74–1.15)* ▪ ***HR 2.10 (1.35–3.27)***
BARI 2D (2009)[163]	USA, Canada, Brazil, Mexico, Czech Rep, Austria	▪ T2D ▪ With CAD	2,368	Mean 5.3 years	Insulin-sensitisation (1,183) *vs* insulin-provision treatment (1,185), stratified by revascularisation (2x2 factorial design)	Mean 7.0 (±1.2) vs 7.5 (±1.4)	▪ All-cause death (survival 88.2% *vs* 87.9%) ▪ MACE (survival 77.7% *vs* 75.4%)	▪ p=0.89 ▪ p=0.13

HEART2D (2009)[162]	17 countries (Europe, Canada, Asia & S. Africa)	▪ T2D (established) ▪ Acute MI	1,115	Mean 2.7 years	Prandial (557) *vs* basal insulin (558)	Mean 7.7 (±0.1) *vs* 7.8 (±0.1)	▪ Composite of MACE, revascularisation & hospitalisation for ACS (174 *vs* 181) ▪ *All-cause death (51 vs 51)* ▪ *Cardiovascular death (44 vs 42)* ▪ *Non-fatal stroke (19 vs 16)* ▪ *Fatal stroke (3 vs 2)* ▪ *Non-fatal MI (53 vs 50)* ▪ *Fatal MI (12 vs 12)* ▪ *Congestive HF (33 vs 37)*	▪ HR 0.98 (0.8–1.21) ▪ *HR 1.00 (0.68–1.48)* ▪ *HR 1.05 (0.69–1.60)* ▪ *HR 1.21 (0.62–2.35)* ▪ *HR 1.50 (0.25–8.99)* ▪ *HR 1.07 (0.73–1.58)* ▪ *HR 1.01 (0.45–2.25)* ▪ *HR 0.90 (0.56–1.44)*
ORIGIN (2012)[161]	40 countries (worldwide)	▪ T2D or IFG or IGT (established & incident) ▪ Cardiovascular risk factors	12,537	Median 6.2 years	Insulin glargine (6,264) *vs* standard care (6,273)	Median 6.2 (5.8–6.8) *vs* 6.5 (6.0–7.1)	▪ MACE (1,041 *vs* 1,013) ▪ Composite of MACE, revascularisation or hospitalisation for HF (1,792 *vs* 1,727) ▪ *Cardiovascular death (580 vs 576)* ▪ *Composite MI (336 vs 326)* ▪ *Unstable angina (238 vs 261)* ▪ ***New-onset angina (100 vs 138)*** ▪ *Composite stroke (331 vs 319)* ▪ *Hospitalisation for HF (310 vs 343)*	▪ HR 1.02 (0.94–1.11) ▪ HR 1.04 (0.97–1.11) ▪ *HR 1.00 (0.89–1.13)* ▪ *HR 1.02 (0.88–1.19)* ▪ *HR 0.91 (0.76–1.08)* ▪ ***HR 0.72 (0.56–0.93)*** ▪ *HR 1.03 (0.89–1.21)* ▪ *HR 0.90 (0.77–1.05)*
SAVOR-TIMI 53† (2013)[168]	25 countries (America, Europe & Asia/Pacific)	▪ T2D (established) ▪ History of or at risk for cardiovascular event	16,492	Median 2.1 years	Addition of saxagliptin (8,280) *vs* placebo (8,212) to usual care	Mean 7.7 *vs* 7.9	▪ MACE (613 *vs* 609) ▪ *Composite of cardiovascular death, MI, stroke, hospitalisation for unstable angina/HF/ revascularization (1,059 vs 1,034)*	▪ HR 1.00 (0.89–1.12) ▪ *HR 1.02 (0.94–1.11)*
EXAMINE† (2013)[169]	49 countries (worldwide)	▪ T2D (established) ▪ With ACS within 15 to 90 days before randomisation	5,380	Median 1.5 years	Addition of alogliptin (2,701) *vs* placebo (2,679) to usual care	Mean 7.7 *vs* 8.0	▪ MACE (305 *vs* 316) ▪ *Composite of MACE or urgent revascularisation due to unstable angina (344 vs 359)*	▪ HR 0.96 (UCL ≤1.16) ▪ *HR 0.95 (UCL ≤1.14)*
TECOS† (2015)[156]	38 countries (worldwide)	▪ T2D (established) ▪ Established CVD ▪ ≥50 years old	14,671	Median 3.0 years	Addition of sitagliptin (7,332) *vs* placebo (7,339) to usual care	Mean 7.2 *vs* 7.3	▪ Composite of MACE or hospitalization for unstable angina (695 *vs* 695) ▪ *MACE (609 vs 602)* ▪ *Hospitalisation for HF (228 vs 229)* ▪ *Hospitalisation for unstable angina (116 vs 129)* ▪ *All-cause death (547 vs 537)*	▪ HR 0.98 (0.89–1.08) ▪ HR 0.99 (0.89–1.10) ▪ HR 1.00 (0.83–1.20) ▪ HR 0.90 (0.70–1.16) ▪ HR 1.01 (0.90–1.14)
ELIXA† (2015)[157]	49 countries	▪ T2D (established) ▪ HbA1c 5.5-11.0% ▪ Aged ≥30 years	6,068	Median 25 months	Addition of lixisenatide (3,034) *vs* placebo (3,034) to usual care	Mean 7.1 *vs* 7.4	▪ Composite of MACE or hospitalisation for unstable angina (406 *vs* 399) ▪ Cardiovascular death (156 vs 158)	▪ HR 1.02 (0.89–1.17) ▪ HR 0.98 (0.78–1.22)

		▪ With MI or hospitalized for unstable angina within 180 days ▪ No PCI within the previous 15 days ▪ No CABG for the qualifying event ▪ No planned coronary revascularisation within the next 90 days ▪ eGFR ≥30 ml/min/1.73 m^2					▪ Non-fatal MI (270 vs 261) ▪ Non-fatal stroke (67 vs 60) ▪ Unstable angina (11 vs 10) ▪ *Composite of MACE or hospitalisation for HF* ▪ *Composite of MACE, hospitalisation for HF or revascularization* ▪ *Hospitalisation for HF* ▪ *All-cause death*	▪ HR 1.03 (0.87–1.22) ▪ HR 1.12 (0.79–1.58) ▪ HR 1.11 (0.47–2.62) ▪ *HR 0.97 (0.85–1.10)* ▪ *HR 1.00 (0.90–1.11)* ▪ *HR 0.96 (0.75–1.23)* ▪ *HR 0.94 (0.78–1.13)*
EMPA-REG OUTCOME† (2015)[160]	42 countries	▪ T2D (established) ▪ Aged ≥18 years ▪ Had established CVD ▪ BMI ≤45 kg/m^2 ▪ eGFR ≥30 ml/min/1.73 m^2 ▪ Did not receive glucose-lowering agents within the previous 12 weeks with HbA1c 7.0-9.0%, or ▪ Received stable glucose-lowering agents within the previous 12 weeks with HbA1c 7.0-10.0%	7,020	Median 3.1 years	Addition of empaliflozin (4,687) *vs* placebo (2,333) to usual care	Mean 7.8 *vs* 8.2	▪ **MACE (490 *vs* 282)** ▪ *Composite of MACE or hospitalisation for unstable angina (599 vs 333)* ▪ ***Cardiovascular death (172 vs 137)*** ▪ ***All-cause death (269 vs 194)*** ▪ *Fatal or non-fatal MI (223 vs 126)* ▪ *Fatal or non-fatal stroke (164 vs 69)* ▪ *TIA (39 vs 23)* ▪ *Hospitalisation for unstable angina (133 vs 66)* ▪ ***Hospitalization for HF (126 vs 95)*** ▪ *Coronary revascularisation (329 vs 186)*	▪ **HR 0.86 (0.74–0.99)** ▪ *HR 0.89 (0.78–1.01)* ▪ ***HR 0.62 (0.49–0.77)*** ▪ ***HR 0.68 (0.57–0.82)*** ▪ *HR 0.87 (0.70–1.09)* ▪ *HR 1.18 (0.89–1.56)* ▪ *HR 0.85 (0.51–1.42)* ▪ *HR 0.99 (0.74–1.34)* ▪ ***HR 0.65 (0.50–0.85)*** ▪ *HR 0.86 (0.72–1.04)*
LEADER† (2016)[158]	32 countries	▪ T2D (established) ▪ HbA1c ≥7.0% ▪ Aged ≥50 years, had established CVD or CKD, or ▪ Aged ≥60 years, had risk factor for CVD	9,340	Median 3.8 years	Addition of liraglutide (4,668) vs placebo (4,672) to usual care	Mean 7.8 *vs* 8.2	▪ **MACE (608 vs 694)** ▪ ***Composite of MACE or coronary revascularisation or hospitalisation for unstable angina or HF (948 vs 1,062)*** ▪ ***Cardiovascular death (219 vs 278)*** ▪ ***All-cause death (381 vs 447)*** ▪ ***Fatal or non-fatal MI (292 vs 339)***	▪ **HR 0.87 (0.78–0.97)** ▪ ***HR 0.88 (0.81–0.96)*** ▪ ***HR 0.62 (0.49–0.77)*** ▪ ***HR 0.78 (0.66–0.93)*** ▪ ***HR 0.85 (0.74–0.97)***

		▪ Treated or not with ≥1 OHA, insulin or combination of both ▪ No cardiovascular event within the previous 14 days					▪ *Fatal or non-fatal stroke (173 vs 199)* ▪ *TIA (48 vs 60)* ▪ *Hospitalisation for unstable angina (122 vs 124)* ▪ *Hospitalisation for HF (218 vs 248)* ▪ *Coronary revascularisation (405 vs 441)*	▪ *HR 0.86 (0.73–1.00)* ▪ *HR 0.86 (0.71–1.06)* ▪ *HR 0.98 (0.76–1.26)* ▪ *HR 0.87 (0.73–1.05)* ▪ *HR 0.91 (0.80–1.04)*
SUSTAIN-6† (2016)[159]	20 countries	▪ T2D (established) ▪ HbA1c ≥7.0% ▪ Aged ≥50 years and had established CVD or CKD, or ▪ Aged ≥60 years and had risk factor for CVD ▪ Either treated or not with ≤2 glucose-lowering agents (with or without insulin) ▪ No CVD within the previous 90 days ▪ No planned revascularisation (coronary, carotid, or peripheral artery) ▪ No long-term dialysis	3,297	Median 2.1 years	Addition of semaglutide (1,648) vs placebo (1,649) to usual care	Mean 7.6 (0.5 mg) *vs* 8.3 7.3 (1.0 mg) *vs* 8.3	▪ **MACE (108 vs 146)** ▪ ***Composite of MACE or coronary revascularisation or hospitalisation for unstable angina or HF (199 vs 264)*** ▪ *Cardiovascular death (44 vs 46)* ▪ *All-cause death (62 vs 60)* ▪ *Non-fatal MI (47 vs 64)* ▪ ***Non-fatal stroke (27 vs 44)*** ▪ *Hospitalization for unstable angina (22 vs 27)* ▪ *Hospitalisation for HF (59 vs 54)* ▪ ***Revascularisation (83 vs 126)***	▪ **HR 0.74 (0.58–0.95)** ▪ ***HR 0.74 (0.62–0.89)*** ▪ *HR 0.98 (0.65–1.48)* ▪ *HR 1.05 (0.74–1.50)* ▪ *HR 0.74 (0.51–1.08)* ▪ ***HR 0.61 (0.38–0.99)*** ▪ *HR 0.82 (0.47–1.44)* ▪ *HR 1.11 (0.77–1.61)* ▪ ***HR 0.65 (0.50–0.86)***

Italicised cardiovascular outcomes are secondary endpoints. *Unless otherwise noted, number in parenthesis is number of events. **Effect sizes in bold denote significant associations. †Non-inferiority trials.
Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; HR, hazard ratio; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MACE, major adverse cardiovascular events (cardiovascular mortality, non-fatal MI, non-fatal stroke); MI, myocardial infarction; NS, non-significant; PAD, peripheral arterial disease; RR, relative risk; SU, sulphonylurea; T2D, type 2 diabetes; UCL, upper confidence limit.

2.7.3.4 Cardiovascular outcome trials of pharmacological interventions targeting blood pressure levels

Cardiovascular outcomes. Nine trials meeting the criteria were identified (**Table 2.6 on pages 73-74**). The UKPDS extended the classical cardiovascular endpoints used to angina, heart failure, sudden death and PAD. Significant reductions in the intensive treatment arm with ACEI or β-blocker were documented for diabetes-related endpoints and death, all stroke and heart failure.[87] The Heart Outcomes Prevention Evaluation (HOPE) trial reaffirms the cardioprotective effects of ACEI as shown by reduced risk of cardiovascular mortality, myocardial infarction, stroke, heart failure and TIA, despite a neutral effect for unstable angina.[170] However, these beneficial effects were not observed in another trial.[171] In the ADVANCE trial, unstable angina, TIA and subarachnoid haemorrhage were among composite endpoints studied but risk reductions by combination of ACEI and diuretic were only seen for all-cause and cardiovascular mortality.[91] A more recent trial of renin inhibitor – a new antihypertensive – documented an increased risk of cardiac arrest.[172]

The efficacy of ARBs were tested in three RCTs[173-175] with significant risk reductions seen for myocardial infarction and heart failure in one trial only.[173] Calcium channel blocker also confers lower risk of myocardial infarction,[174] while risk of stroke is reduced by intensive treatment with any antihypertensives.[89]

Blood pressure levels achieved. Only two trials documented final achievement of systolic blood pressure below 140 mmHg;[91,175] target achievement in the remaining trials did not exceed 145 mmHg.

Discussion. Unlike findings from diabetes medication trials, the cardiovascular benefits of most antihypertensive agents for T2D management appear to be greater than the blood pressure decrement, suggesting greater efficacy of the medications through modest reductions in blood pressure levels. TIA and unstable angina were used as specific endpoints in one trial only,[170] so was cardiac arrest.[172] Greater benefit was seen for more severe cardiovascular events; however, no attempt was made by newer trials to include TIA and unstable angina as specific endpoints. All cardiovascular risk estimations were derived from a population with established T2D except in one trial.[87]

Table 2.6 Randomised controlled, cardiovascular outcome trials of medical interventions targeting blood pressure control in T2D population

Study (year)	Setting	Population	N patients	Follow-up	Intervention (N patients)	Blood pressure (mmHg) achieved	Cardiovascular endpoints*	Effect sizes (95% CI)**
UKPDS 38 (1998)[87]	UK	▪ T2D (incident) ▪ With hypertension	1,148	Median 8.4 years	Tight control with captopril or atenolol (758) *vs* less tight control avoiding both (390)	Mean 144/82 *vs* 154/87	▪ **DM-related endpoint (259 *vs* 170)** ▪ **DM-related death (82 *vs* 62)** ▪ All-cause death (134 *vs* 83) ▪ *Composite MI (107 vs 69)* ▪ ***Composite stroke (38 vs 34)*** ▪ *Composite PAD (8 vs 8)* ▪ *Sudden death (11 vs 4)* ▪ ***Heart failure (21 vs 24)*** ▪ *Angina (45 vs 22)*	▪ **RR 0.76 (0.62–0.92)** ▪ **RR 0.68 (0.49–0.94)** ▪ RR 0.82 (0.63–1.08) ▪ *RR 0.79 (0.59–1.07)* ▪ ***RR 0.56 (0.35–0.89)*** ▪ *RR 0.51 (0.19–1.37)* ▪ *RR 1.39 (0.31–6.26)* ▪ ***RR 0.44 (0.20–0.94)*** ▪ *RR 1.05 (0.54–2.06)*
HOPE/ MICRO-HOPE (2000)[170]	19 countries (America & Europe)	▪ DM (established) ▪ CVD history or ≥1 cardiovascular risk factor ▪ ≥55 years old	3,577 (T2D 98%)	Mean 4.5 years	Ramipiril (1,808) *vs* placebo (1,769)	Mean 140/77 *vs* 143/77	▪ **Composite of cardiovascular death, MI & stroke (277 *vs* 351)** ▪ **MI (185 *vs* 229)** ▪ **Stroke (76 *vs* 108)** ▪ **Cardiovascular death (112 *vs* 172)** ▪ ***All-cause death (196 vs 248)*** ▪ *Unstable angina (213 vs 207)* ▪ ***HF (198 vs 236)*** ▪ ***TIA (80 vs 104)***	▪ **RR reduction 25% (12–36)** ▪ **RR reduction 22% (6–36)** ▪ **RR reduction 33% (10–50)** ▪ **RR reduction 37% (21–51)** ▪ ***RR reduction 24% (8–37)*** ▪ *RR reduction 0% (-21–17)* ▪ ***RR reduction 20% (4–34)*** ▪ ***RR reduction 26% (1–45)***
IDNT (2001)[174]	27 countries (America, Europe, Australasia, Asia)	▪ T2D (established) ▪ With nephropathy & hypertension	1,715	Median 2.6 years	Addition of irbesartan (579) *vs* amlodipine (567) *vs* placebo (569) to usual care	Mean 140/77 *vs* 141/77 *vs* 144/80	Irbesartan *vs* placebo ▪ Composite cardiovascular event (259 *vs* 284) ▪ Cardiovascular death (52 *vs* 46) ▪ Congestive HF (80 *vs* 113) ▪ MI (48 *vs* 51) ▪ Stroke (30 *vs* 28) Amlodipine *vs* placebo ▪ Composite cardiovascular event (278 *vs* 284) ▪ Cardiovascular death (37 *vs* 46) ▪ Congestive HF (143 *vs* 113) ▪ **MI (29 *vs* 51)** ▪ Stroke (18 *vs* 28)	 ▪ HR 0.90 (0.74–1.10) ▪ HR 1.08 (0.72–1.60) ▪ HR 0.72 (0.52–1.00) ▪ HR 0.90 (0.60–1.33) ▪ HR 1.01 (0.61–1.67) ▪ HR 1.00 (0.83–1.21) ▪ HR 0.79 (0.51–1.22) ▪ HR 1.11 (0.83–1.50) ▪ **HR 0.58 (0.37–0.92)** ▪ HR 0.65 (0.35–1.22)
RENAAL (2001)[173]	28 countries (Asia, Europe, America)	▪ T2D (established) ▪ With nephropathy	1,513	Mean 3.4 years	Addition of losartan (751) *vs* placebo (762) to usual care	Mean 140/74 *vs* 142/74	▪ *Fatal & non-fatal cardiovascular events (247 vs 268)* ▪ *MI (50 vs 68)*	▪ *RR reduction 10% (p=0.26)* ▪ *RR reduction 28% (p=0.08)*

							▪ ***Hospitalisation for HF (89 vs 127)***	▪ ***RR reduction 32% (p=0.005)***
DIABHYCAR (2004)[171]	16 countries (Europe & N. Africa)	▪ T2D (established) ▪ With micro-albuminuria/ proteinuria ▪ ≥5o years old	4,912	Mean 47 months	Addition of ramipiril (2,443) vs placebo (2,469) to usual care	Mean 142/80 *vs* 143/80	▪ Composite cardiovascular event (362 *vs* 377) ▪ Cardiovascular death (141 *vs* 133) ▪ MI (52 *vs* 59) ▪ Stroke (89 *vs* 84) ▪ Congestive HF (76 *vs* 91)	▪ RR 0.97 (0.85–1.11) ▪ RR 1.07 (0.85–1.35) ▪ RR 0.89 (0.61–1.29) ▪ RR 1.07 (0.80–1.44) ▪ RR 0.84 (0.62–1.14)
ADVANCE (2007)[91]	20 countries (Asia, Australasia, Europe, N. America)	▪ T2D (established) ▪ ≥55 years old ▪ History of macro/ microvascular disease or ≥1 cardiovascular risk factor	11,140	Mean 4.3 years	Perindopril + indapamide (5,569) *vs* placebo (5,571)	Mean 136/73 *vs* 140/73	▪ MACE (480 *vs* 520) ▪ ***Cardiovascular death (211 vs 257)*** ▪ ***All-cause death (408 vs 471)*** ▪ *Major coronary events (265 vs 294)* ▪ *Unstable angina, revascularisation, silei MI (283 vs 384)* ▪ *Heart failure (N/A)* ▪ *Major cerebrovascular events (215 vs 218)* ▪ *TIA & SAH (79 vs 99)*	▪ RR reduction 8% (0–17) ▪ ***RR reduction 18% (2–32)*** ▪ ***RR reduction 14% (2–25)*** ▪ *RR reduction 11% (-6–24)* ▪ *RR reduction 14% (-1–27)* ▪ *RR reduction 2% (-20–19)* ▪ *RR reduction 2% (-16–19)* ▪ *RR reduction 21% (-6–41)*
DIRECT-Protect 2 (2008)[175]	30 countries (worldwide)	▪ T2D (established) ▪ Normoalbuminuria ▪ Mild to moderate retinopathy	1,905	Median 4.7 years	Candesartan (951) *vs* placebo (954)	Mean 136/77 *vs* 139/78 (on antihyperten-sives at baseline), 128/74 *vs* 132/76 (normotensive)	▪ MACE (48 vs 56) ▪ *Cardiovascular death (18 vs 25)* ▪ *Fatal MI (9 vs 12)* ▪ *Non-fatal MI (22 vs 22)* ▪ *Fatal stroke (4 vs 2)* ▪ *Non-fatal stroke (15 vs 14)*	▪ HR 0.84 (0.57–1.25) ▪ *N/A* ▪ *N/A* ▪ *N/A* ▪ *N/A* ▪ *N/A*
ACCORD (2010)[89]	USA & Canada	▪ T2D (established) ▪ With established CVD or additional cardiovascular risk factors ▪ HbA1c ≥7.5%	4,733	Mean 4.7 years	Intensive (any BP-lowering agents) (2,362) *vs* standard treatment (2,371)	Mean (1st year) 119/64 *vs* 134/71	▪ MACE (208 *vs* 237) ▪ *All-cause death 150 vs 154)* ▪ *Cardiovascular death (60 vs 58)* ▪ *Non-fatal MI (126 vs 146)* ▪ ***Non-fatal stroke (34 vs 55)*** ▪ *Fatal & non-fatal HF (83 vs 90)*	▪ HR 0.88 (0.73–1.06) ▪ *HR 1.07 (0.85–1.35)* ▪ *HR 1.06 (0.74–1.52)* ▪ *HR 0.87 (0.68–1.10)* ▪ ***HR 0.63 (0.41–0.96)*** ▪ *HR 0.94 (0.70–1.26)*
ALTITUDE (2012)[172]	36 countries	▪ T2D (established) ▪ With albuminuria or CVD	8,561	Median 32.9 months	Addition of aliskiren (4,274) *vs* placebo (4,287) to usual care	Mean 141/74 *vs* 142/74 (increased from baseline)	▪ *Cardiovascular death (246 vs 215)* ▪ *Cardiac arrest (19 vs 8)* ▪ *Composite MI (147 vs 142)* ▪ *Composite stroke (147 vs 122)* ▪ *Hospitalisation for HF (205 vs 219)* ▪ *All-cause mortality (376 vs 358)*	▪ *HR 1.16 (0.96–1.39)* ▪ *HR 2.40 (1.05–5.48)* ▪ *HR 1.04 (0.83–1.31)* ▪ *HR 1.22 (0.96–1.55)* ▪ *HR 0.5 (0.78–1.14)* ▪ *HR 1.06 (0.92–1.23)*

Italicised cardiovascular outcomes are secondary endpoints. *Unless otherwise noted, number in parenthesis is number of events. **Effect sizes in bold denote significant associations.
Abbreviations: ACS, acute coronary syndrome; CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events (cardiovascular mortality, non-fatal MI, non-fatal stroke); MI, myocardial infarction; NS, non-significant; PAD, peripheral arterial disease; RR, relative risk; SAH, subarachnoid haemorrhage; T2D, type 2 diabetes; TIA, transient ischaemic attack.

2.7.3.5 Cardiovascular outcome trials of pharmacological interventions targeting lipid levels

Cardiovascular outcomes. Five trials investigating statin's efficacy were identified (two of which did not exclusively target a T2D population), whilst another trial focused on fibrate (**Table 2.7 on page 76**). Two trials of statin reported risk reduction for coronary[176,177] and cardiovascular events, [176,178] and only one trial reported risk reduction for stroke.[176] The beneficial effect of fibrate was only seen for non-fatal myocardial infarction.[179]

Lipid levels achieved. Total cholesterol and LDL levels were substantially lower in statin-treated arms but never reached below 4 and 1.9 mmol/L, respectively.[176,180] HDL levels were unaffected by either statin or fibrate treatment; in contrast, lower triglyceride levels were observed following either treatment.

Discussion. Cardiovascular benefits of lipid lowering medications for T2D management appear to be consistent with decreases in lipid levels, with HDL being an exception. None of the identified trials – mostly dating back to over a decade ago – had a targeted population with newly diagnosed T2D and none used contemporary cardiovascular endpoints.

2.7.4 Limitation of this review

Identification of observational studies included in this review has been restricted by the use of somewhat specific terms for the literature search, initial filtering by title and abstract only and omission of smaller studies, potentially compromising several relevant publications. The cardiovascular outcome trials of diabetes-related treatment were not as systematically searched as the observational studies, but backward citation from reference lists of current guidelines and meta-analysis proved instead to be efficient in retrieving more relevant publications.

2.7.5 Conclusion

Identified observational studies evaluating the effect of quality of care for T2D on cardiovascular outcomes have focused exclusively on prevalent cases and have been limited by use of conventional CVD phenotypes including myocardial infarction and stroke together with composite measures for intermediate outcomes. Additionally, contemporary cardiovascular endpoints appeared to be underrepresented in most trials investigating diabetes-related treatments. How individual achievement of an intermediate outcome target following diagnosis of T2D affects the onset of disaggregated cardiovascular outcomes remains unclear and warrants further research. Information on this substantial issue will help in the identification of intervention targets as well as assessment for a wider range of CVDs.

Table 2.7 Randomised controlled, cardiovascular outcome trials of medical interventions targeting lipid control in T2D (sub)population

Study (year)	Setting	Population	N patients	Follow-up	Intervention (N T2D patients)	Lipid level (mmol/L) achieved	Cardiovascular endpoints*	Effect sizes (95% CI)**
ALLHAT-LLT (2002)[181]	USA, Canada, Puerto Rico	▪ ≥55 years old ▪ Hypercholesterolemic ▪ Hypertensive	10,355 (35% T2D)	Mean 4.8 years	Pravastatin (1,855) vs usual care (1,783)	N/A	▪ All-cause mortality (N/A) ▪ Major coronary event (coronary death & non-fatal MI) (N/A)	▪ HR 1.03 (0.86–1.22) ▪ HR 0.89 (0.71–1.10)
HPS (2003)[177]	UK	▪ 40-80 years old ▪ Total cholesterol ≥3.5 mmol/L ▪ Had DM, occlusive arterial disease or treated hypertension	20,536 (26% T2D)	Mean 4.8 years	Simvastatin (2,665) vs placebo (2,683)	N/A	▪ **Major vascular event (558 vs 695)**	▪ **HR 0.78 (0.69–0.88)**
CARDS (2004)[176]	UK & Ireland	▪ T2D (established) ▪ 40-75 years old ▪ Had hypertension, retinopathy or albuminuria	2,838	Median 3.9 years	Atorvastatin (1,428) vs placebo (1,410)	Mean (2nd year) total cholesterol 4.03 *vs* 5.34, LDL 1.94 *vs* 3.04, HDL 1.35 *vs* 1.33, triglyceride 1.61 *vs* 1.98	▪ **Acute coronary event (51 *vs* 77)** ▪ Coronary revascularisation (24 *vs* 34) ▪ **Stroke (21 *vs* 39)** ▪ *All-cause death (61 vs 82)* ▪ ***All acute cardiovascular event (134 vs 189)***	▪ **HR 0.64 (0.45–0.91)** ▪ HR 0.69 (0.41–1.16) ▪ **HR 0.52 (0.31–0.89)** ▪ *HR 0.73 (0.52–1.01)* ▪ ***HR 0.68 (0.55–0.85)***
4D (2005)[178]	Germany	▪ T2D (established) ▪ 18-80 years old ▪ Received haemodialysis	1,255	Median 4 years	Atorvastatin (619) vs placebo (636)	Median (4 weeks) LDL 1.86 *vs* 3.10	▪ MACE (226 vs 243) ▪ *All-cause death (297 vs 320)* ▪ ***All cardiovascular event (205 vs 246)*** ▪ *All cerebrovascular event (79 vs 70)*	▪ RR 0.92 (0.77–1.10) ▪ *RR 0.93 (0.79–1.08)* ▪ ***RR 0.82 (0.68–0.99)*** ▪ *RR 1.12 (0.81–1.55)*
FIELD (2005)[179]	Australia, New Zealand, Finland	▪ T2D (established) ▪ 50-75 years old ▪ Statin naïve	9,795	Median 5 years	Fenofibrate (4,895) vs placebo (4,900)	Mean total cholesterol 4.23 *vs* 4.56, LDL 2.43 *vs* 2.60, HDL 1.13 *vs* 1.12, triglyceride 1.47 *vs* 1.87	▪ Coronary event (256 *vs* 288) ▪ Coronary death (110 *vs* 93) ▪ **Non-fatal MI (158 *vs* 207)** ▪ *All-cause death (356 vs 323)* ▪ *Cardiovascular death (140 vs 127)* ▪ *Ischaemic stroke (144 vs 158)*	▪ HR 0.89 (0.75–1.05) ▪ HR 1.19 (0.90–1.57) ▪ **HR 0.76 (0.62–0.94)** ▪ *HR 1.11 (0.95–1.29)* ▪ *HR 1.11 (0.87–1.41)* ▪ *HR 0.91 (0.73–1.14)*
ASPEN (2006)[180]	14 countries (Europe, N. America, Australasia, S. Africa)	▪ T2D (established) ▪ 40-75 years old ▪ LDL below target	2,410	Median 4 years	Atorvastatin (1,211) vs placebo (1,199)	Mean total cholesterol 4.0 *vs* 4.9, LDL 2.0 *vs* 2.9, HDL 1.2 *vs* 1.2, triglyceride 1.6 *vs* 1.5	▪ *Cardiovascular* death (24 vs 19) ▪ Composite MI (28 vs 34) ▪ Composite stroke (27 vs 29) ▪ Hospitalisation for angina (21 vs 15)	▪ HR >1 (NS) ▪ HR <1 (NS) ▪ HR <1 (NS) ▪ HR >1 (NS)

Italicised cardiovascular outcomes are secondary endpoints. *Unless otherwise noted, number in parenthesis is number of events. **Effect sizes in bold denote significant associations.
Abbreviations: DM, diabetes mellitus; HF, heart failure; HR, hazard ratio; LDL, low density lipoprotein; MACE, major adverse cardiovascular events (cardiovascular mortality, non-fatal MI, non-fatal stroke); MI, myocardial infarction; NS, non-significant; RR, relative risk; T2D, type 2 diabetes.

2.8 Methods and results (Part II)

2.8.1 Search strategy

A second systematic literature search was performed using MEDLINE and Embase through the Ovid® database to identify epidemiological studies addressing long-term glycaemic control and vascular complications. Terms or keywords used for combined searches by Boolean operators were listed in **Table 2.8 on page 78**, and the search was limited to articles published in the English language since 2000. Terms or keywords with similar syntax were probed by truncation (denoted by '*' or '?'). Additional sources included key papers previously identified but not captured by the literature search and articles traced using backward and forward citation methods.

2.8.2 Inclusion criteria

Potential studies were screened using titles and abstracts for relevance and were further reviewed to assess whether or not they fulfilled the following criteria:

- Observational design
- Adequate sample size (≥1,000 individuals in study for cardiovascular outcomes or ≥500 individuals in study for microvascular outcomes)
- Full-text available
- Involved individuals with T2D
- Assessed the association of long-term glycaemic control (indicated by use of repeated HbA1c data collected over one year) with cardio- or microvascular outcomes

Observational studies were prioritised in this search to represent real-world clinical practice; however, post-hoc analysis from randomised trials was also retained to represent less biased studies for comparison on estimates. Sample size criteria were set lower for studies investigating microvascular outcomes since the complications generally develop later than for cardiovascular outcomes, thus study follow-up needs to be lengthy enough to identify microvascular complications, otherwise a study with a shorter follow-up allows capture of the outcomes at the expense of smaller study size.

2.8.3 Results

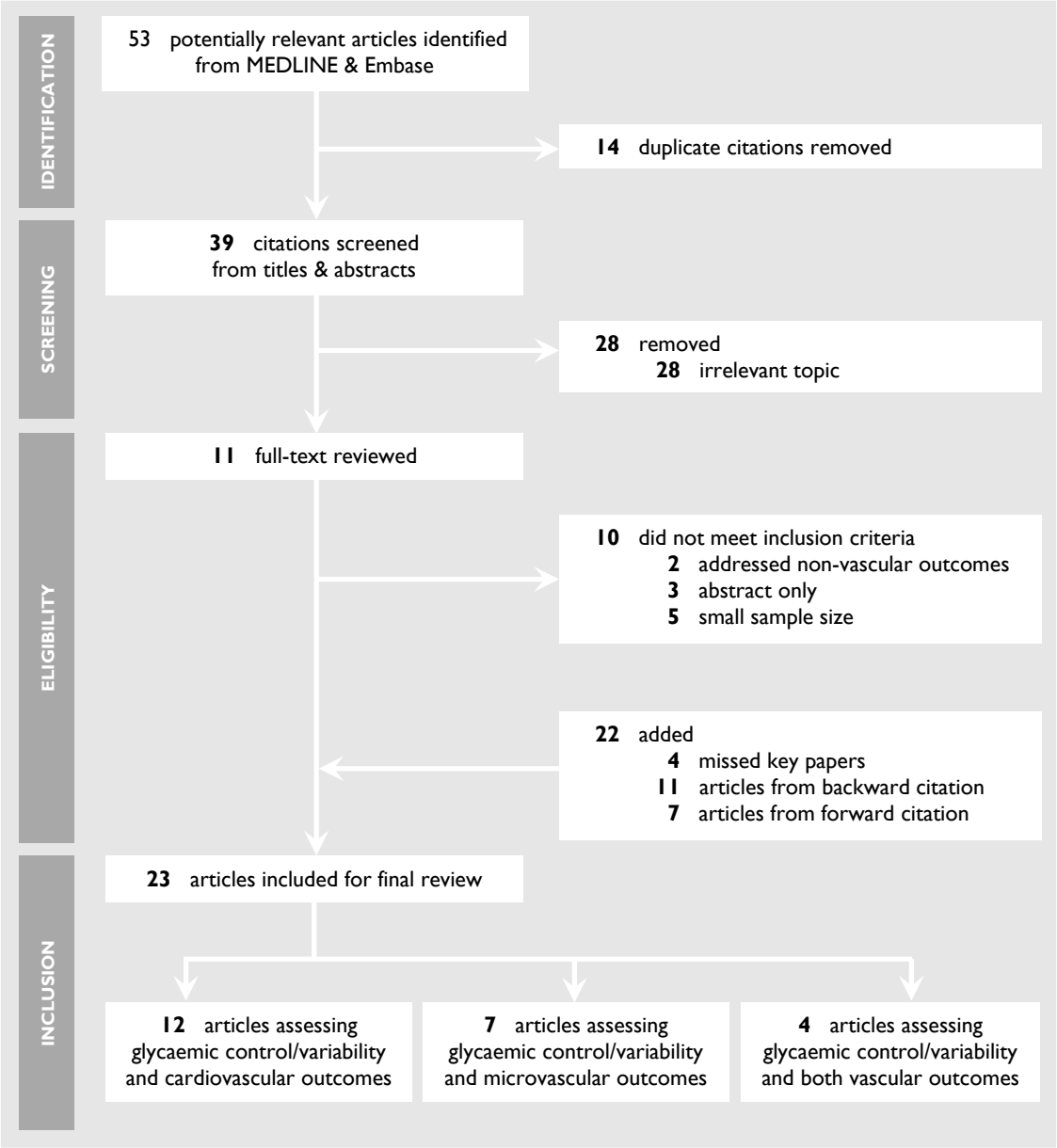
An updated search using the terms 'type 2 diabetes mellitus' and 'incident' generated 27,897 citations, which were restricted to 1,446 when combined with the term 'long-term glycaemic control' (or similar keywords). Further combination with the terms 'macrovascular' and 'microvascular outcomes' narrowed the retrieval down to 541 citations, and narrowing the search by keywords for study type returned 61 citations. Using the term 'electronic health record' limited the retrieval to three citations only and was therefore ignored to ensure an adequate number of articles for review. Overall, 39 citations were retrieved after de-duplication (**Table 2.8 on page 78**).

Table 2.8 Search strategy for systematic literature review on long-term glycaemic control/variability and vascular outcomes

Search number	Search terms or keywords and search strategy	∑ articles retrieved[†]
1	type 2 diabetes mellitus OR non?insulin dependent diabetes mellitus OR NIDDM OR adult onset diabetes mellitus OR maturity onset diabetes mellitus	257,082
2	inciden* OR newly diagnosed	2,184,849
3	1 AND 2	27,897
4	blood glucose OR HbA1c OR A1c OR glycosylated h?emoglobin OR glycated h?emoglobin	402,376
5	diabetes control OR diabetes target OR glucose control OR glyc?emic control OR glucose target OR glyc?emic target OR glyc?emic variability	112,060
6	long?term OR longitudinal OR duration OR over time OR repeat* measure* OR trajector*	4,025,515
7	4 AND 5 AND 6	23,762
8	1 AND 7	9,481
9	3 AND 7	1,446
10	isch?emic heart disease OR angina pectoris OR stable angina OR unstable angina OR acute coronary syndrome OR coronary artery disease OR myocardial infarct OR acute infarct* OR cardiac infarct* OR coronary infarct* OR heart infarct* OR heart attack* OR STEMI OR STEAMI OR AMI	914,998
11	heart failure OR congestive heart failure OR arrhythmi* OR cardiac arrhythmia* OR atrial fibrillation OR ventricular arrhythmia* OR sudden cardiac death OR sudden coronary death OR cardiovascular mortality OR cardiovascular death	971,053
12	cardiovascular disease* OR cardiovascular complication*	567,843
13	10 OR 11 OR 12	2,127,863
14	stroke OR cerebrovascular stroke OR acute stroke OR transient isch?emic attack OR isch?emic stroke OR basilar artery isch?emia OR basilar artery insufficiency	627,434
15	brain h?emorrhage OR cerebral h?emorrhage OR subarachnoid h?emorrhage OR intracranial h?emorrhage OR h?emorrhagic stroke OR aneurysmal subarachnoid h?emorrhage	200,896
16	cerebrovascular disease* OR cerebrovascular complication* OR cerebrovascular accident*	254,084
17	14 OR 15 OR 16	880,746
18	peripheral arterial disease OR peripheral vascular disease	56,724
19	abdominal aortic aneurysm OR abdominal aorta rupture OR abdominal aorta leak*	29,450
20	macrovascular disease* OR macrovascular complication*	8,137
21	cardiovascular outcome* OR cardiovascular endpoint* OR cardiovascular prognosis OR cardiovascular event*	92,794
22	13 OR 17 OR 18 OR 19 OR 20 OR 21	2,862,198
23	diabetic nephropathy OR diabetic kidney disease OR diabetic renal disease OR nephropathy OR chronic kidney disease	239,082
24	diabetic retinopathy OR diabetic maculopathy OR macular ?edema OR retinopathy OR maculopathy	142,460
25	diabetic eye disease* AND (glaucoma OR cataract OR blind* OR visual loss OR visual impair* OR sight impair*)	408
26	24 OR 25	142,505
27	diabetic neuropathy OR neuropathy	243,398
28	microvascular disease* OR microvascular complication* OR microvascular outcome* OR microvascular endpoint* OR microvascular prognosis OR microvascular event*	13,067
29	23 OR 26 OR 27 OR 28	601,421
30	8 AND (22 OR 29)	3,080
31	9 AND (22 OR 29)	541
32	cohort stud* OR longitudinal stud*	780,275
33	30 AND 32	200
34	31 AND 32	61
35	electronic health record OR electronic medical record* OR computeri?ed medical record OR computeri?ed patient record OR electronic health database	70,272
36	33 AND 35	6
37	34 AND 35	3
38	limit 34 to yr="2000-Current"	53
39	Remove duplicates from 38	39

[†]As of 10 February 2017.

Figure 2.2 Flow chart of article inclusion (Part II)



Of the 39 abstracts screened by inspection of the title and abstract, 28 discussed irrelevant topics. Of the remaining eleven articles, ten did not fulfil inclusion criteria but four key papers previously identified were added, resulting in the retrieval of five eligible studies. Ten articles were referenced by the eligible studies and six articles cited the eligible studies, providing a total of 21 articles extracted for this review (**Figure 2.2 above**). Of these, four articles examined the association of glycaemic control with both macro- and microvascular diseases, twelve articles assessed the association with macrovascular diseases only, and five examined the association with microvascular diseases only.

2.9 Long-term glycaemic control and CVDs

2.9.1 Findings of literature search

A total of 16 relevant studies were identified, nine of which investigated long-term glycaemic control while the remaining studies discussed glycaemic variability between HbA1c measures in their respective association with cardiovascular outcomes (**Table 2.9 on pages 81-86**).

Glycaemic control. Of the nine studies addressing the association of glycaemic control and cardiovascular outcomes, four were bespoke cohort studies[182-185] and one was a post-hoc analysis of the ADVANCE trial.[186] Of the eight observational studies, three studies targeted a newly diagnosed T2D population,[48,138,187] two exclusively involved an Asian population[182,185] and five utilised linked EHR databases.[48,138,183,185,188]

There were several metrics used to define glycaemic control longitudinally, updated mean HbA1c being the most common metric assessed in four studies.[48,138,184,188] Latest HbA1c value was examined in two studies, [48,138] whereas mean and median HbA1c were each examined in one study.[182,187] HbA1c was modelled as a time-dependent variable in one study where the follow-up time was split each time the Hba1c category changed; thus any switch to another category contributed to patient-years for the HbA1c category.[183] Another study defined glycaemic control as a latent class growth model of HbA1c pattern over time from which four distinct patterns of glycaemic stability were identified.[185]

Mean and latest HbA1c levels were demonstrated to have linear association with myocardial infarction risk, but the latest HbA1c category was shown to have a J-shaped association where either lower or higher HbA1c groups conferred greater risk relative to the HbA1c 6-<7% group.[48] The excess risk for myocardial infarction was also seen in patients with high-decrease glycaemic pattern relative to low-stable pattern of nearly threefold.[185] Another study, however, failed to document a significant association of updated mean HbA1c with myocardial infarction.[184]

Another J-shaped association was observed for heart failure in patients in low and high time-updated HbA1c categories (<6% and >10%, respectively).[183] The curvilinear association was again seen in patients in low and high latest HbA1c categories, yet linear association was observed through use of updated mean HbA1c categories or latest and updated mean levels.[138] In a study looking at hospitalisation for heart failure as the outcome, the J-shaped association was retained through use of updated mean HbA1c category.[188]

Excess risk for stroke was documented in patients with median HbA1c of >7% or with moderate-stable, moderate-increase or high-decrease HbA1c patterns over time.[182,185] A 1% increase of updated mean HbA1c was also associated with modest stroke risk.[184] The excess risks of poorer long-term glycaemic control measured by different metrics remained observed for composite cardiovascular outcomes, related hospitalisation, and mortality.[182,185-187]

Table 2.9 Reviewed studies that investigate the association of long-term glycaemic control and/or variability with cardiovascular outcomes

Study (year)	Setting	Design	Data source	Inclusion criteria	N patients	Follow-up	HbA1c metric	N HbA1c measures	Cardiovascular endpoints*	Effect sizes (95% CI)**
Glycaemic control										
Hayashi (2011)[182]	Japan	Longitudinal cohort (bespoke)	Primary care data	▪ T2D (prevalent) ▪ Without prior heart disease, stroke, hepatic disease, renal disease, malignancy, severe illness, or intention to undergo surgery	4,014	2 years	Median (>7% vs ≤7%)	2	▪ Ischaemic heart disease (17 vs 15 in 870 patients aged ≤70 years) ▪ Stroke (17 vs 15 in 870 patients aged ≤70 years)	▪ OR 1.16 (0.40–4.37) - unadjusted ▪ **OR 4.11 (1.01–13.40)**
Lind (2012)[188]	Sweden	Longitudinal cohort	National diabetes registry linked with discharge and mortality registries	T2D (prevalent)	83,021	Mean 7.2 years	▪ Updated mean (per 1% increase) ▪ Updated mean category (<6% as reference group)	Varied	Hospitalisation for heart failure (10,969)	▪ **HR 1.12 (1.10–1.14)** ▪ **HR 0.91 (0.84–0.98)** - in 6-<7% group HR 0.99 (0.91–1.07) - in 7-<8% group **HR 1.10 (1.01–1.20)** - in 8-<9% group **HR 1.27 (1.15–1.41)** - in 9-<10% group **HR 1.71 (1.51–1.93)** - in ≥10% group
Zoungas (2012)[186]	20 countries (Asia, Australasia, Europe, North America)	Post-hoc analysis	ADVANCE trial	▪ T2D (prevalent) ▪ Aged ≥55 years ▪ Had ≥1 risk factor for vascular disease ▪ Had HbA1c data at baseline	11,086	NR	Mean (weighted by time intervals between measures and prior to first event - per 1% increase)	At baseline, 6 months and annually thereafter	▪ Macrovascular events (NR) ▪ All-cause mortality (NR)	▪ HR 1.02 (0.86–1.21) - below 7% knot **HR 1.38 (1.30–1.47)** - above 7% knot ▪ HR 1.01 (0.85–1.21) - below 7% knot **HR 1.38 (1.29–1.48)** - above 7% knot
Nichols (2013)[187]	USA	Non-concurrent longitudinal cohort	Medical insurance claim data (Kaiser Permanente Northwest)	▪ T2D (incident) ▪ Without insulin dispense 1 year since diagnosis ▪ Without prior CVD hospitalisation ▪ Aged ≥18 years ▪ Had ≥3 HbA1c measures (≤6 months apart) after diagnosis	26,636	Mean (SD) 5.6 (2.5) years	▪ Mean (per 1 SD increase) ▪ Mean (<7% *vs* ≥7%) ▪ Mean (only HbA1c in control *vs* all HbA1c, SBP & LDL-C in control)	≥4	▪ CVD hospitalisation (1,943 vs 24,693) ▪ CVD hospitalisation (917 vs 11,260) ▪ CVD hospitalisation (299/2,494 vs 179/3,408)	▪ HR 1.01 (0.95–1.08) ▪ **HR 1.14 (1.02–1.27)** ▪ **HR 2.76 (2.25–3.40)**

				▪ Had ≥1 HbA1c measure during follow-up					
Parry (2015)[183]	UK (Scotland)	Longitudinal cohort (bespoke)	Diabetes audit database (DARTS & Go-DARTS) linked with ECG data and health informatics centre datasets	▪ T2D (prevalent)	8,683	Mean (SD) 5.5 (2.8) years	Time-updated HbA1c category (follow-up time was split each time Hba1c category changed, 6-<7% as reference group)	Varied (mean 21.1)	Heart failure (701)	▪ **HR 1.60 (1.38–1.86)** - <6% group ▪ HR 1.04 (0.84–1.25) - 7-8% group ▪ HR 1.07 (0.82–1.33) - 8-9% group ▪ HR 1.18 (0.88–1.50) - 9-10% group ▪ **HR 1.80 (1.60–2.16)** - >10% group
Freemantle (2016)[184]	12 countries (Europe, Canada, Japan)	Longitudinal cohort (bespoke)	Primary care data	▪ T2D (prevalent) ▪ Aged >40 years ▪ Started insulin therapy within 12 months ▪ Had an HbA1c measure <3 months before starting insulin	2,999	54 months	Updated mean (per 1% increase)	Varied (every 6 months)	▪ MACE (161) ▪ Cardiovascular mortality (60) ▪ Stroke (57) ▪ MI (44) ▪ Any CVD (447)	▪ **HR 1.25 (1.12–1.40)** ▪ **HR 1.31 (1.10–1.57)** ▪ **HR 1.36 (1.17–1.59)** ▪ HR 1.05 (0.83–1.32) ▪ **HR 1.16 (1.07–1.26)**
Olsson (2015)[48]	UK	Longitudinal cohort	Primary and secondary care data (CPRD & HES)	▪ T2D (incident) ▪ Aged ≥18 years ▪ ≥1 record in the CPRD at least 1 year before diagnosis ▪ Had data on sex, age and blood pressure ▪ No prior MI within 1 year before diagnosis ▪ ≥1 HbA1c measure at baseline ▪ Not on insulin only at diagnosis and follow-up	101,799	Median 5.4 years	Per 1% increase: ▪ Baseline ▪ Updated latest ▪ Updated mean By HbA1c category (6-<7% as reference group): ▪ Baseline ▪ Latest ▪ Updated mean	Varied	MI (5,104)	▪ **HR 1.05 (1.03–1.06)** ▪ **HR 1.11 (1.09–1.13)** ▪ **HR 1.15 (1.13–1.18)** ▪ Linear association, **HR 0.84 (0.74–0.96)** in <6% group to **HR 1.24 (1.14–1.34)** in ≥10% group ▪ J-shaped association, **HR 1.19 (1.09–1.30)** in <6% group to **HR 1.85 (1.65–2.07)** in ≥10% group ▪ Linear association, HR 0.88 (0.78–1.00) in <6% group to **HR 1.79 (1.57–2.03)** in ≥10% group

Skrtic (2016)[138]	UK	Longitudinal cohort	Primary and secondary care data (CPRD & HES)	▪ T2D (incident) ▪ Aged ≥18 years ▪ ≥1 record in the CPRD at least 3 years before diagnosis ▪ Had data on sex, age, BMI, blood pressure, cardio-vascular medications ▪ No prior heart failure within 3 years before diagnosis ▪ ≥1 HbA1c measure at baseline ▪ Not on insulin only at diagnosis and follow-up	94,332	Median 5.8 years	Per 1% increase: ▪ Baseline ▪ Updated latest ▪ Updated mean By HbA1c category (6-<7% as reference group): ▪ Baseline ▪ Latest ▪ Updated mean	Varied	Heart failure (6,068)	▪ **HR 1.06 (1.04–1.07)** ▪ **HR 1.06 (1.04–1.08)** ▪ **HR 1.15 (1.13–1.18)** ▪ Linear association, HR 0.98 (0.88–1.09) in <6% group to **HR 1.36 (1.26–1.46)** in ≥10% group ▪ J-shaped association, **HR 1.16 (1.07–1.25)** in <6% group to **HR 1.41 (1.24–1.60)** in ≥10% group ▪ Linear association HR 1.02 (0.92–1.15) in <6% group to **HR 1.84 (1.60–2.13)** in ≥10% group
Luo (2017)[185]	Singapore	Longitudinal cohort (bespoke)	Primary and secondary care data linked with national disease registry	▪ T2D (prevalent) ▪ Aged ≥21 years ▪ Without major psychiatric illness ▪ Had ≥1 HbA1c measure a year for 3 consecutive years before recruitment ▪ Consented for data linkage with outcomes ▪ Without disease of outcomes before recruitment ▪ Without missing values on covariates	6,079	Median (IQR) 4.1 (3.5-4.6) years for HbA1c trends (pre-baseline), 7.0 (4.4-7.8) years for acute MI, 7.1 (4.4-7.9) years for stroke, 8.3 (5.0-9.4) years for all-cause mortality	4 groups by latent class growth model: ▪ Low-stable (reference group) ▪ Moderate-stable (group 2) ▪ Moderate-increase (group 3) ▪ High-decrease (group 4)	Varied	▪ Acute MI (401/5,474) ▪ Stroke (237/5,478) ▪ All-cause mortality (946/5,513)	▪ HR 1.25 (0.93–1.69) - group 2 HR 1.61 (0.82–3.14) - group 3 **HR 2.83 (1.76–4.57)** - group 4 ▪ **HR 1.58 (1.08–2.31)** **HR 3.22 (1.27–8.15)** **HR 2.16 (1.02–4.57)** ▪ HR 1.09 (0.89–1.34) **HR 1.88 (1.15–3.07)** **HR 2.79 (1.97–3.95)**
Glycaemic variability										
Luk (2013)[189]	Hong Kong	Longitudinal cohort	National diabetes registry linked with secondary care data (hospital authority)	▪ T2D (prevalent) ▪ Chinese ethnicity ▪ ≥1 HbA1c repeat measure during follow-up ▪ Had no prior CVD & CKD	8,439 (6,983 CVD-free)	Median 7.2 years	▪ Mean (per 1% increase) ▪ Adjusted SD (per 1% increase)	Varied (median 10, IQR 5-17)	Any CVD (698)	▪ **HR 1.13 (1.03–1.24)** ▪ **HR 1.27 (1.15–1.40)**

Penno (2013)[194]	Italy	Serial cross-sectional analysis (bespoke)	Secondary care data	▪ T2D (prevalent) ▪ Caucasian ethnicity ▪ No prior history of dialysis or renal transplantation	8,290	2 years	▪ Mean ▪ Adjusted SD	3–5	▪ Any CVD (2,133) ▪ Any coronary events (1,373) ▪ Any cerebrovascular events (902) ▪ Lower limb vascular events (584) ▪ Ulceration/gangrene (319) ▪ Acute MI (949) ▪ Stroke (257)	▪ **OR 1.06 (1.01–1.11)** - per 1% mean increase ▪ **OR 1.07 (1.01–1.13)** - per 1% mean increase ▪ **OR 1.10 (1.03–1.17)** - per 1% mean increase ▪ OR 1.09 (1.00–1.18) - per 1% mean increase OR 1.21 (0.97–1.50) - per 1% adj SD increase ▪ **OR 1.41 (1.13–1.75)** - per 1% adj SD increase ▪ OR 0.96 (0.76–1.20) - mean quartile 2 **OR 1.68 (1.10–1.71) -** mean quartile 3 OR 1.08 (0.85–1.36) - mean quartile 4 ▪ N/A
Hirakawa (2014)[70]	20 countries (Asia, Australasia, Europe, North America)	Post-hoc analysis	ADVANCE trial	▪ T2D (prevalent) ▪ Aged ≥55 years ▪ Had a history of major macro-/microvascular disease or ≥1 other risk factor for vascular disease ▪ No macro-/microvascular disease or death during the first 24 months ▪ Had HbA1c and/or fasting glucose data during the first 24 months	4,399 (intensive arm)	Median 3.0 years	▪ SD ▪ CV ▪ VIM ▪ RSD ▪ ARV	5	▪ MACE (234) ▪ All-cause mortality (211)	▪ **HR 1.06 (1.01–1.12)** - per decile SD increase **HR 1.23 (1.10–1.38)** - per 1 SD increase of CV **HR 1.17 (1.04–1.32)** - per 1 SD increase of VIM **HR 1.25 (1.13–1.38)** - per 1 SD increase of RSD **HR 1.26 (1.13–1.39)** - per 1 SD increase of ARV ▪ **HR 1.11 (1.04–1.17)** **HR 1.37 (1.23–1.53)** **HR 1.29 (1.15–1.44)** **HR 1.38 (1.25–1.52)** **HR 1.42 (1.28–1.57)**
Bonke (2016)[193]	Germany	Longitudinal cohort	Disease management programme data (Kassenärztliche Vereinigung Bayerns)	▪ T2D (prevalent) ▪ Received insulin treatment (initiation or intensification) ▪ Baseline HbA1c was ≥6.5% or ≥7.5% with records on additional OHA at baseline	13,777	Median 5.8 years	Mean absolute difference scaled by time between measures, grouped into: ▪ Low variability (0.5%)	Varied	▪ MI (171/8,582) ▪ Stroke (348/8,535) ▪ Severe hypoglycaemia (412/8,873)	▪ J-shaped association for MI, stroke and severe hypoglycaemia with lowest risk at variability of about 0.5% per quarter

							▪ Increased variability (1%) ▪ High variability (1.5%)		▪ Emergency admission (380/8,982)	▪ Linear association for emergency admission with lower risk at variability <0.5% per quarter
Prentice (2016)[192]	USA	Longitudinal cohort	Administrative data (Veterans Health Administration) linked with health insurance claim data (Medicare)	▪ T2D (prevalent) ▪ Received metformin ▪ Initiated a second diabetes medication ▪ ≥4 HbA1c measures during baseline period ▪ No missing data on relevant covariates	50,861	Mean 3.3 years	Quartiles of: ▪ SD ▪ Adjusted SD ▪ CV Quartile 1 as reference group	Varied (≥4 at baseline)	▪ All-cause mortality (4,759)	▪ **HR 1.14 (1.04–1.25)** - quartile 3 of adj SD **HR 1.42 (1.28–1.58)** - quartile 4 of adj SD Linear association by CV and SD quartiles
									▪ MI or stroke (2,676)	▪ **HR 1.25 (1.10–1.41)** **HR 1.23 (1.07–1.42)** Linear association by CV and SD quartiles
									▪ Hospitalisation for ambulatory care-sensitive conditions (9,261)	▪ **HR 1.10 (1.03–1.18)** **HR 1.11 (1.03–1.20)** Linear association by CV and SD quartiles
Wan (2016)[190]	Hong Kong	Longitudinal cohort	Primary care data	▪ T2D (prevalent) ▪ Aged ≥18 years ▪ No history of CVD ▪ ≥5 HbA1c measures during follow-up period	91,866	Median 58.5 months	▪ SD ▪ CV ▪ VIM ▪ RSD ▪ ARV ▪ SV	Varied (mean 6.47, SD 1.30)	▪ Any CVD (2,755)	▪ HR 1.10 (1.00–1.21) - per 1 SD increase **HR 1.01 (1.00–1.02)** - per 1 CV increase **HR 1.16 (1.05–1.29)** - per 1 VIM increase **HR 1.14 (1.05–1.24)** - per 1 RSD increase HR 0.98 (0.88–1.09) - per 1 ARV increase HR 1.03 (0.95–1.11) - per 1 SV increase
									▪ All-cause mortality (1,415)	▪ **HR 1.70 (1.52–1.91)** **HR 1.04 (1.04–1.05)** **HR 1.88 (1.68–2.09)** **HR 1.68 (1.51–1.87)** **HR 1.72 (1.53–1.93)** **HR 1.49 (1.36–1.63)**
									▪ Composite of CVD and all-cause mortality (3,847)	▪ **HR 1.28 (1.18–1.38)** **HR 1.02 (1.02–1.03)** **HR 1.39 (1.28–1.51)**

										HR 1.30 (1.22–1.40) **HR 1.20 (1.11–1.30)** **HR 1.17 (1.10–1.24)**
Lee (2017)[191]	Taiwan	Longitudinal cohort	Secondary care data	▪ T2D (prevalent) ▪ Received hypoglycaemic agents ▪ HbA1c ≥6.5% ▪ Had ≥3 HbA1c measures ▪ Did not received insulin treatment	8,259	Mean 6.3 years	SD (per 1% increase)	Varied (every 12 months)	▪ Any CVD (1,057) ▪ CAD (876) ▪ Stroke (100) ▪ PAD (54)	▪ **HR 1.29 (1.01–1.65)** - if eGFR ≥60 unit HR 1.01 (0.80–1.28) - if eGFR <60 unit HR 1.09 (0.80–1.47) - if CKD stage 3 HR 1.22 (0.78–1.89) - if CKD stage 4 HR 1.62 (0.90–2.91) - if CKD stage 5 ▪ **HR 1.35 (1.02–1.79)** - eGFR ≥60 unit ▪ HR 1.61 (0.89–2.89) - eGFR ≥60 unit ▪ HR 1.25 (0.48–3.30) - eGFR ≥60 unit

*Number in parenthesis is number of events. **Effect sizes in bold denote significant associations.

Abbreviations: ACS, acute coronary syndrome; ARV, average real variability; CAD, coronary artery disease; CKD, chronic kidney disease; CV, coefficient of variation; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; IQR, interquartile range; LDL-C, low density lipoprotein cholesterol; MACE, major adverse cardiovascular events (cardiovascular mortality, non-fatal MI, non-fatal stroke); MI, myocardial infarction; NR, not reported; OHA, oral hypoglycaemic agent; OR, odds ratio; PAD, peripheral arterial disease; RSD, residual standard deviation; SAH, subarachnoid haemorrhage; SBP, systolic blood pressure; SD, standard deviation; SV, successive variation; T2D, type 2 diabetes; TIA, transient ischaemic attack; VIM, variation independent of mean.

Glycaemic variability. I found six observational studies (one of which was a bespoke cohort study[189]) and a post-hoc analysis of trial[70] investigating the associations of HbA1c variability between measures with cardiovascular outcomes. Three studies focused on an Asian population,[189-191] two utilised linked EHR databases,[189,192] but none targeted a newly diagnosed T2D population.

Glycaemic variability was defined by several metrics in these publications. SD between HbA1c measures was examined in all studies but one, in which mean absolute difference of HbA1c scaled by time between measures was applied instead.[193] Two studies reported a range of contemporary glycaemic variability metrics and their associations with cardiovascular outcomes.[70,190]

Quartiles of SD, adjusted SD and CV of HbA1c were shown to have linear associations with a composite of myocardial infarction and stroke.[192] However, a 1% HbA1c-SD increase was only significantly associated with risk for CAD but not stroke and PAD in T2D patients without impaired renal function.[191] Another study also documented a null association with lower limb vascular events by 1% adjusted SD increase.[194] In the study where mean absolute difference of HbA1c was estimated, J-shaped associations were observed for either myocardial infarction or stroke with lowest risk at HbA1c variability of about 0.5% per 3 months.[193]

HbA1c-SD levels or quartiles were also positively associated with any CVD,[189,191] MACE,[70] and all-cause mortality,[70,190,192] as were other contemporary metrics such as CV, VIM and residual standard deviation (RSD) of HbA1c.[70,190] A similar association between higher ARV and SV values was only reported in one study.[70]

2.9.2 Discussion

This literature review has identified large-scale (and mostly population-based) studies which demonstrated the association between long-term glycaemic control – extended to tight control in some studies – and cardiovascular outcomes and all-cause mortality. Although traditional factors (i.e. demographics and cardiovascular risks) remain to play some important roles, findings from the studies also underscore the benefits of maintaining glycaemic control over time within a safe range and imply that using a single HbA1c measurement for risk assessment – in research and clinical settings alike – may result in an underestimation of the importance of glycaemic control. Despite similar positive findings, the identified studies were heterogeneous in terms of targeted population (established *versus* incident T2D), the way long-term glycaemic control was defined (HbA1c levels *versus* variability) and analysed (as categorical or continuous variables), data source used (primary care or not), choice and definition of study outcomes and level of adjustment for risk factors. Glycaemic control estimates from studies targeting prevalent T2D population did not differ considerably from those in incident population. With regards to data sources, only a few studies built their analyses on medical insurance claims or post-trial data, yet this allows confirmation of findings from other studies with actual clinical records. Despite being published recently, no studies attempted to report contemporary, specific CVDs such as unstable angina, arrhythmia, TIA or AAA, possibly owing to their rarity.

Mean HbA1c has been found to be a significant predictor of cardiovascular outcomes, due, in part, to the fact that it incorporates multiple measures over time and therefore better reflects the glycaemic burden for the patient. The updated mean HbA1c even seems to be a better metric as it gives equal weight to all historical HbA1c measures. The metric estimates were similar when reported as continuous or categorical variable (quartiles) but the latter is easier to interpret. Although mean and updated mean HbA1c indicate longitudinal measures, only two studies had specifically developed or modified the glycaemic control metric which explicitly reckoned time element.[183,186] This is an important consideration not addressed by mean or updated mean calculation since the intervals between HbA1c measures are not always equally spaced in real-world clinical settings.

Additionally, there is a growing interest in taking a different view of glycaemic control as variability of serially measured HbA1c to reflect glycaemic fluctuation. All reviewed studies reported positive associations between various glycaemic variability metrics (with HbA1c-SD being most commonly used) and cardiovascular outcomes, except one study where mean HbA1c was more predictive of most cardiovascular outcomes than HbA1c-SD.[194] Yet again only one study incorporated time factor into the variability metric (which happened to be absolute mean difference, not SD of HbA1c).[193] Nevertheless, these lines of emerging evidence suggest that greater glycaemic variability also carries significant risk of CVDs and may be an independent risk predictor, supporting the concept that T2D management may be more complex than focusing solely on HbA1c levels.

Still, most glycaemic control or variability metrics in their naïve estimation cannot provide information on the true exposure period during which a T2D patient is well-controlled over the disease course. A potentially more accurate assessment of HbA1c's predictive function for vascular outcomes would be incorporation of not only the HbA1c level *per se* but also the length of time a patient has been at the targeted level, thus accounting for the natural fluctuation of HbA1c as well as glycaemic target attainment and its temporal effect on diabetes complications. To give near true estimates, such assessment would be best carried out from initial T2D diagnosis. Apparently, no studies have attempted to explore this potential approach and it justifies conducting CALIBER research in order to fill in the knowledge gap.

2.9.3 Limitation of this review

Despite efforts to supplement articles from reference lists and citing publications, some relevant studies may have been missed in this review because of the initial screening method using title and abstract. Studies not explicitly mentioning glycaemic control or variability metrics or terms in the title or abstract were, therefore, not well-flagged and filtered. This review only included large, recent studies published in the English language with the full-text available; however, they are deemed to be of high quality and more likely to show true association if it exists at all.

2.9.4 Conclusion

Previous studies investigating the association of glycaemic control with cardiovascular outcomes have been limited by the lack of time factor incorporation when estimating glycaemic control longitudinally. Development of a novel metric which accounts for period at glycaemic control proportionally is therefore warranted. Information on the duration of time under glycaemic control and its effects on cardiovascular risk will provide insight into the quality and effectiveness of continual T2D management.

2.10 Long-term glycaemic control and microvascular diseases

2.10.1 Findings of literature search

A total of eleven studies investigated the association of long-term glycaemic control with microvascular diseases, five of which examined glycaemic variability between measures (**Table 2.10 on pages 92-94**).

Glycaemic control. Of the six studies addressing the association of glycaemic control and microvascular outcomes, three were bespoke cohort studies,[139,185,195] one was a post-hoc analysis of a trial,[186] four were specifically conducted in Asia,[185,196] two used linked EHR databases,[185,195] and all recruited prevalent T2D cases. Two studies focusing on diabetic retinopathy were both relatively small in size.[139,197] Unlike studies investigating cardiovascular outcomes, the most common metric used to define glycaemic control longitudinally for microvascular outcomes was mean HbA1c over a follow-up period. Long-term glycaemic control was defined differently as a latent class growth model in one study.[185]

In a nested case-control study, a J-shaped association of mean HbA1c with overt nephropathy was subtly observed, the non-significance of which was possibly due to choice of reference group; compared with patients in the lowest category (mean HbA1c <6.16%), attenuated risk was observed in patients with mean HbA1c 6.16-7.37% (OR 0.52, 95% CI 0.31-0.88) but no higher risk was documented in patients with mean HbA1c >8.32% (OR 1.26, 95% CI 0.78-2.03).[195] A cohort study, however, clearly reported an excess risk for end stage renal disease (ESRD) in patients with moderate-increase (HR 4.76) and high-decrease (HR 3.05) glycaemic patterns relative to those with a low-stable pattern.[185]

A more consistent finding was found for diabetic retinopathy where a 1% mean HbA1c increase was associated with higher retinopathy risk.[139,197] The risk was even fourfold in patients with mean HbA1c ≥9% relative to those with mean HbA1c <7%.[139] Post-hoc analysis from the ADVANCE trial reported higher risk for combined retinopathy and development of nephropathy (HR 1.40) in patients with increased mean HbA1c of above 6.5%.[186]

My literature search did not return a single study addressing diabetic peripheral neuropathy (DPN), but I identified another study documenting a positive association of mean HbA1c with diabetic autonomic neuropathy (DAN); patients with mean HbA1c 9-11% or >11% had at least double the risk for cardiovascular autonomic neuropathy (CAN) relative to those with mean

HbA1c ≤7%.[196] Diabetic neuropathy can broadly take two forms: DPN and DAN – thus, despite the name which may be mistakenly regarded as a cardiovascular complication, CAN is essentially a form of DAN affecting the cardiovascular system and is therefore correctly clustered into microvascular complication.

Glycaemic variability. I found four observational studies and a post-hoc analysis of trial investigating the association of glycaemic variability with microvascular outcomes. All identified observational studies drew their population from prevalent T2D cases in secondary care; two were Asia-based harnessing linkage of EHR databases[189,198] and two were bespoke cohort studies.[194,198] HbA1c-SD and CV were the most commonly used metrics to define glycaemic variability for microvascular outcomes, whereas other contemporary metrics were only reported in one study.[70]

In all studies, either HbA1c-SD levels or quartiles appeared to be linearly associated with diabetic nephropathy as a single disease entity or across stages. HbA1c-CV was also positively associated with nephropathy.[198,199] A 1% HbA1c-SD increase was not associated with higher risk for non-advanced retinopathy,[194] but post-hoc analysis of the ADVANCE trial reported higher risk for combined retinopathy and nephropathy using an SD decile increase as well as 1-SD increase of CV, RSD and ARV.[70]

2.10.2 Discussion

This literature review found studies which, despite their heterogeneity, documented greater risk for microvascular outcomes being resulted from poor long-term glycaemic control (or variability), reaffirming the importance of maintaining and stabilising glycaemic control over time. The kidney appeared to be the most important target of microvascular damage in T2D despite varying definitions in the reviewed studies, while neuropathy appeared to be the rarest – if not neglected – microangiopathy explored.

Although not directly comparable among studies, the risk for microvascular outcomes attributable to higher mean HbA1c appeared to be greater than for cardiovascular and this was most evident in the Singaporean study reporting up to a fourfold risk for ESRD as compared to about a threefold risk for stroke or acute myocardial infarction.[185] There were no cohort studies incorporating time factor in their mean estimation or applying updated mean HbA1c to measure glycaemic control which implies that the reported estimates did not account for unequal interval between measures and were not derived from weighted historical HbA1c measures. Analysis from post-trial, however, has documented the effects of time-weighted mean HbA1c on microvascular risk.[186]

All reviewed studies using glycaemic variability metrics also consistently reported positive associations of greater variability with microvascular outcomes (mostly nephropathy), the magnitudes of which were similar to cardiovascular outcomes. The risk for ESRD from a unit increase of HbA1c-SD was slightly higher than that from mean HbA1c increase.[189] When treated as a categorical variable, however, only the last quartile of HbA1c-SD was associated with higher risk for nephropathy.[194] HbA1c-SD was not shown to be linearly associated with retinopathy,[194] but its

association with combined retinopathy and nephropathy was noticeable in another study, including association of other variability metrics (CV, RSD and ARV).[70] It is worth noting that generalisability of the studies applying glycaemic variability was limited to some extent since they drew their populations from secondary care.

As with reviewed studies for cardiovascular outcomes, the true effect of glycaemic exposure period on microvascular outcomes remain unaddressed by use of the existing metrics which fail to recognise proportional duration above (or under) glycaemic control. This leaves a gap in the knowledge which warrants further research particularly among a newly diagnosed T2D population in order to yield a more accurate estimate since none of the identified studies targeted this population.

2.10.3 Limitation of this review

Provided the same literature search strategy for studies on long-term glycaemic control, limitations previously mentioned for cardiovascular review (**Section 2.9.3 on page 88**) also apply for the microvascular outcomes. I might have missed some relevant studies not stating glycaemic control terms in their titles and abstracts, studies with a small cohort size despite examining pertinent diseases or outcomes, or pre-millennial publications despite their being landmark studies.

2.10.4 Conclusion

The existing studies examining microvascular outcomes have also lacked a time element consideration when defining long-term glycaemic control. This issue can be addressed by developing a new metric which calculates proportional period over the length of T2D during which a patient has been at glycaemic control, thereby shedding light on the effectiveness of continuing T2D management for preventing or delaying the onset of microvascular outcomes.

Table 2.10 Reviewed studies that investigate the association of long-term glycaemic control and/or variability with microvascular outcomes

Study (year)	Setting	Design	Data source	Inclusion criteria	N patients	Follow-up	HbA1c metric	N HbA1c measures	Microvascular endpoints*	Effect sizes (95% CI)**
Glycaemic control										
Yoshida (2001)[197]	Japan	Longitudinal cohort	Secondary care data	▪ T2D (prevalent) ▪ Aged <70 years ▪ No prior diabetic retinopathy ▪ Treated for at least 3 years	787	Mean 6.7 years	Mean (per 1% increase)	Varied (every 6 months)	Development of diabetic retinopathy	**RR 1.77 (1.56–2.01)**
Bruno (2003)[195]	Italy	Longitudinal bespoke cohort (nested case-control)	Primary and secondary care data linked with prescription and sale records of reagent strips and syringes	▪ T2D (prevalent)	1,253	Median 5.3 years	Mean category (<6.16% as reference group)	Varied (every 3-4 months)	Progression to overt nephropathy (202/1,103)	**OR 0.52 (0.31–0.88)** - 6.16–7.37% group OR 0.67 (0.40–1.12) - 7.38–8.32% group OR 1.26 (0.78–2.03) - >8.32% group
Ko (2008)[196]	South Korea	Longitudinal cohort	Secondary care data	▪ T2D (prevalent) ▪ Aged 25-75 years ▪ Not mentally ill nor unable to undertake the required test ▪ Had no arrhythmia ▪ Had no severe illness	1,021	Median 7.5 years	Mean category (≤7.0 as reference group)	Varied (every 6 months)	Progression to cardiovascular autonomic neuropathy (270/883)	OR 1.14 (0.90–2.13) - 7.01–9.0% group **OR 2.57 (1.53–4.31)** - 9.01–11.0% group **OR 2.75 (1.08–7.05)** - >11.0% group
Zoungas (2012)[186]	20 countries (Asia, Australasia, Europe, N America)	Post-hoc analysis	ADVANCE trial	▪ T2D (prevalent) ▪ Aged ≥55 years ▪ Had ≥1 risk factor for vascular disease ▪ Had HbA1c data at baseline	11,086	NR	Mean (weighted by time intervals between measures and prior to first event - per 1% increase)	At baseline, 6 months and annually thereafter	Microvascular events (NR)	HR 1.02 (0.76–1.39) - below 6.5% knot **HR 1.40 (1.33–1.47)** - above 6.5% knot
Yun (2016)[139]	South Korea	Longitudinal cohort (bespoke)	Secondary care data	▪ T2D (prevalent) ▪ Aged 25-75 years ▪ No prior diabetic retinopathy, secondary diabetes, alcoholism, any severe illness ▪ Not pregnant nor had prior gestational DM	759	Mean 6.7 years	▪ Mean (per 1% increase) ▪ Mean category (<7% as reference group)	Varied (every 6 months)	Diabetic retinopathy (235/523)	▪ **HR 1.37 (1.10–1.72)** ▪ **HR 1.83 (1.08–3.09)** -7-8.9% group **HR 4.32 (2.52–7.40)** - ≥9% group
Luo (2017)[185]	Singapore	Longitudinal cohort (bespoke)	Primary and secondary care data linked with national disease registry	▪ T2D (prevalent) ▪ Aged ≥21 years ▪ Without major psychiatric illness	6,079	Median (IQR) 4.1 (3.5-4.6) years for HbA1c trends (pre-baseline),	4 groups by latent class growth model: ▪ Low-stable (reference group)	Varied	ESRD (134/5,505)	

				▪ Had ≥1 HbA1c measure a year for 3 consecutive years before recruitment ▪ Consented for data linkage with outcomes ▪ Without disease of outcomes before recruitment ▪ Without missing values on covariates		7.0 (4.4-7.8) years for acute MI, 7.1 (4.4-7.9) years for stroke, 8.3 (5.0-9.4) years for all-cause mortality	▪ Moderate-stable (group 2) ▪ Moderate-increase (group 3) ▪ High-decrease (group 4)			▪ HR 1.17 (0.70–1.96) - group 2 ▪ **HR 4.76 (1.92–11.83)** - group 3 ▪ **HR 3.05 (1.54–6.07)** - group 4
Glycaemic variability										
Rodriguez-Segade (2012)[199]	Spain	Longitudinal cohort	Secondary care data	▪ T2D (prevalent) ▪ On insulin or OHAs ▪ Had no known haemoglobinopathy or erythrocyte disorder	2,103	Mean 6.6 years	▪ SD (per 1% increase) ▪ CV (per 1% increase)	Varied (median 10)	Progression to nephropathy (384)	▪ **HR 1.37 (1.12–1.69)** ▪ **HR 1.03 (1.01–1.04)**
Lin (2013)[198]	Taiwan	Longitudinal cohort (bespoke)	Secondary care data linked with diabetes care management programme data	▪ T2D (prevalent) ▪ Aged ≥30 years ▪ Had no diabetic nephropathy ▪ ≥1 year follow-up ▪ Had no missing data	3,220	Mean 4.4 years	CV category (<6.68% as reference group)	Varied (every 3-6 months)	Diabetic nephropathy (82 vs 112 vs 135)	HR 1.18 (0.88-1.58) - 6.68-13.44% group **HR 1.58 (1.19-2.11)** - >13.44% group
Luk (2013)[189]	Hong Kong	Longitudinal cohort	National diabetes registry linked with secondary care (hospital authority) data	▪ T2D (prevalent) ▪ Chinese ethnicity ▪ ≥1 HbA1c repeat measure during follow-up ▪ Had no prior CVD & CKD	8,439 (6,983 CVD-free patients)	Median 7.2 years	▪ Mean ▪ Adjusted SD (per 1% increase)	Varied (median 10, IQR 5-17)	▪ CKD (1,414) ▪ ESRD (248)	▪ HR 1.16 (1.09–1.24) - per 1% mean increase **HR 1.16 (1.10–1.22)** - per 1% SD increase ▪ HR 1.26 (1.09–1.44) - per 1% mean increase **HR 1.53 (1.35–1.73)** - per 1% SD increase
Penno (2013)[194]	Italy	Longitudinal cohort (bespoke)	Secondary care data	▪ T2D (prevalent) ▪ Caucasian ethnicity ▪ No prior history of dialysis or renal transplantation ▪ Had no missing data or implausible values	8,260	2 years	Adjusted SD	3-5	▪ Microalbuminuria (1,829) ▪ Macroalbuminuria (408)	▪ **OR 1.25 (1.11–1.41)** - per 1% adj SD increase OR 1.03 (0.88–1.22) - quartile 2 OR 1.14 (0.97–1.35) - quartile 3 **OR 1.31 (1.10–1.56)** - quartile 4 ▪ **OR 1.35 (1.09–1.67)** OR 0.94 (0.67–1.31)

									▪ eGFR <60 mL/min/1.73 m^2 (1,642) ▪ Stages 1–2 CKD (1,529) ▪ Stages 3–5 albuminuric CKD (708) ▪ Non-advanced retinopathy (NR)	OR 1.04 (0.76–1.44) **OR 1.41 (1.03–1.93)** ▪ **OR 1.15 (1.00–1.33)** OR 1.00 (0.84–1.20) **OR 1.23 (1.03–1.48)** **OR 1.24 (1.02–1.51)** ▪ **OR 1.22 (1.07–1.40)** OR 1.08 (0.91–1.29) OR 1.14 (0.95–1.37) **OR 1.31 (1.08–1.58)** ▪ **OR 1.33 (1.10–1.61)** OR 0.93 (0.71–1.23) OR 1.27 (0.97–1.66) **OR 1.47 (1.10–1.96)** ▪ OR 0.93 (0.76–1.11) - per 1% adj SD increase
Hirakawa (2014)[70]	20 countries (Asia, Australasia, Europe, North America)	Post-hoc analysis	ADVANCE trial	▪ T2D (prevalent) ▪ Aged ≥55 years ▪ Had a history of major macro-/microvascular disease or ≥1 other risk factor for vascular disease ▪ No macro-/microvascular disease or death during the first 24 months ▪ Had HbA1c and/or fasting glucose data during the first 24 months	4,399 (intensive arm)	Median 3.0 years	▪ SD (per decile increase) ▪ CV (per 1 SD increase) ▪ VIM (per 1 SD increase) ▪ RSD (per 1 SD increase) ▪ ARV (per 1 SD increase)	5	Major microvascular events (309)	▪ **HR 1.06 (1.01–1.12)** ▪ **HR 1.23 (1.12–1.36)** ▪ HR 1.06 (0.95–1.19) ▪ **HR 1.26 (1.15–1.37)** ▪ **HR 1.29 (1.19–1.41)**

*Number in parenthesis is number of events. **Effect sizes in bold denote significant associations.
Abbreviations: ARV, average real variability; CKD, chronic kidney disease; CV, coefficient of variation; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; HR, hazard ratio; IQR, interquartile range; NR, not reported; OHA, oral hypoglycaemic agent; OR, odds ratio; RR, risk ratio; RSD, residual standard deviation; SD, standard deviation; SV, successive variation; T2D, type 2 diabetes; VIM, variation independent of mean.

2.11 Chapter summary

This review has highlighted important knowledge gaps in a range of quality of care aspects following diagnosis of T2D. The complexity of T2D argues the importance of recognising the trajectory of care delivery from onset of T2D, predictors and cardiovascular consequences of early HbA1c, blood pressure and lipid control, and the need to redefine glycaemic control longitudinally and explore its potential as a more informative measure for vascular risk assessment. Knowledge of these issues can be useful for clinicians, health policy makers and trialists to help improve T2D management and guide potential future treatment in order to reduce the disease burden.

The following chapter will describe the CALIBER research framework, its constituent EHR data sources, development of the study cohort, phenotyping for T2D and specific CVDs, and measurement of related variables for addressing the research question in this thesis.

Chapter 3

CALIBER – a linked electronic health records research platform

"Data! Data! Data!" he cried impatiently. "I can't make bricks without clay."
— Arthur Conan Doyle, *The Adventure of the Copper Beeches*

3.1 Chapter outline

This chapter describes the ClinicAI research using LInked Bespoke studies and Electronic health Records (CALIBER), a research platform through which I seek to address the thesis objectives. I describe CALIBER's constituent data sources and generation of a newly diagnosed T2D cohort for my thesis. I also describe how the linked CALIBER data were used to identify and measure quality indicators for T2D care, potential covariates, diabetes associated treatment and initial presentation of a wide array of CVDs.

3.2 Introduction

EHRs have the huge potential to revolutionise healthcare by providing clinicians with quick and comprehensive access to patient records, evidence-based decision-making tools, drug databases to produce recommendations, clear prescription notes, clinical alerts and follow-up reminders, and other measures for patient care. In the meantime, the United Kingdom is unique in having a long-implemented universal health system with single identification numbers as well as having relatively centralised EHRs available at scale for research spanning the entire translational cycle. Primary care has been the core strength of the UK health system as practices have responsibility for a defined population that enables them to be held accountable for the quality of care they provide, become the gatekeepers to specialist care, and importantly have frequently used EHRs.[200] The UK also has a detailed CVD registry and standard hospitalisation databases. In comparison, the United States has either regional (Mayo Clinic, Kaiser Permanente) or national but segmented health insurance schemes (Medicare, Veteran Affairs),[128,201] Sweden has primary care databases organised regionally despite a national initiative for CVD (SwedeHeart),[202] Denmark probably has the most efficient EHR infrastructure for primary care to date with nearly 100% adoption rate by GPs but the population is much smaller (<10%) than the UK and there still some issues with interoperability for health information exchange,[203,204] while Canada has a national health insurance scheme but a regional health informatics initiative (Institute for Clinical Evaluative Sciences in Ontario).[128,201,205] Some Asia-Pacific countries also have health databases with high accessibility for research. Japan has national but privately held databases for claims (Japan Medical Data Centre) and acute secondary care (Medical Data Vision),[206,207] while Australia has a national health insurance scheme (Medicare, Veteran Affairs) and prescription database (Pharmaceutical Benefit Scheme) and has set up several initiatives similar to Canada's (e.g. Centre for Health Record Linkage in New South Wales and Canberra, Victorian Data Linkages in Victoria).[206,208,209] Taiwan also has national insurance scheme (National Health Insurance Research Database) and has recently established a large repository which centralises all Taiwan's health databases (Health and Welfare Data Center).[210,211] However, the population of either Australia and Taiwan is only about one-third of the UK's. These factors have all set the UK apart internationally, offering unparalleled opportunities for it to become a world-leader in EHR research.

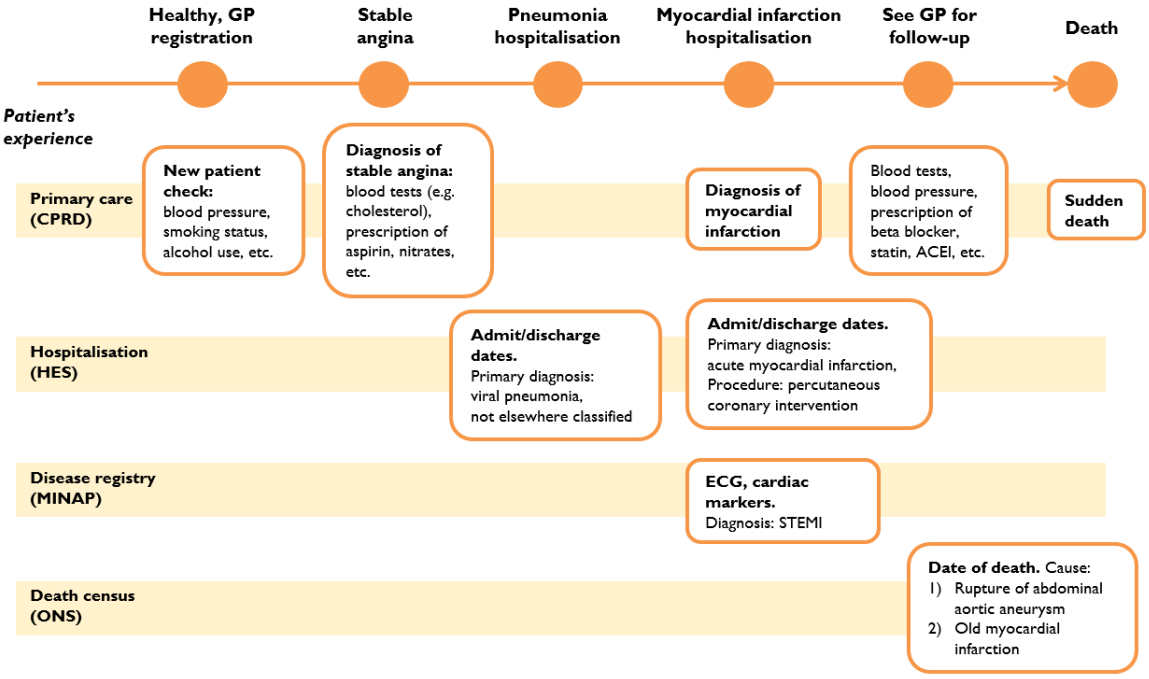
CALIBER is a collaborative research platform of linked EHRs and administrative databases in the UK, led from the Farr Institute of Health Informatics Research at University College London. CALIBER brings together primary care records in CPRD, hospital discharge records in HES, the MINAP database, and ONS mortality and social deprivation statistics. These national databases are linked using unique NHS identifiers, creating a versatile resource for health research that tracks the patient journey through pathways of care from GP registration, through disease onset and clinical investigations to non-fatal and fatal endpoints (**Figure 3.1 on page 98**). CALIBER's real world patient population ensures that its research outputs are generalisable, its public health contribution being further enhanced by its discovery and evaluation potential. This large scale resource plays an important role in determining disease aetiology and prognosis, particularly as applied to specific cardiovascular phenotypes that may complicate chronic disease.[128]

3.3 Data sources

3.3.1 Clinical Practice Research Datalink (CPRD)

CPRD, formerly known as the GPRD, is a primary care database which contains pseudonymised, longitudinal records of nearly 14 million patients (5 million actively registered) from 644 GP practices in 2012, covering about 7.1% of the UK population.[212] Since nearly all people in Britain are registered with a GP and the participating practices are a representative sample, patients within CPRD largely represent the national population. As the world's largest healthcare database to date, CPRD has been used extensively for disease epidemiology, drug safety, health outcomes and health economics research with over 1,700 publications.[213]

Figure 3.1 A hypothetical example of a patient's medical history recorded in CALIBER data sources



Reproduced from: Denaxas, et al. (*Int J of Epidemiology*, 2012)[128]

Established in 1987, GPRD has been owned by the Secretary of State for Health since 1994 and managed by the Medicines and Healthcare products Regulatory Agency (MHRA) since 2000. Further efforts to enhance size and coverage as well as to allow linkage with other registries, clinical data and cohort studies has led to the name change to CPRD in 2012. The research databank has been contributed to by participating GPs who were given free computers with installed Vision systems implementing the Read codes.[214] The eponymous codes, as developed by Dr James Read, consist of over 100,000 classification codes for symptoms, examinations and diagnoses.[215] Data collection by GPs is performed as part of routine clinical care and covers demographic and behavioural information, signs and symptoms, clinical tests and procedures, diagnoses, prescriptions, vaccinations, treatment outcomes, referral to specialists and hospital admissions. Anonymised Read-coded data are uploaded daily to the CPRD data warehouse.[213]

Data structure. CPRD data are recorded in a number of linkable tables (**Table 3.1 below**). Linkage to generate a complete picture of a patient's health experience can be performed using a patient identifier. A patient can have any number of events, each of which is linked to a single consultation and has an event date, a medical dictionary (Read) code, a test code or a product dictionary (Multilex) code.[125,213]

Table 3.1 Data structure of CPRD records[214]

File type	Contents	Example of contents
Patient	Demographic and registration status of patients	Patient identifier, month and year of birth, gender, registration status, death date, transfer out date
Practice	Practice administrative data	Practice identifier, geographical region, date practice became UTS, last data collection date
Staff	Data on staff members entering data	Staff identifier, gender, role
Consultation	Administrative information about consultation	Date of clinical event, date of data entry, type of consultation, staff identifier and duration of consultation
Clinical	Clinical data regarding medical history (symptoms, signs and diagnoses)	Date of clinical event, date of data entry, CPRD medical code for the chosen Read code, additional details identifier, entity type*
Additional Clinical Details (ACD)	Specific data about a clinical event	Type of information held (entity), specific clinical details relating to that entity
Referral	Details on referrals to secondary care or specialists	CPRD medical code for the chosen Read code, method of referral, referral specialty, urgency of referral
Immunisation	Data on immunisation records	Reason for immunisation, type, stage, status and the compound used
Test	Data on test records	Type of test (entity), result with a Read code, normal range of result, unit of measure
Therapy	Data on all prescription issued by GP	CPRD product code for medication, BNF code, quantity of product, dose, pack size, number of days prescribed

BNF, British National Formulary.
*Entity codes refer to different information model, usually correspond to Read codes yet less specific.

Data quality. CPRD recommends two methods to ensure the completeness, continuity and plausibility of data recording for research purposes.[126,213,214] Firstly, at the patient-level, only patients without gaps or inconsistencies in records and whose data is 'acceptable research quality (ARQ)' are deemed to be of research quality. Secondly, the overall data quality in practices is mediated by use of an 'up to standard (UTS)' date at which data in the practice is considered to have continuous high quality data fit for use in research. **Table 3.2 on page 100** lists the ARQ and UTS criteria. CPRD recommends that analyses are performed on data following the practice UTS date. CPRD data serves as the main data source in CALIBER and currently includes approximately 4.7 million registered patients meeting UTS criteria.

The quality of the CPRD data has been further enhanced during the last decade by QOF implementation which has incentivised GPs to deliver (and record) quality of care metrics for major clinical domains, including diabetes and CVDs. In 2010, up to 244 CPRD practices have consented to linkage with other healthcare databases, including hospitalisation data, disease registry and national statistics.[214]

Data accuracy. Peer-reviewed publications have independently examined the validity of CPRD records. A systematic review of over 200 studies validating CPRD diagnoses reported a median PPV of 88% across a range of diagnoses, 85.3% for cardiovascular diagnoses, and 87.7% for endocrine, nutritional and metabolic diagnoses.[216] Stroke was shown to have a PPV of 86%, while PAD had a PPV of 71% when validated against GP questionnaire.[217] Prevalence or incidence rates of hypertension and dyslipidaemia in CPRD were reported to be broadly comparable to those documented in the Health Survey for England or HES.[218] Current smoking diagnosis – validated against the GPs' own records – had a sensitivity of 78% and a PPV of 70%.[219] Data on issued prescriptions, but not dispensed medications, appear to be highly complete and, therefore, CPRD has been used extensively for pharmacoepidemiological studies.[220]

Table 3.2 Data quality standards for CPRD[214]

Acceptable research quality (ARQ) - Patient-level quality standards*	Up to standard (UTS) - Practice-level quality standards
An empty of invalid first registration date†	Percentage of patients of ARQ
An empty of invalid current registration date	
Absence of a record for a year of birth	Monthly prescription rate comparable to other practices
A first registration date prior to birth year	Percentage of prescriptions with a medical indication
A transferred out reason with no transferred out date‡	Death rates comparable to other practices
A transferred out date with no transferred out reason	Cause of death recorded
A transferred out date prior to their first registration date	Outcome of pregnancy recorded
A transferred out date prior to their current registration date	Referral rate comparable to other practices
A current registration date prior to their first registration date	Percentage of referrals with recorded clinical specialty
A current registration date prior to their birth year	
A gender other than Female/Male/Indeterminate	
An age >115 at end of follow up	
Recorded health care episodes in years prior to birth year	
All recorded health care episodes have empty or invalid event dates	
Registration status of temporary patients	

*Patient is labelled unacceptable and not recommended for use in research if any of the criteria are true.
†Date when first registered to a GP.
‡Date when a patient leaves practice.

Strengths. The strengths of CPRD data lie in the breadth of coverage, size, representativeness, long-term follow-up and data quality. CPRD is one of only a few large databases that include data on morbidity and lifestyle variables with linkage to secondary care and mortality data, enabling epidemiological associations to be explored in more detail and more accurately estimated. The median prospective follow-up is roughly five years overall and nine years for active patients, enabling research into diseases with long latency and study of long-term outcomes.[214] CPRD patients are broadly representative of the UK population in terms of age, sex, ethnicity and body mass index (BMI) distribution,[221,222] although those in northern England tend to be underrepresented.[223]

Limitations. Data completeness across patients and time is an important issue with complex patterns of 'missingness'. For example, BMI and blood pressure may be recorded more frequently in patients with a health issue. In contrast, other health aspects such as level of social support, number of people in a household, over-the-counter medication use and prescriptions in secondary care may be rarely or never recorded. Certain patient groups such as prisoners, private patients, some residential homes residents and the homeless are also missing from primary care records. Following on individual patients over time (e.g. moving practices, emigrating) adds another issue. Other important weaknesses are the selected volunteer practices and potential misclassification – the latter arising partly due to GP variations in coding diagnoses, GPs entering information as free text, or patients presenting to the GP without a disease (thus the absence of a Read code for disease must be interpreted as an absence of the disease itself). Additionally, information received about patient contacts with secondary care may be incomplete as practices must manually enter the information into the patient record. In the absence of standardised definitions for diagnoses and other details, a researcher has to develop Read code lists and algorithms to specify study exposures and outcomes of interest, which explains the inconsistent definitions and results between studies using the same data.[214]

Comparison with other primary care databases in the UK. In addition to the Vision, EMIS and SystmOne are among major operating systems in the UK to support electronic recording in primary care. The databases built upon these systems have also been harnessed for research resources, and are briefly discussed below:

1. **The Health Improvement Network (THIN)**

   Established in 2003, THIN is a primary care database derived from pseudonymised records collected using the Vision system (50-60% overlap with GPRD). THIN is therefore similar to CPRD in terms of data structure, collection method and use of Read codes to catalogue the clinical data. THIN has socioeconomic indicators linked to medical record, thus is more efficient for matching patient characteristics. Being developed later than GPRD, THIN does not implement the UTS criteria for research as data entered by all practices are considered to be of sufficiently high quality. In 2014, THIN holds records of 11.1 million patients (3.7 million actively registered) collected from 562 general practices in the UK, covering 6.2% of the UK population. The de-identified patient data are regularly collected from the practices and sent to CSD Medical Research UK (EPIC) which processes, validates and supplies the THIN data to researchers for studies. THIN is currently hosted by University College London (UCL).[224]

2. **QResearch**

   QResearch database is derived from GP records collected using the Egton Medical Information Systems (EMIS), the most widely used primary care computer system to date in the UK. QResearch data contains 754 practices with over 13 million patients registered in 2014 (no known data on active registration), covering nearly 7% of the UK population. Data maintained are from current registered as well as historical patients who may have died or left. EMIS enables practices to receive regular quality improvement reports and earn extra income from questionnaires and clinical research. Patients are pseudonymised for data extraction but the

University of Nottingham (as the EMIS data custodian) provides fully encrypted data containing no EMIS-allocated patient unique numbers for researchers.[225] QResearch database has been used to develop risk clinical prediction tools for a range of diseases, an exemplar being QRISK for estimating individualised lifetime risk of CVD which was shown to have better discrimination for the UK population than the Framingham risk score.[226,227] Additionally, the widespread use and upgraded features of the EMIS system have attracted CPRD to also exercise data extraction from GP practices using the software in order to expand the scope of clinical research questions that cannot be addressed by CPRD data alone.[212]

3. **ResearchOne**

   ResearchOne is a centralised database which contains 26 million patient records from both administrative and clinical practice across primary and secondary settings on the SystmOne system. ResearchOne is hosted by the University of Leeds and reported to have excellent geographic and demographic representation across England. Currently, there are over 120,000 active users of SystmOne across GP practices, child health units, community health units, accident and emergency (A&E) and acute hospitals. Healthcare providers must opt-in and a patient can opt-out for their data to be included in the database. Data held are all pseudonymised and include diagnoses, procedures, laboratory tests, prescriptions, deprivation indices and care pathways which are coded using a variety of terminologies, classifications and data dictionaries depending on the type of data and recording provider. Records are updated on a weekly basis as part of routine practice and centrally checked on a continuous basis against national data sources (e.g. prescribing, mortality rates, aggregate census data, deprivation index) to ensure data integrity, quality and representation. Researchers can directly extract the most up-to-date patient data from the database without needing an additional linkage step since patient records from different providers are already shared. ResearchOne also allows continuous outcome data from any new research-driven interventions to be analysed within a short time frame. With these breakthroughs, ResearchOne has the potential to be one of the world's largest, most convenient healthcare databases for research.[228]

3.3.2 Hospital Episode Statistics (HES)

HES is a national data warehouse of hospitalisation episodes that is used, among other things, to monitor and compare hospital performance across different geographical areas and hospital trusts in England.[126,229] HES stores data from inpatients (since 1989), outpatient attendance (since 2003), A&E (since 2007) and adult critical care. In addition to patients' demographic and administrative data, clinical data on each episode of care delivery are input at the end of admission for submission to HES on a monthly basis. HES information on outpatients has not been linked in CALIBER.

Data structure. HES utilises the World Health Organization's International Classification of Disease tenth revision (ICD-10) codes for diagnosis and the Office of Population, Censuses and Surveys Classification of Interventions and Procedures fourth revision (OPCS-4) codes for procedures. The record of each clinical episode includes up to 22 diagnoses using ICD-10 and 24

procedures using OPCS-4. Both codes have fewer terms than Read and use a chronological list of codes divided into chapters based on body system; the ICD-10 chapters, however, do not correlate to OPCS-4 chapters. For valid recording of conditions affecting more than one body system, related documents are provided detailing which certain codes or combination of codes may be used.[230,231]

Data quality. In secondary care settings, the clinician initially documents diagnosis in the clinical notes and the hospital management transfers patient record after discharge (a completed 'spell') to the clinical coders who later classifies diagnoses and procedures – in accordance with NHS definitions – using relevant codes. A primary diagnosis, one subsidiary and up to five secondary diagnoses are recorded in ICD-10, and up to four procedures in OPCS-4. HES further ensures the quality of data received through mapping, cleaning, further derivation and regular audits of coding before making it available to researchers.[126,232]

Data accuracy. The timing of coding, which is done after patient discharge, could lead to inaccuracy and 'missingness'. A study examining the reproducibility of codes entered concluded that subtypes of a diagnosis may be recorded poorly, though the general diagnosis is likely to be correct.[233] More recent evidence, however, suggested improvement for discharge coding of T1D, and concordance with a diabetes register increasing from 52% in 1992-1999 to 91% in 2000-2006.[234] Agreement between HES diagnosis and GP records in women with and without vascular diseases (ischaemic heart disease, stroke or venous thromboembolism) reached 93% (i.e. true positive value) and 97% (i.e. true negative value), respectively, despite lower estimates for more specific diagnoses, suggesting that HES records provide diagnostic information for vascular disease of sufficient reliability.[232] In terms of completeness, a review reported that inpatient and day-case episodes as well as procedures were not all captured.[235] In a population-based study, acute myocardial infarction was found to be substantially underestimated at 53% when captured using HES discharge diagnostic coding,[236] though the PPV was reportedly high (91.5%) when compared against that defined in a disease registry.[237]

Strengths. HES is representative of patients in England. Information on over 16 million episodes of inpatient care are collected annually as part of routine care, allowing researchers to examine the burden of rare diseases and subgroup analyses for more common conditions, as well as to explore the primary cause and secondary conditions for hospitalisation.[237]

Limitations. HES is essentially an administrative database not originally intended for research purposes. Since data are inputted by coding clerks, there have been concerns about accuracy, consistency and completeness of HES data (e.g. primary, secondary, tertiary and quaternary level of diagnosis being recorded at admission only),[237] suggesting that linkage with other health databases is needed.

3.3.3 Myocardial Ischaemia National Audit Project (MINAP)

Established in 1998, MINAP is a national registry of patients with ACS admitted to one of over 225 participating NHS acute hospitals in England and Wales. The data are collected from ambulance

paramedics, A&E departments, cardiac care and other hospital wards, and about 85,000 episodes of care are accrued annually in the registry. MINAP provides a mechanism for the participating hospitals to audit their performance against the National Service Framework (NSF) for CHD and other benchmarks. MINAP is managed by the National Institute for Cardiovascular Outcomes Research (NICOR), based at UCL.[126,238]

Data structure. Data are recorded using dedicated MINAP software with provision of detailed guidelines, technical advice and a helpdesk for data entry to ensure data quality and continuity of data collection. There are 123 data fields – nearly half of which are compulsory – which include demographics, admission method, timing of care, clinical features, medical and treatment history, reperfusion details, treatment and outcomes in hospital, complications, discharge diagnosis, and referral to specialists. Linkage to subsequent events or procedures under-gone by the patient as well as to other databases and national registries is possible using NHS numbers. All patients' identifiable numbers are encrypted before the data are uploaded to a secure central database.[237,238]

Data quality. Data extraction from hospital records is usually performed weeks after admission by a local audit nurse who later submits it to the Central Cardiac Audit Database (CCAD). The dataset is revised biannually to meet the user requirements and to respond to changes in clinical guidelines. There is also an annual validation exercise for which each hospital is required to re-assess diagnosis, treatment, outcome and discharge data for 20 randomly selected patients, permitting identification and resolution for improvement of areas with inadequate agreement of the original with re-entered data.[237]

Data accuracy. Completeness of key fields was reported to be very high,[238] while the overall performance of hospitals and data quality assessed through comparison against re-audit data showed a good agreement at nearly 90%.[239]

Strengths. MINAP data are representative of all ACS patients hospitalised in England and Wales. Over 800,000 ACS events with detailed supporting data have now been collected, offering unprecedented power to address research questions pertinent to small subsets. Importantly, MINAP holds data on ACS type, which are not available in HES or ONS and are infrequently recorded in CPRD.[237,238]

Limitations. Patients with non ST-elevation myocardial infarction (NSTEMI) may be underrecorded in the lack of an agreed national standard of care for NSTEMI and other ACS, and their ascertainment is likely to be less complete when they are not exclusively admitted to cardiology wards. ACS patients who die before or soon after reaching hospital, or are admitted to private hospitals, can lead to incomplete capture within hospitals, raising concerns about the representativeness of MINAP data. Inter-hospital patient transfers during the index event also makes data capture more difficult although this issue can be addressed by linking MINAP records between hospitals. The cost of local data entry is borne by each hospital and the financial contribution is subject to inter-hospital variability which can, in turn, affect the data accuracy. Missingness is expected in some data fields and can lead to a selection bias if patients with missing data – given

the potentially different characteristics to those with complete data – are omitted from analysis.[237,238]

3.3.4 Office for National Statistics (ONS) mortality

The ONS mortality statistics record information on cause-specific mortality from death registration in England and Wales.[240] ONS uses the ICD-10 coding system, mostly referring to the Medical Certificate of Cause and Death (MCCD) completed by treating physicians, or else to post-mortem reports when death occurred outside the clinical setting or its cause was unclear. The ICD-10 allows code recording of primary, underlying and up to 14 secondary causes of death.

Data quality. Death information is entered into an online system by registrars at Local Registration Services. Uploaded data are checked and validated by ONS to ensure that they are correct, complete and consistent. Problems with data (e.g. incompatibility of condition stated on the death certificate with gender and age) are identified through regular diagnostic tests.[237,240]

Strengths and limitations. ONS mortality data is a complete source of death records since death registration is mandatory within the UK. However, the ONS mortality registry does not record information on British nationals who die abroad.[240]

3.4 Data linkage

An implication of the UK's universal health system under the NHS is that babies born in England, Wales or the Isle of Man and anyone registered with a GP or receiving treatment from a hospital will have a unique 10-digit NHS number – equivalent to the Community Health Index in Scotland and the Health and Care Number in Northern Ireland – which is the primary key common to multiple data sources to allow information on individuals in different datasets to be linked.[241] The linkage process has, however, to be performed carefully to avoid errors – and in turn biases – and further cross-referencing between sources is needed.[242]

The CALIBER research platform was created by linking the four national data sources. Data linkage was performed in 2010 adhering to the principles for protecting patient confidentiality. Of the 630 participating CPRD practices in 2010, 244 (38.7%) consented to having their data used for linkage with other sources.[237] For the main linkage of CPRD data to MINAP, the assigned Trusted Third Party (TTP) to perform the linkage received a list of unique identifiers (NHS number), demographic information (date of birth, sex and postcode of residence) and their associated source-specific pseudo-identifiers. Linkage was performed using a pre-defined deterministic linkage algorithm (if an exact match is found for record linkage) and a probabilistic method (if otherwise similar sounding names or common misspellings are found). Once completed, the patient identifiable data were removed, leaving the key file which links CPRD patient pseudo-identifiers to MINAP hospital record number pseudo-identifiers. Previously, linkage of CPRD data to HES and ONS mortality and deprivation data were similarly performed but, in addition to having a valid NHS number, a patient must not violate the ARQ standards and must be actively registered with a

consenting practice at some point during the period for which data are available for the second data source to be put forward for linkage.[126]

It is reported that, of 5.8 million patients eligible for record linkage, 96% had a valid NHS number for deterministic linkage between NHS number, date of birth and gender,[128,243] and approximately 77% and 73% were matched with HES and MINAP linkage, respectively.[126] There was only a 2.1% mismatch for linkage of CPRD to ONS mortality data due to the unavailability of ONS records on British nationals who died abroad, GP not being informed of the death, or simply a data entry error.[125]

3.5 Converting raw clinical data into research-ready variables

The way EHRs are collected as part of clinical routine implies that records are variable in quality. A patient may have lines of records often with multiple events occurring on the same day, some records may be duplicative or inconsistent, but others may be incomplete. CALIBER data linked by the TTP were not in a usable form as each data source has its own structure, reason for data recording, coding system and level of clinical detail. Extensive processes have been conducted by the CALIBER group to integrate the complexities and make the raw data ready for researchers, which involved three stages:[126]

1. Development of code lists used to define the exposures, risk factors and endpoints and select relevant data from each data file
2. Definition of such variables – how the records extracted from data files will be used to specify the value of research variables
3. Development of algorithms for dealing with duplication and contradiction in the variables created.

The first stage – applied to CPRD – includes developing a list of: 1) Read codes to indicate the diagnosis, specific symptoms, management, treatments and procedures for the condition, 2) Read codes which indicate clinical tests, the results of which can define disease (e.g. HbA1c and diabetes), 3) relevant entity codes which indicate further specific information held in the additional clinical details file (e.g. results of height and weight measures), and 4) medications specific to the diagnosis (e.g. insulin prescription indicates diabetes). Similar list developments were sought from ICD-10 and OPCS-4 codes.[237] Generation of each code list requires at least two clinicians agreeing on initial search terms and matching codes from the relevant code dictionary. Additional codes were identified by hand searching the NHS Read code browser, asking for suggestions from colleagues who had produced lists for other studies, or identifying code lists in published studies or reports. Two clinicians rated the identified codes for relevance against agreed definitions and assigned response categories (i.e. 'not indicated', 'possible', 'definite', 'history of'). Any disagreements were resolved assuming worst case scenario in order to increase the sensitivity of the code search.[126]

The next stage was to define the way in which the information in relevant records is combined to create research-ready data, which must be agreed upon by both clinical and non-clinical researchers. A response category was created if there were code conflicts arising from different data sources, allowing researchers to use their discretion to handle the conflicts.[126] A final format for CALIBER variable definitions included several elements as depicted in **Figure 3.2 on page 108**.

Development of algorithms resolved duplication and contradiction in the final CALIBER variables created as well as helping to maintain consistencies for further creation of a phenotyping algorithm for a study (disease endpoint, disease start-point, exclusions, and covariates).[126] In addition to coded data, EHR can store a considerable volume of clinical information entered as free-text, often documenting early symptoms before a formal diagnosis. In response to the growing interest in methods for retrieving free-text data for research purposes, the CALIBER group has also developed an algorithm to extract information from the free-text fields of EHRs.[125]

Development of CALIBER variables and coding algorithms had gone through a process of multiple clinical specialty review across two institutions (UCL and London School of Hygiene and Tropical Medicine [LSHTM]). Professor Harry Hemingway (clinical epidemiology), Professor Liam Smeeth (general practice), Professor Adam Timmis (clinical cardiology), Dr Anoop Shah (clinical pharmacology), Dr Kate Walters (general practice) and Dr David Osborne (psychiatry), all provided clinical expertise in the development of the CALIBER code lists. Professor Spiros Denaxas provided technical advice and wrote the programs to extract the relevant records. Dr Emily Herrett and Dr Julie George wrote the Stata do-files for selecting the Read code lists and drafted CALIBER variable definitions, Dr Ruzan Udumyan further developed do-files and drafted variable definitions for the mental health portion of the CALIBER manual.[126,237]

3.6 Storage and access

Master raw data are stored in a secure server in a MySQL database which are accessible only to the data manager. Data extraction for a particular research project is restricted to the definition of the study cohort and datasets can be supplied in a raw form or CALIBER variables. I chose to request the latter to ease data processing and analysis for my thesis. The final datasets released to researchers are treated as sensitive data because the amount of individual information remains quite detailed despite being presented in a pseudonymised form. Access to CALIBER data operates in a safe-haven environment, requiring researchers to be physically present at UCL, LSHTM or other collaborating institutions.[128]

CALIBER staff have curated more than 300 base and composite variables on medical history, diagnosis, investigations, procedures and prescriptions using established metadata standards in a transparent and reproducible manners. A web portal (www.caliberresearch.org) is dedicated to document descriptions of CALIBER variables or phenotypes, algorithms or flow diagrams for phenotype creation, and lists of Read, ICD-10 or OPCS codes used to define variables. The portal facilitates data preparation for research but users need to register to access such information in detail.

Figure 3.2 Screenshot of CALIBER portal displaying diabetes phenotyping

CALIBER Home Publications Data Portal Tracker Contact Hafidha

Definition Images Comments

Diabetes phenotype

Name	phenotype_diabetes
Chapter	Endocrine, nutritional, metabolic/Diabetes
Definition	Classification of diabetes as type 1, type 2, unclassified diabetes or no diabetes on a particular index date per patient. The algorithm uses only diagnosis information (not medication) recorded on or before the index date; this avoids the problem of immortal time bias (patients who survive are more likely to have their diabetes classified as type 1 or type 2; those that die are more likely to remain unclassified). The age at diagnosis is frequently unclear so it is not used in this algorithm. The algorithm combines information from specific diagnostic codes for type 1 and type 2 diabetes with less specific codes for 'insulin dependent diabetes' (IDDM) and 'non-insulin dependent diabetes' (NIDDM). This algorithm is designed primarily to detect patients with type 2 diabetes who can be on any medication, so medication is not particularly helpful for identifying these patients. Further refinements and validation would be required to detect a patients with type 1 diabetes with greater recall.
Data sources	GPRD, HES
Dictionaries	Read, ICD 10
Repeated	No
Agreed	31/10/2013 (Revision 1)
Implementation	IF there is at least one record for code for type 2 diabetes (diabdiag_gprd = 4) and no record for type 1 diabetes (no record with diabdiag_gprd = 3) then classify the patient as type 2 diabetes ELSE if there is at least one record for code for type I diabetes (diabdiag_gprd = 3) and no record for type 2 diabetes (no record with diabdiag_gprd = 4) then classify the patient as type 1 diabetes ELSE if there is at least one record of type 1 diabetes (diabdiag_gprd = 3) and type 2 diabetes (diabdiag_gprd = 4) then classify as diabetes of uncertain type ELSE if there are no diabdiag_gprd records for this patient: If there is at least one record for NIDDM (dm_gprd = 4 or dm_hes = 4) and no record for IDDM (no record with dm_gprd = 3 or dm_hes = 3) then classify the patient as type 2 diabetes ELSE there is at least one record for IDDM (dm_gprd = 3 or dm_hes = 3) and no record for NIDDM (no record with dm_gprd = 4 or dm_hes = 4) then classify the patient as type 1 diabetes ELSE if there is at least one record of diabetes (dm_gprd or dm_hes category 3, 4 or 6) then classify as diabetes of uncertain type ELSE classify as no diabetes

Phenotype components

Variable	Title	Categories
diabdiag_gprd	GP diagnosis of diabetes	
dm_gprd	Diabetes diagnosis (primary care)	
dm_hes	Diabetes diagnosis (secondary care)	

← Back

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3.7 Strengths and limitations

3.7.1 Strengths

As a research platform aiming to provide translational evidence across different clinical stages, the strengths of CALIBER stem from the combination of its data sources which allow coverage of the whole spectrum of clinical care in a large UK population.

Efficiency and temporal resolution. Data gathering and patient recruitment is made easier once the participating practices or institutions agree to opt in for linkage. All data from consenting patients becomes automatically available for research purposes and may incur no research cost. The updated clinical recording also means that follow-up monitoring, particularly in primary care, can be done with relatively little effort for either investigations, treatments or outcomes. Additionally, the CALIBER data's timespan of at least 12 years allows researchers to flexibly define the study time window with adequate temporal resolution.[128] This makes CALIBER an ideal platform for identifying newly diagnosed cases, investigating healthcare sustainability as well as specifying the first manifestation of chronic complications. The latter becomes increasingly important over aggregated endpoints as often used by many studies investigating vascular diseases (e.g. combining fatal myocardial infarction with cardiovascular death) in the sense that it distinguishes onset from progression and enables more appropriate intervention to primary prevention of across vascular beds.[128,244]

Large sample size, accuracy and generalisability. Holding a considerable volume of real-world clinical data, CALIBER enables exploration of differential effects across different subgroups with adequate accuracy and power that often cannot be shown by traditional epidemiological studies. A large CALIBER study has documented higher incidence of twelve CVDs by T2D status and different risk levels for CVDs by age and gender, the results of which are applicable to the general population.[4] Such research is of great importance since personalised care can help promote more effective healthcare delivery.

Inclusion criteria flexibility. Unlike bespoke cohorts, participants covered by EHRs are not restricted to particular health condition. This offers flexibility to carry out varied research targeting different populations without having to be logistically busied by new recruitment. In this regard, though all my studies focused on incident T2D cases, they were not similar in terms of cohort size due to the application of different inclusion criteria.[128,244]

Resolution of clinical phenotypes. The massive CALIBER data pool allows in-depth exploration of diverse risk factors and disease phenotypes at a high level of resolution. Numerous types of measurement on risk factors in primary care offer flexibility for investigation of a line of exposures, enabling individual risk assessment. Importantly, disaggregation of unified CVDs with shared underlying cause into distinct, contemporary coronary, cerebral and other vascular bed endpoints is made possible by linkage to secondary care data and the disease and death registry. This implies that milder stages of CVDs such as angina and TIA or rare endpoints such as AAA can now be detected.[128,244]

3.7.2 Limitations

Unfortunately, the EHRs also carry many challenges for they have been developed to facilitate clinical management rather than research purposes.

Completeness. CALIBER data can be largely missing in the senses that patients move to other practices for their care, data are only recorded during clinical episodes, or data are simply missing by mistake. Patient transfer to other practices may result in data fragmentation for research and, importantly for my study, partial assessment of clinical care. Even data linkage by single patient identifier may not be adequately pervasive to address this issue. In addition, data recording usually corresponds to illness; irrelevant conditions to illness, risk factors in healthy individuals, investigations or measurements often seen as trivial (such as ethnicity, physical activity, smoking status, or BMI) may not be well-recorded. Data that would normally be expected in the records can also be missing unintentionally. Consequently, the absence of possibly requisite data can be treated by a researcher as missing information or else interpreted as a negative finding.[128,237]

Data quality and validation. Errors can occur anywhere in the recording process – from patient observation, through conceptualisation of results, to data recording – which can impact on the study accuracy and, in turn, predictive power. A study drawn from the THIN database with a combined population of 72,000 and diabetes prevalence of 2.9% reported that 10% of diabetes diagnoses had coding errors, 12.1% were misclassified and 17.0% were misdiagnosed as having diabetes.[245] Even in the absence of errors, there still may be a mismatch between the nominal definition of a system-defined concept and the purpose of the researcher,[125,126] a potential case in the context of my thesis being the definition of diabetic nephropathy (discussed later on in **Section 3.10.2 on pages 116-117**). Additionally, selecting a measurement of interest in the availability of multiple parameters (e.g. laboratory data) and further checking the outliers and consistency of the measurement unit can add another challenge. These nuisances entail assiduous data exploration and cleaning before analysis, rigorous justification for phenotyping and, importantly, validation to minimise biases.[125,126]

Complexity. System heterogeneity among CALIBER's data sources indicates that training on informatics can be fundamental for a researcher in order for them to have a good knowledge of the individual database and its structure. Healthcare data can involve a complex set of processes with many feedback cycles (e.g. from laboratory results, treatment intensification due to a patient's non-responsiveness to intervention, advice from specialists), producing non-linear recording effects that do not reflect the underlying physiology that researchers may wish to study.[237] Linking different data sources is not a simple process either as inconsistencies can transpire in many forms. Some examples are the differences in values of measurements, different types of diseases between datasets, creation of new variables that are more suitable for analysis, linking to wrong patients, and differences in the dates of events or risk factor recording. The latter needs particular treatment if chronological presentation of disease is emphasised as in my study; sorting multiple data recorded on the same day is a stochastic process (i.e. rendering unstable order when

performed repeatedly), thus recoding the dates into an ordinal number would be useful to maintain chronological stability.

3.8 Ethics and governance

CALIBER has received ethics approval (09/H0810/16) from the Lewisham Local Research Ethics Committee for a record linkage project and ECC approval (ECC 2-06(b)/2009) for the CALIBER dataset.[128] Individual studies using CALIBER data have been approved by the CPRD Independent Scientific Advisory Committee (ISAC) of the MHRA and MINAP Academic Group (MAG). Ethics approval is, therefore, not specifically required for this thesis study because only anonymised data is used. The study investigating the association of T2D with initial presentation of CVDs falls within the remit of ISAC 'Initial presentation of cardiovascular diseases' protocol 12_53R and is registered on clinicaltrials.gov (unique identifier NCT01804439).[4]

3.9 T2D phenotyping and generation of thesis cohort

The phenotype of a patient refers to a set of observable characteristics of the patient which can include either clinical measurements or disease status.[125] Lack of common data fields and data definitions among multiple data sources can be highly challenging. To that effect, CALIBER develops algorithms to capture, ascertain and validate a sizeable number of disease phenotypes. This harmonisation effort standardises and improves the accuracy of diagnosis and, by drawing on all constituent data sources, avoids the underestimation of disease incidence that occurs if just one EHR source is used. Disease phenotyping is performed through a combination of diagnostic codes, investigational codes (e.g. clinical examinations and biomarkers), clinical procedure codes and medication prescription codes. By using different data sources, disease phenotypes can be inferred from relevant investigations or procedures in the absence of explicit diagnosis.[128]

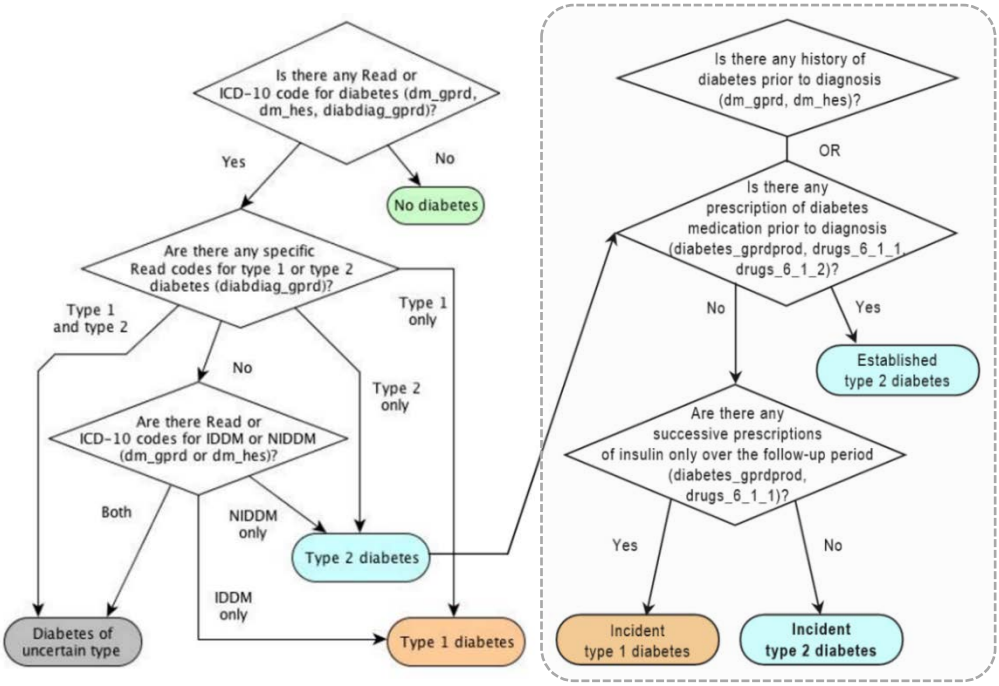
Numerous studies utilising CALIBER data have been published, most of which typically used diabetes – being an important confounder – for adjustment in the association models for gender,[246] ethnicity,[247] deprivation,[248] smoking,[249] blood pressure,[250] and depression[251] with initial presentation of a wide array of CVDs. One particular study has investigated the contemporary association of T2D with CVDs and described in detail the phenotyping algorithm for T2D[4] that I adopted to define my study cohorts. In this large cohort study with over 1.9 million individuals, around 34,000 (1.8%) were identified as having T2D at baseline and another 51,690 were newly diagnosed with diabetes during follow-up with a median time to diagnosis of 4.9 years. The algorithm for T2D phenotyping combined specific diagnostic codes for T2D with less specific codes for non-insulin dependent diabetes mellitus (NIDDM) from either primary or secondary care. C10 is the 'parent' Read code for T2D, whereas the 3-digit E11 code from ICD-10 covers all diagnoses relevant to NIDDM (**Appendix D, Table D1 on pages 330-333** for detailed codes). Diabetes phenotypes (including T1D and unspecified type) are curated under diabdiag_gprd, dm_gprd and dm_hes variables in CALIBER.

Incident T2D phenotyping algorithm. Due to the limitations of natural clinical coding (e.g. variability among practices in diagnosis, level of diagnosis resolution, and the associated

codes) the current CALIBER algorithm for T2D phenotyping was not designed to accurately identify incident T2D cases. The approach for algorithm development is somewhat conservative in the sense that only diagnostic codes were used for capturing the disease; therefore, not all patients can be classified into a particular diabetes type. In fact, nearly 50% of patients were reportedly left as unclassified types.[4] Consequently, T2D prevalence is likely to be underestimated as suggested by other studies documenting a higher estimate.[48,134] However, in the absence of explicit or indicative codes for diabetes type, it remains speculative to infer a particular type of diabetes from other pertinent investigation and medication data. Thus, for this PhD, the focus has been to ascertain whether a T2D case identified by the current algorithm is newly diagnosed rather than to further ensure whether patients falling within unclassified types do indeed have T2D.

In my attempt to identify incident T2D cases, I examined whether the index diagnosis was preceded by any historical record of diabetes. I have also added medication criteria into the existing phenotyping algorithm (**Figure 3.3 below**, right panel) based on the assumption that prior diabetes prescriptions before index T2D diagnosis indicates an established case or history of the disease. This entails the use of diabetes medication data in CALIBER variables, namely drugs_6_1_1, drugs_6_1_2 and diabetes_gprdprod variables to further restrict the T2D cohort to new cases only.

Figure 3.3 Phenotyping algorithm for incident T2D in CALIBER



Modified from: https://caliberresearch.org/portal/phenotypes/diabetes

Incident T2D case definition. Patients were identified as being newly diagnosed with T2D on the date of the earliest recorded Read code or ICD-10 code indicative of the diagnosis, so long as there was no prior history of diabetes and/or diabetes medication. With the exception of metformin – which is also indicated for polycystic ovary syndrome – diabetes medications are consi-

dered highly specific for the disease. Thus, a one-off prescription of a diabetes drug prior to diagnosis was sufficient to exclude patients from my study cohorts. I did not, however, infer diagnosis from prescription of diabetes medications for patients who do not have an explicit or indicative diagnostic code for T2D, since doing so may introduce a false negative.[252] Additionally, consecutive prescriptions of insulin after the index diagnosis without prescription of OHAs were considered indicative of T1D and excluded patients from the study. The index date for my study cohorts was defined as the earliest date of T2D diagnosis after applying these criteria.

General inclusion and exclusion criteria for incident T2D cohort. I used the following inclusion criteria when drawing my main study cohort from CALIBER:

- Patients were of AQR
- Gender was recorded as either male or female
- Registered in CPRD practices consenting to data linkage
- Registered on or after 1 January 1997
- ≥30 years of age at the time of T2D diagnosis
- ≥12 months of UTS registration before T2D diagnosis (to provide sufficient time to establish prevalent and historical diagnoses and to measure risk factors[253])
- ≥12 months of follow-up between date of T2D diagnosis and 25 March 2010
- Newly diagnosed T2D

A combination of all constituent data was used to define the general exclusion criteria which include having a date of death before the index date or having multiple dates of death.

The main T2D cohort formed from the above criteria was particularly relevant for Study 1 (temporal trends in care). For the remaining studies, however, I applied dissimilar additional criteria and follow-up period in order to avoid selection bias while trying to answer different research questions. Details of inclusion and exclusion criteria and observation period for each individual study were listed in the corresponding chapters.

3.10 Other diseases phenotyping

Besides diabetes, a wide range of diseases have been phenotyped in a transparent and reproducible manner as documented in the CALIBER portal.

3.10.1 Cardiovascular diseases

CALIBER has successfully phenotyped CVDs into at least twelve specific entities using the constituent data sources summarised in **Table 3.3 on page 116** (more details on the Read and ICD-10 codes used are shown in **Table D2 on pages 333-337**). The CVD phenotypes are replicated in my studies and defined as follows:

Stable angina (SA). Defined by a coded diagnosis of stable angina or ischaemic chest pain in primary or secondary care, prescriptions of at least two antianginal medications, coronary revascularisation beyond 30 days of an admission for unstable angina or myocardial infarction, or an abnormal functional or anatomical test (stress echocardiogram, exercise ECG, coronary angio-

gram or myocardial perfusion scan). Coronary revascularisation encompasses percutaneous coronary intervention (PCI or angioplasty) and coronary artery bypass graft (CABG or heart bypass) which were defined from CPRD, HES and MINAP. CALIBER variables to phenotype SA are curated in the portal as chest_pain_gprd, sa_diagnosis_gprd, cabg_gprd, pci_gprd, stress_echo_gprd, eecg_gprd, recg_gprd, inv_angio_gprd, ct_angio_gprd, mr_angio_gprd, radio_scan_gprd, cabg_opcs, angina_hes, angina_meds, and pci_opcs.

Unstable angina (UA). Defined by a coded diagnosis of unstable angina or acute ischaemic heart disease in primary or secondary care, or an ACS without records of myocardial infarction in the disease registry. CALIBER variables to phenotype UA are curated in the portal as follows: unangina_gprd, acs_gprd, acute_ihd_hes, uangina_hes and uangina_minap.

Non-fatal myocardial infarction (MI). Defined by a coded diagnosis of myocardial infarction in primary or secondary care, coronary reperfusion therapy (thrombolysis, primary PCI) or an acute coronary syndrome with raised troponin in the disease registry. CALIBER variables to phenotype non-fatal MI are curated in the portal as follows: myo_infarct_gprd, myo_infarct_hes, lysis_opcs, mi_minap and mi_ons.

Unheralded coronary death (UCD). Defined as death from coronary heart disease as the underlying cause in ONS without prior history of any CVDs recorded in primary or secondary care or the disease registry. The definition includes patients with myocardial infarction who died on the day of their infarct. CALIBER variables used to phenotype UCD are the same as for MI phenotyping.

Coronary heart disease not otherwise specified (CHD NOS). Defined as patients with a non-specific diagnosis of ischaemic or CHD in primary and secondary care. CHD NOS is not considered a specific CVD endpoint.

Heart failure (HF). Defined by a coded diagnosis of heart failure or left ventricular dysfunction on a resting ECG in primary care, secondary care, or death certificates with heart failure as the underlying cause. CALIBER variables to phenotype heart failure are curated in the portal as follows: hf_gprd, echo_gprd, hf_hes and hf_ons are used to phenotype HF.

Arrhythmia or sudden cardiac death (SCD). Defined from primary care, secondary care or death certificates as a composite diagnosis of ventricular arrhythmia, cardioversion procedures, implanted cardiac defibrillator and sudden cardiac death. This definition with cardioversion included was used in Study 3. As the majority of patients undergoing cardioversion had atrial fibrillation than ventricular arrhythmia, the codes for cardioversion were removed and used later to define atrial fibrillation, an additional endpoint considered in Studies 4 and 5. CALIBER variables to phenotype SCD are curated in the portal as: arrest_gprd, arrest_hes, arrest_opcs, arrest_ons, sudden_death_gprd, sudden_death_hes and sudden_death_ons.

Transient ischaemic attack (TIA). Defined as primary or secondary care diagnosis of transient ischaemic attack. CALIBER variables to phenotype TIA are curated in the portal as follows: tia_gprd and tia_hes variables.

Ischaemic stroke. Defined by a coded diagnosis of ischaemic stroke in primary care, secondary care or death certificates. The definition includes patients with a coded procedure of carotid endarterectomy within 90 days of an unspecified type of stroke. CALIBER variables to phenotype ischaemic stroke are curated in the portal as ischaemic_gprd, ischaemic_hes and ischaemic_ons.

Subarachnoid haemorrhage (SAH) and intracerebral haemorrhage (ICH). Each was defined by a coded diagnosis in primary care, secondary care or death certificates. CALIBER variables to phenotype SAH and ICH are curated in the portal as follows: haem_stroke_gprd, haem_stroke_hes and haem_stroke_ons.

Stroke NOS. Defined as diagnosis of stroke in primary and secondary care which does not explicitly state stroke type (ischaemic or haemorrhagic). Similar to CHD NOS, stroke NOS is not considered a specific CVD endpoint.

Abdominal aortic aneurysm (AAA). Defined by a coded diagnosis or repair procedure in primary or secondary care, or death certificates with abdominal aortic aneurysm as the underlying cause. CALIBER variables to phenotype AAA are curated in the portal as follows: arterial_gprd, arterial_hes, aaa_ops_gprd, aaa_procs_opcs and aaa_ons.

Peripheral arterial disease (PAD). Defined as a primary or secondary care diagnosis of peripheral vascular disease, intermittent claudication, limb ischaemia or gangrene due to leg or aortic embolism or thrombosis, PAD procedures, an abnormal result from PAD tests (i.e. ultrasound scan or angiography) or a coded diagnosis from death certificates as the underlying cause. CALIBER variables to phenotype PAD are curated in the portal as follows: arterial_gprd, pad_ops_gprd, pad_angio_gprd, pad_us_gprd, pad_ procs_opcs, arterial_hes and arterial_ons.

Atrial fibrillation (AF). Defined by a coded diagnosis of AF, related medications and procedures in primary or secondary care. AF was not considered in my first three studies, either as an endpoint or exclusion criterion. CALIBER variables to phenotype AF are curated in the portal as: af_gprd, af_hes, af_gprdprod, af_proc_gprd and af_proc_opcs.

In Study 2 about predictors of meeting target for intermediate outcomes (**Chapter 5**), all of these phenotypes have been used to identify patients with CVD present at baseline, i.e. on or 12 months before the index date. As potential analytic covariates, angina and myocardial infarction have been grouped as coronary heart diseases (CHD), while TIA, ischaemic and haemorrhagic stroke have been grouped as cerebrovascular diseases.

In Study 3 on the relationship between meeting target for intermediate outcomes and CVDs (**Chapter 6**), patients with prior CVD have been excluded. The primary endpoint is initial presentation with any of the twelve CVDs identified in **Table 3.3 on page 116** (excluding CHD

NOS, stroke NOS and atrial fibrillation), defined as the earliest date of diagnosis after the index date in any of CALIBER's data sources. Cardiovascular events that postdate the initial presentation have been ignored. Secondary endpoints are cardiovascular mortality and all-cause mortality, the former defined as a composite of death caused by any CVD, while the latter includes cardiovascular and non-cardiovascular mortality.

In Study 4 about duration at glycaemic target and CVDs (**Chapter 8**), AF was added to exclude patients with an event prior to the index date and as a component of the composite cardiovascular endpoints used.

Table 3.3 EHR sources for CVD phenotypes in CALIBER

Phenotype	CPRD (Read codes)	HES (ICD-10)	HES (OPCS-4)	MINAP	ONS (ICD-10)
Stable angina	●	●	●		
Unstable angina	●	●		●	
Myocardial infarction	●	●	●	●	
Unheralded coronary death	○	○	○	○	●
Coronary heart disease NOS	●	●			
Heart failure	●	●			●
Arrhythmia/sudden cardiac death	●	●	●		●
Transient ischemic attack	●	●			
Ischemic stroke	●	●	●		●
Subarachnoid haemorrhage	●	●			●
Intracerebral haemorrhage	●	●			●
Stroke NOS					
Abdominal aortic aneurysm	●	●	●		●
Peripheral arterial disease	●	●	●		●
Atrial fibrillation	●	●			

● Primary EHR source ○ Secondary EHR source to exclude any CVD
NOS, not otherwise specified.

3.10.2 Microvascular diseases

Microvascular disease phenotypes were used in Study 5 where their associations with time spent at glycaemic target were explored. The existing CALIBER phenotypes for these study endpoints were extracted from a coded diagnosis in primary and secondary care and are currently curated under diabcomp_gprd and diabcomp_hes variables in the portal. Classification includes four microvascular disease phenotypes: diabetic nephropathy, diabetic neuropathy, diabetic retinopathy and other diabetic eye diseases (DEDs). For the purpose of my study, however, I sought to explore other clinical investigation data in order to determine if they can be used to help infer the current phenotypes for greater capture. My approach to redefine, improve and validate microvascular disease phenotyping is discussed in detail in **Chapter 9** but briefly described below:

Diabetic nephropathy. Rather than using a readily available phenotype for diabetic nephropathy, I defined it differently as worsening chronic kidney disease (CKD) towards a higher stage, in order to anticipate a longer period needed for nephropathy as a single disease entity (or a particular CKD stage) to occur. CKD stage was determined from the estimated value within

a particular timeframe of glomerular filtration rate (eGFR). eGFR values were calculated from serum creatinine measurements in primary care using CKD-EPI formula and curated under the egfr_ckdepi_gprd variable in CALIBER. The eGFR-based CKD stage may be different from GP-entered diagnosis for CKD stage because the latter may be based on hospital creatinine measurements and ignores acute kidney injury. Recorded CKD stage, other renal disease diagnoses and renal dialysis procedures were not used to further ascertain the eGFR-based nephropathy phenotype to avoid conflicting or undetermined CKD stages.

Diabetic neuropathy. In addition to the available phenotype for diabetic neuropathy, I explored the possibility of inferring diabetic neuropathy from foot examination performed in primary care. Relevant codes to identify recorded abnormal results from ankle vibration tests are curated under gprd_ra_vibr and gprd_la_vibr variables in CALIBER.

Diabetic retinopathy. In the absence of supporting clinical investigation data to help infer diabetic retinopathy, I used a coded diagnosis only in primary and secondary care (including maculopathy) for phenotyping. CALIBER variables for phenotype diabetic retinopathy are curated under diabcomp_gprd and diabcomp_hes in the portal.

Other DEDs. In addition to the available phenotypes for non-retinal DEDs such as cataract, glaucoma or unspecified DED, I explored other eye-related investigation data in primary and secondary care to help expand capture of these complications. Relevant codes to infer other DEDs (including blindness inferred from visual acuity tests) are curated under glaucoma_gprd, glaucoma_hes, va_right_gprd and va_left_gprd variables in CALIBER.

3.10.3 Comorbidities

Relevant comorbidities including renal disease, COPD, and depression and anxiety, where necessary, will be accounted for in my PhD research.

Renal disease. In Studies 1 to 4, renal disease as a comorbid condition is defined as a primary or secondary care diagnosis for any renal disease (regardless of type and severity) or kidney dialysis procedure. Relevant codes to identify renal diseases and procedures are curated in the CALIBER portal under renal_gprd, renal_hes, nephritic_nephrotic_gprd, ckdstage_gprd, dialysis_gprd and dialysis_opcs variables.

Chronic obstructive pulmonary disease (COPD). Defined as a coded diagnosis of COPD or exacerbation of COPD recorded in primary or secondary care. Relevant codes to identify COPD are curated in CALIBER under copd_gprd, copd_exac_gprd and copd_hes variables.

Anxiety and depression. Anxiety is defined as a coded diagnosis of anxiety or phobia in primary care (anxiety_gprd) or secondary care (anxiety_phobia_hes), whilst depression is defined by a coded diagnosis in primary care (depression_history_gprd).

3.11 Identification of quality indicators of diabetes care

In analysing quality of T2D care, the first three studies in this PhD were orientated towards the 2004 QOF indicators.[112] The main focus has been on measurements of HbA1c, blood pressure and total cholesterol since these are particularly relevant to cardiovascular risk reduction, although the other quality of care QOF indicators listed in **Table 3.4 on pages 120-121** have also been assessed in Study 1. QOF indicators for diabetes currently unavailable in CALIBER are smoking cessation advice (DM 4), retinal screening (DM 8) and influenza vaccination (DM 18); therefore, these were not investigated.

3.11.1 Processes of care

All care process indicators were sourced from CALIBER's primary care record; most of them were dichotomously classified to indicate that a particular indicator was measured (**Table 3.4 on pages 120-121**). Temporal trends in QOF process measurements are reported in Study 1 while they are the main exposure of interest in Study 2. All care process measurements were, therefore, defined as proportions on a yearly basis in Study 1, while HbA1c, blood pressure and total cholesterol were defined as frequency of measurements within the first year in Study 2.

Body mass index. Patients with any record of BMI values (extracted from height and weight data) were classified into measured, otherwise into unmeasured for those without any records.

Smoking status. Patients with any recorded smoking status (non-smoker, ex-smoker, current smoker and conflicting smoking status) were classified into measured, otherwise into unmeasured.

HbA1c. Patients with any HbA1c records were classified into measured, otherwise into unmeasured.

Blood pressure. Patients with any records on blood pressure were classified into measured, otherwise into unmeasured.

Total cholesterol. Patients with at least one total cholesterol record were classified into measured, otherwise into unmeasured.

Peripheral pulse. Patients with at least one record on dorsalis pedis or posterior tibial pulse examination, regardless of the results, were classified into measured, otherwise into unmeasured.

Neuropathy. Patients with at least one record for ankle vibration sense (AVS) test to examine the presence of neuropathy, regardless of the results, were classified into measured, otherwise into unmeasured.

Serum creatinine. Patients with at least one serum creatinine record were classified into measured, otherwise into unmeasured.

Microalbuminuria. Patients with any record for proteinuria test were classified into measured, otherwise into unmeasured.

Proteinuria or microalbuminuria treated with ACEIs/ARBs. Patients with a coded diagnosis of protein- or microalbuminuria were categorised into diagnosed and treated if there were any records on prescription of drugs affecting the renin-angiotensin system (BNF Chapter 2.5.5), otherwise into diagnosed but untreated.

3.11.2 Intermediate outcomes of care

Achievement of intermediate outcome measures are a central component of all my studies but were defined differently across the studies. HbA1c, blood pressure and total cholesterol were all extracted from primary care records as continuous measures and classification of target achievement was subject to the study objectives.

QOF outcome achievements are reported in Study 1 as yearly proportions while they are the main outcome of interest assessed within the second year in Study 2 and the main exposure of interest assessed within the first year since T2D diagnosis in Study 3 (relationship with CVDs). Proportional duration at HbA1c target in Study 4 (relationship with CVDs) and Study 5 (relationship with microvascular diseases) were estimated according to NICE's target for HbA1c.

HbA1c. Patients with at least one HbA1c measure ever reaching 7.4% (57.4 mmol/mol) or less were classified into achieved in Study 1. Similarly, they were classified into achieved in Studies 2 and 3, otherwise into did not achieve if they never reached the target, or unmeasured if they were never tested. HbA1c level was converted from mmol/mol to % in Studies 1 to 3 to conform to the QOF unit of measurement.

In Studies 4 and 5, yearly average of duration at HbA1c target (≤6.5% or 48 mmol/mol) is calculated from longitudinal HbA1c records since the index date up to presentation of a complication. NICE target for HbA1c was chosen over the QOF's in the last two studies to represent most recent recommendation. Duration spent at glycaemic target was measured specifically using a novel metric. Patients were then classified into missing and five time interval categories. A more detailed explanation on development of the metric and the ensuing time-based quantification and classification of glycaemic control is presented in a dedicated chapter (**Chapter 7**).

Blood pressure. Patients with at least one blood pressure record ever reaching ≤145/85 mmHg were classified into achieved in Study 1. Similarly, they were classified into achieved in Studies 2 and 3, otherwise into did not achieve if they never reached the target, or unmeasured if they were never tested.

Total cholesterol. Patients with at least one total cholesterol record ever reaching ≤5 mmol/L were classified into achieved in Study 1. Similarly, they were classified into achieved in Studies 2 and 3, otherwise into did not achieve if they never reached the target, or unmeasured if they were never tested.

Table 3.4 CALIBER variables and categories for quality of diabetes care indicators

Quality of care indicator	QOF indicator	CALIBER variable	Type	Title	Definition
Process of care					
Body mass index measurement	DM 2	bmi_gprd	continuous, repeats	Record of body mass index measurement (primary care)	*binary reclassification by record (recorded/not)*
Smoking status	DM 3	smoking_status_gprd	categorical, repeats	Record of smoking status (primary care)	1 – non-smoker 2 – ex-smoker 3 – ex or current smoker* 4 – current smoker 5 – code conflict (ex & current)* 6 – code conflict (non & current)*
HbA1c measurement	DM 5	hba1c_gprd	continuous, repeats	Record of HbA1c measurement (primary care)	*binary reclassification by record (recorded/not)*
Peripheral pulse check†	DM 9	pulse_ldp_gprd	categorical, repeats	Record of left dorsalis pedis pulse examination (primary care)	1 – normal/increased 2 – absent 3 – diminished
		pulse_rdp_gprd	categorical, repeats	Record of right dorsalis pedis pulse examination (primary care)	1 – normal/increased 2 – absent 3 – diminished
		pulse_lpt_gprd	categorical, repeats	Record of left posterior tibial pulse examination (primary care)	1 – normal/increased 2 – absent 3 – diminished
		pulse_rpt_gprd	categorical, repeats	Record of right posterior tibial pulse examination (primary care)	1 – normal/increased 2 – absent 3 – diminished
Neuropathy test†	DM 10	la_vibr_gprd	categorical, repeats	Record of left ankle vibration sense test (primary care)	1 – normal 2 – absent 3 – diminished
		ra_vibr_gprd	categorical, repeats	Record of right ankle vibration sense test (primary care)	1 – normal 2 – absent 3 – diminished

Blood pressure measurement	DM 11	bp_gprd	continuous, repeats	Record of blood pressure measurement (primary care)	*binary reclassification by record (recorded/not)*
Microalbuminuria test	DM 13	proteinuria_tested_gprd	categorical, repeats	Record of proteinuria test (primary care)	1 – tested
Serum creatinine measurement	DM 14	crea_gprd	continuous, repeats	Record of serum creatinine measurement (primary care)	*binary reclassification by record (recorded/not)*
Protein-/microalbuminuria treated with ACEI/ARB‡	DM 15	proteinuria_diag_gprd	categorical, repeats	Record of proteinuria diagnosis (primary care)	5 – diagnosis (proteinuria) 6 – microalbuminuria
		blood_pressure_lowering_medication_gprd	categorical, repeats	Record of prescription of blood pressure lowering medication (primary care)	BNF chapter 2.5.5 – drugs affecting the renin-angiotensin system
Total cholesterol measurement	DM 16	total_chol_gprd	continuous, repeats	Record of total cholesterol measurement (primary care)	*binary reclassification by record (recorded/not)*
Intermediate outcome					
HbA1c ≤7.4% or 57.4 mmol/mol (HbA1c ≤6.5% or 48 mmol/mol)	DM 6 (NICE)	hba1c_gprd	continuous, repeats	Record of HbA1c measurement (primary care)	▪ *categorical reclassification by threshold (attained/not/unmeasured)* ▪ *categorical reclassification by time-based threshold (duration at target categories)*
Blood pressure ≤145/85 mmHg	DM 12	bp_gprd	continuous, repeats	Record of blood pressure measurement (primary care)	*categorical reclassification by threshold (attained/not/unmeasured)*
Total cholesterol ≤5 mmol/L	DM 17	total_chol_gprd	continuous, repeats	Record of total cholesterol measurement (primary care)	*categorical reclassification by threshold (attained/not/unmeasured)*

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNF, British National Formulary.
Italicised categories are reclassification for the purpose of this study. Shaded rows are key variables of interest.
*Conflicting categories for smoking status (i.e. 3, 5 and 6) remained counted towards trends in attainment of process of care (Study 1) since these indicate that records were taken despite inconsistent coding. Yet along with missing values for smoking status, these categories were reclassified as undetermined or unknown in Studies 2 and 3.
†Reclassified in Study 1 into binary variables, defined as recorded if there was at least one record taken from any component variables.
‡Reclassified in Study 1 into binary variable (diagnosed and treated *vs* diagnosed but untreated).

3.12 Identification of risk factors and covariates

In addition to comorbidities previously described in **Section 3.10.3 on page 117**, demographic and cardiovascular risk factors have been controlled for in Studies 2 to 5.

3.12.1 Demographic variables

Age and gender. Year of birth and gender are more accurately recorded in primary care than in hospital settings; therefore, data on age and gender were obtained from CPRD. Age at study entry (i.e. index T2D diagnosis) has been analysed as either a continuous or categorical (10-year bands) variable. Patients with indeterminate gender were excluded from my study cohorts.

Ethnicity. Ethnicity was obtained from CPRD and HES, and classified into white, black, south Asian, other, and unknown. Where there was discordance within or between data sources, ethnicity was determined from the latest record before the index date.

Social deprivation. Socioeconomic status has been obtained from ONS, provided as a weighted composite score based on the 2007 Index for Multiple Deprivation (IMD).[254] IMD measures deprivation in seven dimensions: income, education and training, employment, health and care, housing, crime, and living environment. The IMD data have been presented as quintile groups, the 5th quintile representing the most deprived group.

Duration of registration. Duration of registration prior to index date has been calculated as the time in years between the registration date with the GP practice and the date of initial diagnosis of T2D.

3.12.2 Cardiovascular risk factors

Physical activity. CPRD provides data on physical activity. The most proximate record in the year before the index date was used to classify baseline physical activity as inactive, moderate, vigorous or gentle. For patients without any record, physical activity was classified as unknown.

Body mass index. Baseline BMI was calculated from CPRD data using the most proximate height and weight measurements recorded in the year before the index date. BMI was categorised as underweight (BMI <18.5 kg/m^2), normal weight (≥18.5 to <25 kg/m^2), overweight (≥25 to <30 kg/m^2), obese class I (≥30 to <35 kg/m^2), obese class II (≥35 to <40 kg/m^2) or obese class III (≥40 kg/m^2). In patients with missing data on height and weight within the specified timeframe, BMI was classified as unknown.

Smoking status. Baseline smoking status was obtained using the most proximate record in the 12 months before the index date from CPRD. Classification was into non-smoker, ex-smoker and current smoker. In patients with conflicting or no clear smoking codes within the CALIBER data sources, smoking status was recorded as undetermined/unknown.

Blood pressure and hypertension. Blood pressure in CPRD is recorded as a systolic and/or diastolic continuous measure. In my studies, systolic blood pressure was also classified into <120 mmHg, 120 to <140 mmHg, 140 to <160 mmHg, 160 to <180 mmHg, ≥180 mmHg, and unknown

in patients with missing data. Diastolic blood pressure was classified into <60 mmHg, 60 to <85 mmHg, 85 to <95 mmHg, 95 to <105 mmHg, ≥105 mmHg and unknown. Baseline blood pressure was determined from the most proximate measurements in the year before the index date.

Hypertension was defined as at least two systolic and/or diastolic blood pressure readings of >145 mmHg and >85 mmHg, respectively. A record of blood pressure lowering medication was not used to diagnose hypertension because of competing indications for many of these agents.

Lipid profiles and dyslipidaemia. Blood lipid measurements (total cholesterol, LDL, HDL and triglyceride) were extracted from CPRD as a continuous measure, baseline values being those most proximate to the index date. Total cholesterol was further classified as normal/ desired (≤5 mmol/L), high (>5 mmol/L) and unknown in patients with missing data. LDL was also classified as normal (≤3 mmol/L), high (>3 mmol/L) and unknown, HDL was classified as normal (≥1 mmol/L), low (<1 mmol/L) and unknown, and triglyceride was classified as normal (≤1.7 mmol/L), high (>1.7 mmol/L) and unknown.

3.12.3 Diabetes medications

CALIBER provides detailed prescription data with diabetes medications being curated under the diabetes_gprdprod, drugs_6_1_1 and drugs_ 6_1_2 variables. Drug classes of interest for Studies 1 to 3 were insulin, metformin, sulphonylureas, thiazolidinediones, acarbose, DPP4 inhibitors and GLP1 receptor agonists.

In Study 1, the annual proportions of patients receiving any blood glucose lowering drugs within a defined year after diagnosis was estimated. Diabetes treatment patterns over time were then categorised into OHA monotherapy, multiple OHAs, insulin only, OHA plus add-on insulin, and no diabetes medication.

In Studies 2 to 5, diabetes treatment was dichotomously defined as whether or not any diabetes medication was prescribed during the first year after the index date.

3.12.4 Cardiovascular medications

Antihypertensive and lipid lowering agents are commonly prescribed to patients with diabetes for prevention of CVDs. Patients at higher risk of CVD may also receive antiplatelet agents. Prescription of these cardiovascular medications is recorded in CPRD and has been adjusted for – where necessary – in Studies 2 to 5.

Blood pressure lowering medications. Diuretics, β-adrenoceptor blockers, calcium channel blockers, RAS agents, vasodilators, adrenergic neuron blockers, α-adrenoceptor blockers and centrally acting antihypertensives are curated in the CALIBER portal under the blood_ pressure_ lowering_medication_gprd variable. Patients receiving at least two prescriptions within the baseline period were defined as being treated with blood pressure lowering medications.

Lipid lowering medications. Statins, bile acid sequestrants, ezetimibe, fibrates, nicotinic acid and omega-3 fatty acids are curated under lipid_regulating_drugs_gprdprod variable in

CALIBER. Patients with two or more prescriptions within the baseline period were defined as being treated with lipid lowering medications.

Antiplatelets. Aspirin, clopidogrel, prasugrel, dipyridamole, ticlopidine, tirofiban and abciximab are curated in CALIBER under antiplatelet_drugs_gprdprod variable. Patients with two or more prescriptions within the baseline period were defined as being treated with antiplatelet medications.

3.13 Statistical considerations

3.13.1 Missing data

As previously discussed, missing data are a common feature of EHRs and could lead to bias when not handled appropriately. I applied two different methods to deal with missing data in covariates. The first method is easier to implement and reflecting my PhD learning process.

Missingness indicators. In Studies 2 and 3, I used indicators of missingness for missing data in covariates, adopting an approach used by a cohort study using linked EHRs similar to CALIBER (apparently it was among precursor studies before CALIBER was formally established) which sought to determine the persistence of clopidogrel treatment after MI in primary care.[255] This ad-hoc method was done by creating a new category for variables with missing data and produced unbiased estimates of the treatment effect in RCTs irrespective of the missingness mechanism.[256] In observational studies, however, it has been criticised for introducing bias, the direction and size of which depend on the reason for or mechanism of missingness.[257] The indicator method will only provide unbiased estimates if either covariates are not mutually related and missingness is conditionally independent of outcome.[258]

Adopting this method for my studies does not connote a mere repeat of analyses already performed by previous CALIBER studies – in fact, none has attempted to focus on incident cohorts by the time I would have started my research. Datasets requested to the data manager for my studies would be provided individually for each variable. Therefore, for each of my studies where different eligibility criteria (and study period) were to be applied, I would have to (re)define the patient cohorts and, consequently, perform the data linkage repeatedly for each required variable for the cohorts before (re)classifying them and (re)identifying their missing values.

Multiple imputation. In Studies 4 and 5, I refined my approach by using a multivariate imputation using chain equations (MICE) method. An imputation method allows the inclusion of patients with incomplete data in analyses to minimise unnecessary biases, thereby increasing the study power and producing estimates that are more statistically reliable and applicable within clinical practice.[259] In principle, if data are missing at random (i.e. missingness of a variable is related to observed characteristics but not to unobserved characteristics), the observed data can be used to estimate the most likely value and replace (impute) the missing data. Imputation is usually done using a multivariable regression model. In multiple imputation, uncertainty from the imputed values is also accounted for.[258,260]

I separately estimated imputation models for men and women which included**:**

- Baseline covariates used in the main analysis
- Baseline measurements of covariates not considered in the main analysis (diastolic blood pressure, white cell count, haemoglobin, creatinine and alanine aminotransferase)
- Other medications at baseline (psychiatric agents and hormone replacement therapies)
- Comorbidities (history of depression, cancer, renal disease, COPD and liver disease)

Missing values for continuous covariates included prior (between 1-14 years before the index date) and post (up to 1 year after the index date) averages. Non-normally distributed variables were log-transformed for imputation and exponentiated back to their original scale for analysis. Five multiply imputed datasets were generated and logistic models were fitted to each dataset. Coefficients were combined using Rubin's rules.[261] The Kolmogorov-Smirnov test was used to compare the distribution of observed versus imputed covariates.

Where sample size was adequate, sensitivity analyses to assess reliability of both indicator and multiple imputation methods were performed by omitting participants with any missing data from the analysis. However, this complete case analysis results in loss of statistical power and is not considered a valid method for application in observational studies if data are missing at random.[260]

3.13.2 Competing risk analysis

My focusing on initial presentation of vascular complications (as primary endpoints in Study 3 and secondary endpoints in Studies 4 and 5) suggests that multiple vascular risks may be clinically recorded on the same day and, therefore, compete with each other to be defined as the earliest presentation. The concept of competing risks is more frequently used in cancer epidemiology where cancer relapse may compete with metastasis, adverse risks of treatment, or death as the censoring determinant.[262] Treating another presentation as the reason for censoring would violate the key assumptions of time-to-event analysis and potentially lead to overestimation.[263]

A number of CALIBER studies have previously adopted the competing risk analysis to describe and model the association of different risk factors with twelve CVDs.[4,246-250] Crude cumulative incidence function (CIF) was used to calculate the probability of occurrence of a specific endpoint at a given time point by taking competing risks into account. In this descriptive method, individuals were removed from the risk pool whenever a competing event occurred and the proportion of individuals at risk who experience that specific endpoint was summed. The specific-cause hazards of vascular risks and the effect of specific covariates were then modelled jointly using Cox regression.

I used the CIF in Studies 3 to 5 to compare the probability of a specific vascular endpoint using the respective main exposures and, applied the Cox models in Study 3 only, to examine the associations between achieving intermediate outcomes and 12 specific CVDs. In Studies 4 and 5, associations of duration at glycaemic target with CVDs and microvascular diseases were modelled

using logistic regressions rather than Cox regressions since calculation of duration at target could stretch from as early as the index T2D diagnosis to a time point just before the occurrence of an endpoint, suggesting that this exposure is indeed a pooled time function and time-to-event analysis is considered less appropriate in this regard.

3.14 Chapter summary

In this chapter, I have described in detail the constituent data of CALIBER, processes of linkage among data sources and conversion from raw data into research-ready variables, and CALIBER's strengths and weaknesses. CALIBER is a wealthy resource for large population-based studies but presents challenges at times due to the large volume of data held and the ensuing complexity. I further discussed the derivation of the incident T2D cohort and defined covariates and endpoints used across my studies. I also discussed my approach to handling data incompleteness and methods for identifying initial presentation of CVDs.

The following is the first data chapter in which I initially present the results of my cohort generation and characteristics of newly diagnosed T2D population in CALIBER before describing trends in T2D care since diagnosis.

Chapter 4

Study 1 – Temporal trends in quality of care in CALIBER's incident T2D cohort

Success is not final, failure is not fatal: it is the courage to continue that counts.
— Winston Churchill

4.1 Chapter outline

The first data chapter in this thesis presents analyses conducted to address the objective of Study 1, to describe temporal trends in quality of care in the CALIBER's incident T2D cohort. Additionally, this chapter explored the associations of demographic factors with the observed trends in care.

4.2 Abstract

Background. EHRs provide longitudinal data on care provision from real clinical settings. Identification of trends in quality of care in incident T2D can give insights into areas needing improvement and how to optimise care. Observational studies addressing this issue are lacking.

Objectives. To evaluate trends in process and outcomes of diabetes care in a newly diagnosed T2D population.

Methods. A population-based incident T2D cohort was drawn from CALIBER from date of first diagnosis until transferring out of practice, date of death or the last date of data collection. Key processes of care examined during follow-up were HbA1c, blood pressure and total cholesterol measurements, the temporal trends of which were calculated as yearly proportion of patients in receipt of the care processes, the denominator being the number of patients within the given year. Key outcomes of care were yearly proportion of patients ever measured who achieved the targets of the three measurements. Temporal trends in other processes of care and diabetes treatment were also examined. Post hoc analyses were carried out to explore how demographic factors may relate to the observed trends.

Results. A total of 52,379 incident T2D cases were identified from linked primary and secondary care records spanning over 12 years from 1998. Proportion of HbA1c, blood pressure and total cholesterol measurements after T2D presentation showed sigmoid-shaped trends over time, indicated by declines in Years 2 and 7 onwards with a plateau in between (Years 4 to 5). The lowest estimates for HbA1c and cholesterol measurements were less than 70%, whilst for blood pressure was less than 80%. Positive trends were seen for meeting blood pressure ≤145/85 mmHg (from 63% to 73% in Year 10) and total cholesterol ≤5 mmol/L (from 66% to 85%), but inverse trends (from 75% to 58%) were observed for meeting HbA1c ≤7.4% (57.4 mmol/mol). Attainment of HbA1c and blood pressure targets was demonstrated to fall short of their measurements over time. Creatinine tests were relatively stable at above 70% over time, whilst peripheral pulse checks never reached 40%. Diabetes treatment showed upward trends (from 11% to 40%) with multiple oral hypoglycaemic agents (OHAs), but negative trends (from 50% to 20%) with single OHA. Women, being deprived and non-white ethnicities were consistently associated with no receipt of HbA1c, blood pressure and total cholesterol testing over time, whilst older age at diagnosis was associated with attaining these biomarker targets over time.

Conclusion. This study highlights missed opportunities for secondary prevention in patients newly diagnosed with T2D. Achieving glycaemic target appeared to be particularly challenging as compared to achieving blood pressure or total cholesterol targets.

4.3 Introduction

Quality of care plays an important role in T2D management to prevent or delay chronic complications. Assessment of the quality of care looks at how essential T2D care is delivered after T2D

presentation and how surrogate outcomes are achieved accordingly. Existing studies on quality of T2D care generally reported satisfying results with a high proportion of care provision or target achievement.[130,142] However, quality of care studies founded on prevalent cases could potentially give misleading pictures (**Section 1.2.4 on pages 40-42**) where overestimation of care provision can be resulted from addition of newer cases to the existing ones. Similarly, old cases – provided the earlier or longer disease exposure – could have been treated more intensively leading to overestimation of either care provisions or outcomes.

Recognising temporal patterns of care in incident T2D cases offers the opportunity to optimise early intervention and to spot areas needing improvement in order to obtain the best outcomes possible. Given the lack of research on this area, this present study aimed to capture newly diagnosed T2D from linked EHRs through which analysis on trends in provision of care and achievement of surrogate outcomes is enabled. This study also sought to assess whether the temporal trends differed according to demographic factors and baseline CVD status.

4.4 Methods

4.4.1 Study population and study period

This was an observational cohort study targeting newly diagnosed T2D in the CALIBER population. Patients were followed prospectively from the first T2D presentation until the date of censoring, defined as the date of transfer out of the practice, the last date of data collection or the date of death.

4.4.2 Inclusion criteria

Study methods were described in **Section 3.9 on pages 111-113**. Briefly, T2D patients were included if they were aged ≥30 years at diagnosis, consented to data linkage, were registered with their GP practice on or after 1 January 1997, and had at least 1 year of follow-up after the index date. Patients with a prior history of diabetes or use of diabetes medications were excluded. Patients on insulin only throughout the follow-up period were also excluded (**Figure 4.1 on page 131**).

4.4.3 Temporal trends in quality of care

Processes of care. Trends in process of care indicators, as previously defined in **Table 3.4 on pages 120-121**, have been estimated as the proportion of incident T2D patients receiving at least one indicated process of care each year. For the purposes of this study, therefore, the main focus was upon the annual recording of each indicator. For binary care data (e.g. proteinuria testing), the numerator for calculating proportion receiving the given process of care was the number of patients for whom the test was done. For categorical (e.g. smoking status), composite care (e.g. peripheral pulse and neuropathy testing) or continuous (e.g. BMI, HbA1c, blood pressure) data, a binary recorded or not recorded variable was developed, the numerator being the number of

patients in whom the process of care was recorded. Denominators for all variables were the number of incident cases within the given year.

Intermediate outcome targets. These have been defined according to the 2004 QOF indicators for diabetes as HbA1c ≤7.4% (57.4 mmol/mol), blood pressure ≤145/85 mmHg and total cholesterol ≤5 mmol/L. The proportion of T2D patients achieving these targets each year has been estimated. The numerator in calculating the proportions was the number of patients achieving the target, while the denominator was the number of incident cases ever receiving the corresponding care within the given year.

4.4.4 Statistical analysis

Descriptive results for continuous variables were summarised as means (and standard deviations) or medians (and interquartile ranges), whereas categorical variables were summarised as proportions. Missing values for baseline data were not imputed and missingness indicators were applied instead.

Quality of care measures were estimated annually as the percentage of patients receiving at least one relevant process measure and achieving recommended key targets if ever measured. Composite process of care was calculated in a mutually exclusive manner as being in receipt of none, single, dual or triple key measurements of HbA1c, blood pressure and total cholesterol, whereas composite intermediate outcome of care was similarly assessed, being classified as unmeasured, no target attainment, single, dual and triple target attainments. Annual proportions of patients receiving blood glucose lowering drugs were also assessed. With the exception of target attainments, all measures used the number of newly diagnosed T2D patients within the given year as the denominators. Analyses were conducted using Stata 13.0.

4.4.5 Subgroup and post hoc analyses

Subgroup analyses were conducted by comparing trends in key processes and outcomes of care by EHR source, age at diagnosis, gender, ethnicity, deprivation and presence of CVD at baseline.

Post hoc analyses using generalised estimating equations (GEEs) logistic or Poisson with exchangeable correlation structures were further carried out to estimate the marginal (population-averaged) effects of sociodemographic factors on the temporal trends in either processes or intermediate outcomes of care and diabetes medication prescriptions.

4.5 Results

4.5.1 Incident T2D cohort in CALIBER

Of over 2 million patients in CALIBER, 163,249 were identified from diagnostic codes as having diabetes and 60,669 (37.2%) with no indicative codes of T2D were excluded, 41,458 (68.3%) of which being unconfirmed cases. Of 102,580 patients with T2D, 50,201 (48.9%) were further excluded for not meeting the inclusion criteria, generating a total of 52,379 patients newly diagnosed with T2D over 12 years who were eligible for Study 1 (**Figure 4.1 on page 131**). Of this

number, 46,838 (89.4%) patients were detected in CPRD (20,419 with specific T2D codes) and the remaining were detected in HES by NIDDM codes (**Figure 4.2 below**).

Figure 4.1 Patient flow chart for Study 1

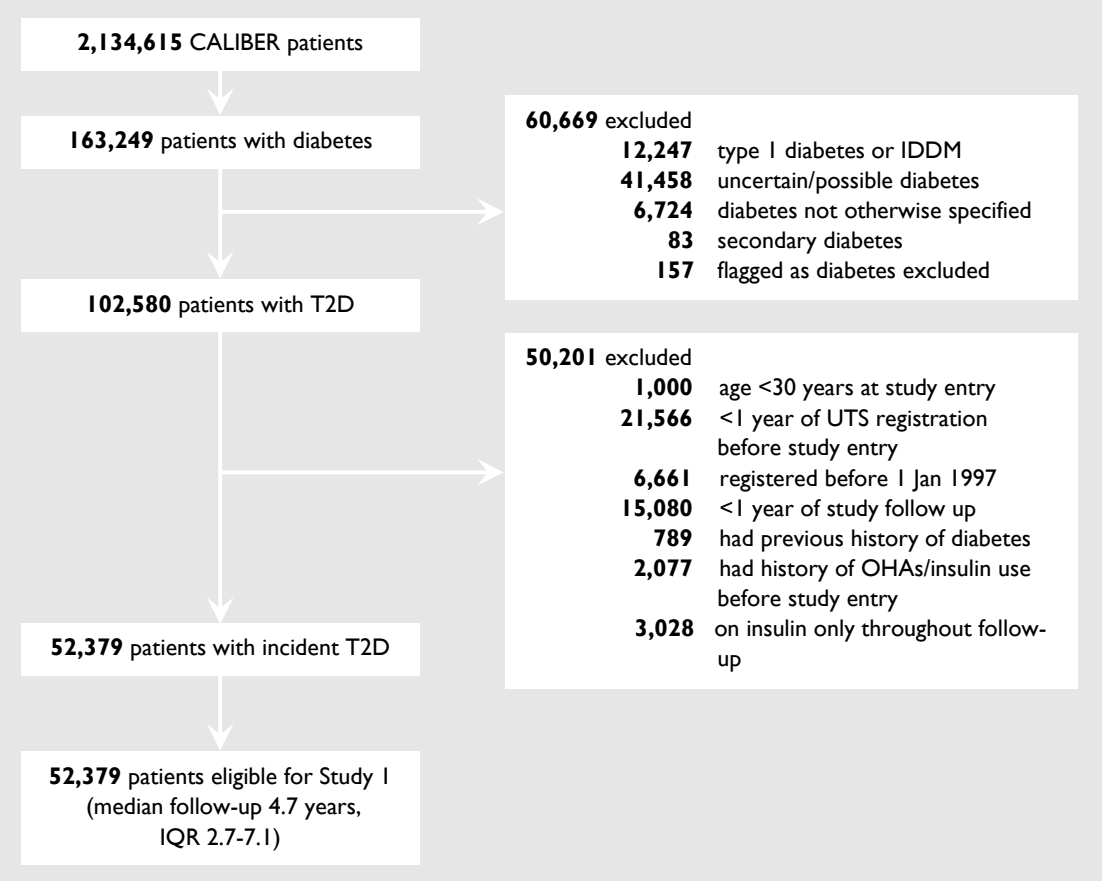
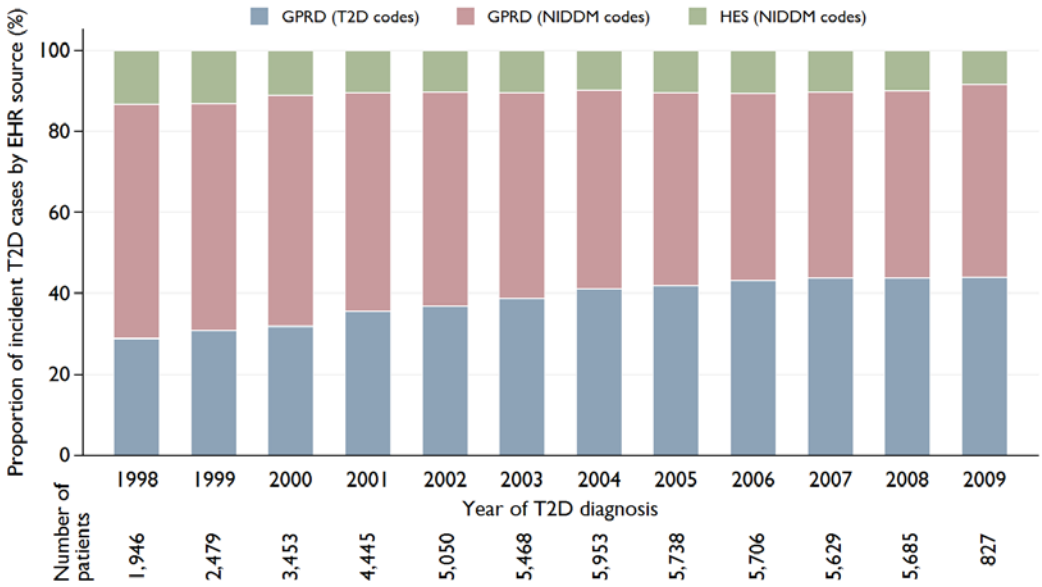


Figure 4.2 Incident T2D cases identified in CALIBER by year of diagnosis and EHR source



The number of incident T2D cases increased progressively from 1998 to 2004 when it started to level off (**Figure 4.2 on page 131**). The small numbers in 2009 represented incident cases during the first 3 months only, following which no further additions were made to allow for the ≥12 months follow-up required by the study protocol.

4.5.2 Patient baseline characteristics

Of the 52,379 T2D cases, 54.9% were men and 27.5% had CVD at baseline. Men were younger at the time of diagnosis, had slightly higher HbA1c before or at study entry, had lower BMI and were more commonly smokers or ex-smokers. Blood pressure and cholesterol values were lower in men who were more commonly prescribed lipid lowering and antiplatelet drugs compared with women, but men tended to have higher triglyceride and creatinine levels (**Table 4.1 on pages 133-134**). Compared with patients identified from CPRD, those identified from HES (10.6%) were older when diagnosed and more commonly being the most deprived. They also had lower baseline HbA1c, blood pressure, total cholesterol and BMI but higher creatinine levels, and had more co-morbidities but received less baseline blood pressure & lipid lowering medications (**Table 4.2 on pages 135-136**).

It is worth noting that the proportion of patients with baseline HbA1c recorded was very low at around 22%. Glucose tests such as fasting plasma glucose, 2-hour post prandial and oral glucose tolerance test were likely chosen over HbA1c as the primary diagnostic tests. Physical activity was also poorly recorded with only 13% at baseline. Records on baseline lipid profiles were slightly higher (ranging from 30% to 50%), whereas record on baseline blood pressure surpassed other biomarkers at 65%. Records on baseline smoking status and body mass index were both less than 40%.

Table 4.1 Baseline characteristics of incident T2D cohort in CALIBER (N=52,379)

Characteristics	non-missing (%)	non-missing ever (%)	Overall (N=52,379)		non-missing (%)	non-missing ever (%)	Men (N=28,779)		non-missing (%)	non-missing ever (%)	Women (N=23,600)	
Demographic												
Age in years, median (IQR)	100	100	63.4	(53.6-73.1)	100	100	61.3	(52.0-70.6)	100	100	66.4	(55.8-66.4)
Age group, n (%)	100	100			100	100			100	100		
<40			2,573	(4.9)			1,575	(5.5)			998	(4.2)
40-<50			6,853	(13.1)			4,338	(15.1)			2,515	(10.7)
50-<60			11,862	(22.7)			7,281	(25.3)			4,581	(19.4)
60-<70			13,874	(26.5)			7,936	(27.6)			5,938	(25.2)
70-<80			11,510	(22.0)			5,644	(19.6)			5,866	(24.9)
>=80			5,707	(10.9)			2,005	(7.0)			3,702	(15.7)
Duration of registration in years, median (IQR)	100	100	11.1	(6.8-16.0)	100	100	11.1	(6.8-15.9)	100	100	11.1	(6.9-16.0)
Social deprivation, n (%)	99.7	99.7			99.7	99.7			99.7	99.7		
Quintile 1 (most affluent)			10,480	(20.0)			6,021	(20.9)			4,459	(18.9)
Quintile 5 (most deprived)			10,440	(19.9)			5,415	(18.8)			5,025	(21.3)
Ethnicity, n (%)	56.0	56.0			54.9	54.9			60.8	60.8		
White			26,542	(50.7)			13,964	(48.5)			12,578	(53.3)
South Asian			1,557	(3.0)			815	(2.8)			742	(3.1)
Black			1,194	(2.3)			569	(2.0)			625	(2.7)
Other			860	(1.6)			461	(1.6)			399	(1.7)
Diabetes diagnosis												
Year of diagnosis	100	100			100	100			100	100		
1998-2003			22,841	(43.6)			12,445	(43.2)			10,396	(44.1)
2004-2006			17,397	(33.2)			9,527	(33.1)			7,870	(33.4)
2007-2009			12,141	(23.2)			6,807	(23.7)			5,334	(22.6)
HbA1c, mean (SD) mmol/L	21.9	99.9	66.9	(24.2)	22.6	99.9	68.0	(24.4)	21.1	99.9	65.4	(23.9)
Cardiovascular risks												
Physical activity	13.0	99.7			13.4	99.7			12.6	99.7		
Inactive			969	(1.9)			485	(1.7)			483	(2.1)
Moderate			2,568	(4.9)			1,561	(5.4)			1,007	(4.3)
Vigorous			147	(0.3)			113	(0.4)			35	(0.2)
Gentle			3,128	(6.0)			1,690	(5.9)			1,438	(6.1)

Smoking status, n (%)	39.0	100			40.3	100			37.4	100		
Never			8,377	(40.9)			3,843	(13.3)			4,538	(19.2)
Ex			7,568	(36.9)			5,058	(17.6)			2,529	(10.7)
Current			4,489	(21.9)			2,699	(9.4)			1,767	(7.5)
Blood pressure	65.1	100			63.7	100			63.7	100		
Systolic, mean (SD) mmHg			145.0	(19.6)			144.4	(19.2)			145.7	(20.0)
Diastolic, mean (SD) mmHg			83.3	(11.2)			84.0	(11.4)			82.6	(10.9)
Hypertension, n (%)	65.1	100	7,671	(22.5)	63.7	100	4,043	(14.0)	63.7	100	5,227	(18.2)
Total cholesterol, mean (SD) mmol/L	51.8	100	5.5	(1.3)	53.6	100	5.3	(1.3)	49.7	100	5.6	(1.3)
LDL cholesterol, mean (SD) mmol/L	31.8	99.8	3.2	(1.1)	32.2	99.8	3.1	(1.0)	31.4	99.8	3.3	(1.1)
HDL cholesterol, mean (SD) mmol/L	40.6	99.9	1.2	(0.4)	41.8	99.9	1.1	(0.3)	39.1	99.9	1.3	(0.4)
Triglycerides, mean (SD) mmol/L	43.1	99.9	2.5	(2.2)	44.7	99.9	2.6	(2.5)	41.3	99.9	2.2	(1.7)
Serum creatinine, mean (SD) µmol/L	57.4	100	91.4	(29.7)	57.0	100	97.9	(30.6)	57.8	100	83.5	(26.6)
BMI, mean (SD) kg/m^2	35.6	100	31.8	(6.6)	36.0	100	31.2	(5.9)	35.2	100	32.6	(7.3)
BMI category, n (%)	35.6	100			36.0	100			35.2	100		
Underweight (<18.5)			116	(0.6)			36	(0.1)			80	(0.3)
Normal weight (18.5-24.9)			2,222	(11.9)			1,210	(4.2)			1,012	(4.3)
Overweight (25.0-29.9)			5,870	(31.4)			3,618	(12.6)			2,252	(9.5)
Obese class I (30.0-34.9)			5,538	(29.7)			3,269	(11.4)			2,269	(9.6)
Obese class II (35.0-39.9)			2,898	(15.5)			1,444	(5.0)			1,454	(6.2)
Obese class III (≥40)			2,024	(10.8)			785	(2.7)			1,239	(5.3)
Medications prescribed												
Blood pressure lowering agent, n (%)	100	100	23,181	(44.2)	100	100	11,741	(40.8)	100	100	11,440	(48.5)
Lipid lowering drug, n (%)	100	100	9,862	(18.8)	100	100	5,791	(20.1)	100	100	4,071	(17.3)
Antiplatelet, n (%)	100	100	9,134	(17.4)	100	100	5,272	(18.3)	100	100	3,862	(16.4)
Comorbidities												
Coronary heart disease, n (%)	100	100	9,451	(18.0)	100	100	5,730	(19.9)	100	100	3,721	(15.8)
Cerebrovascular disease, n (%)	100	100	3,067	(5.9)	100	100	1,632	(5.7)	100	100	1,435	(6.1)
Peripheral arterial disease, n (%)	100	100	1,704	(3.3)	100	100	1,067	(3.7)	100	100	637	(2.7)
Renal disease, n (%)	100	100	1,181	(2.3)	100	100	535	(1.9)	100	100	646	(2.7)

Baseline was defined as 365 days before index date (first T2D diagnosis).

Table 4.2 Baseline characteristics of incident T2D cohort in CALIBER by EHR source (N=52,379)

Characteristics	non-missing (%)	non-missing ever (%)	CPRD (N=46,838)		non-missing (%)	non-missing ever (%)	HES (N=5,541)	
Demographic								
Age in years, median (IQR)	100	100	62.9	(53.2-72.2)	100	100	70.4	(58.2-80.1)
Age group, n (%)	100	100			100	100		
<40			2,346	(5.0)			227	(4.1)
40-<50			6,377	(13.6)			476	(8.6)
50-<60			10,994	(23.5)			868	(15.7)
60-<70			12,735	(27.2)			1,139	(20.6)
70-<80			10,088	(21.5)			1,422	(25.7)
>=80			4,298	(9.2)			1,409	(25.4)
Women, n (%)	100	100	20,793	(44.4)	100	100	2,807	(50.7)
Duration of registration in years, median (IQR)	100	100	11.2	(7.1-16.3)	100	100	9.9	(4.5-14.2)
Social deprivation, n (%)	99.7	99.7			99.8	99.8		
Quintile 1 (most affluent)			9,478	(20.2)			1,002	(18.1)
Quintile 5 (most deprived)			9,081	(19.4)			1,359	(24.5)
Ethnicity, n (%)	54.9	54.9			52.2	52.2		
White			23,814	(50.8)			2,728	(49.2)
South Asian			1,412	(3.0)			145	(2.6)
Black			1,100	(2.4)			94	(1.7)
Other			791	(1.7)			69	(1.3)
Diabetes diagnosis								
Year of diagnosis	100	100			100	100		
1998-2003			20,313	(43.4)			2,528	(45.6)
2004-2006			15,600	(33.3)			1,797	(32.4)
2007-2009			10,925	(23.3)			1,216	(22.0)
HbA1c, mean (SD) mmol/L	23.9	99.9	67.1	(24.2)	5.0	99.9	56.9	(24.1)
Cardiovascular risks								
Physical activity	13.8	99.7			6.3	99.7		
Inactive			909	(1.9)			60	(1.1)
Moderate			2,454	(5.2)			114	(2.1)
Vigorous			139	(0.3)			8	(0.1)
Gentle			2,960	(6.3)			168	(3.0)

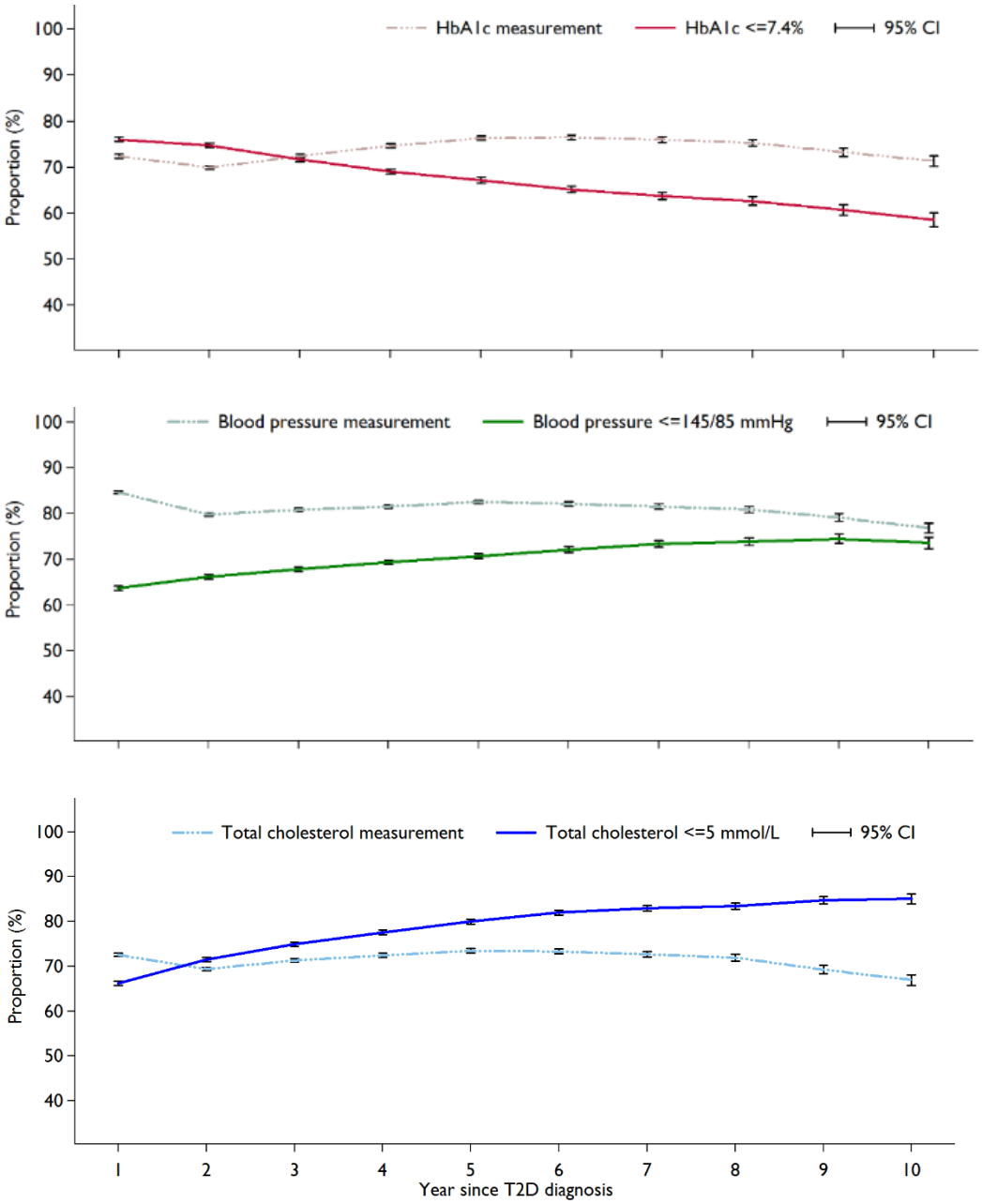
Smoking status, n (%)	40.6	99.9			25.3	99.9		
Never			7,859	(16.8)			518	(9.4)
Ex			7,032	(15.0)			536	(9.7)
Current			4,143	(8.9)			346	(6.2)
Blood pressure	67.6	100			43.9	100		
Systolic, mean (SD) mmHg			145.4	(19.5)			140.7	(20.0)
Diastolic, mean (SD) mmHg			83.6	(11.1)			80.0	(11.1)
Hypertension, n (%)	67.6	100	7,275	(15.5)	43.9	100	396	(7.2)
Total cholesterol, mean (SD) mmol/L	55.3	100	5.5	(1.3)	22.7	100	5.1	(1.3)
LDL cholesterol, mean (SD) mmol/L	34.0	99.8	3.2	(1.1)	13.4	99.8	2.9	(1.0)
HDL cholesterol, mean (SD) mmol/L	43.3	99.9	1.2	(0.4)	17.1	99.9	1.3	(0.4)
Triglycerides, mean (SD) mmol/L	46.2	99.9	2.5	(2.2)	16.8	99.7	2.0	(1.6)
Serum creatinine, mean (SD) µmol/L	60.5	100	86.8	(30.1)	30.7	100	93.9	(40.2)
BMI, mean (SD) kg/m^2	37.4	100	31.9	(6.5)	20.5	100	29.8	(7.5)
BMI category, n (%)	37.4	100			20.5	100		
Underweight (<18.5)			77	(0.2)			39	(0.7)
Normal weight (18.5-24.9)			1,961	(4.2)			261	(4.7)
Overweight (25.0-29.9)			5,519	(11.8)			351	(6.3)
Obese class I (30.0-34.9)			5,287	(11.3)			251	(4.5)
Obese class II (35.0-39.9)			2,760	(5.9)			138	(2.5)
Obese class III (≥40)			1,928	(4.1)			96	(1.7)
Medications prescribed								
Blood pressure lowering agent, n (%)	100	100	21,195	(45.3)	100	100	1,986	(35.8)
Lipid lowering drug, n (%)	100	100	9,026	(19.3)	100	100	836	(15.1)
Antiplatelet, n (%)	100	100	8,077	(17.2)	100	100	1,057	(19.1)
Comorbidities								
Coronary heart disease, n (%)	100	100	7,997	(17.1)	100	100	1,454	(26.2)
Cerebrovascular disease, n (%)	100	100	2,492	(5.3)	100	100	575	(10.4)
Peripheral arterial disease, n (%)	100	100	1,417	(3.0)	100	100	287	(5.2)
Renal disease, n (%)	100	100	981	(2.1)	100	100	200	(3.6)

Baseline was defined as 365 days before index date (first T2D diagnosis).

4.5.3 Temporal trends in quality of diabetes care

Key processes of care. In general, key processes of T2D care (i.e. HbA1c, blood pressure and cholesterol measurements) showed similar trends with time after diagnosis, with a decline seen in the second year followed by a rise in the proportion of patients tested during the first 4-5 years, but thereafter plateauing with another decline in years 7 to 10 (**Figure 4.3 below**). The proportion of patients tested per year after diagnosis was highest for blood pressure but was never lower than 70% for HbA1c or 65% for cholesterol.

Figure 4.3 Temporal trends in key measurements and target attainments in CALIBER's incident T2D cohort



Analyses by EHR source showed substantial disparities in all HbA1c, blood pressure and total cholesterol measurements from year-to-year, with HbA1c and cholesterol estimates for HES-identified patients starting as low as 30% and 40% respectively, although the gaps tended to slowly converge with time (**Figures 4.4A, 4.5A and 4.6A on pages 140-142**). When analysed by ethnicity, the trends consistently showed a significant gap over time, with higher receipt of the three measurements in whites relative to non-whites (**Figures 4.4D, 4.5D and 4.6D on pages 140-142**). The temporal gaps were also observed during about the first 5 years when the most affluent patients received more measurements than the most deprived (**Figures 4.4E, 4.5E and 4.6E on pages 140-142**). The latter trend was seen again for blood pressure when analysed by age at diagnosis and presence of CVD at baseline; patients who were older and with prior CVD received more measurement than their respective counterparts (**Figures 4.5B and 4.5F on page 141**). A contrasting trend was seen for HbA1c; patients without prior CVD appeared to receive more measurement from year 5 onwards (**Figure 4.4F on page 140**).

When the processes of care were combined, the sigmoid temporal trends remained with most patients (60-70%) having received all the three measurements (**Figure 4.7A on page 143**).

Key outcomes of care. Overall, the proportion of patients meeting blood pressure and cholesterol targets increased year-by-year after diagnosis, peaking at approximately 75% and 85%, respectively, towards the end of the follow-up period (**Figure 4.3 on page 137**). For HbA1c, however, the pattern was different, the proportion of patients meeting the target declining progressively year-by-year after diagnosis to <60% by the end of the follow-up period (**Figure 4.3 on page 137**).

The trends were maintained for HbA1c target attainment (showing downward) and blood pressure and total cholesterol (upward) in either patients identified from CPRD or HES (**Figures 4.4A, 4.5A and 4.6A on pages 140-142**) with narrower gaps than their respective measurements. A wide temporal gap, from 10% at year 1 to 30% at year 10, was observed when HbA1c target attainment was analysed by age at diagnosis where proportion of older patients meeting the target was consistently higher over time (**Figure 4.4B on page 140**). A similar gap was observed for total cholesterol although narrower (about 10%) and shorter (until year 7) (**Figure 4.6B on page 142**). The proportion of women meeting glycaemic target appeared to be higher over time (**Figure 4.4C on page 140**), yet proportion of men meeting total cholesterol target was higher over time (**Figure 4.6C on page 142**). Subgroup analyses showed higher proportions of patients meeting the three targets of intermediate outcomes in the presence of prior CVD (**Figures 4.4F, 4.5F and 4.6F on pages 140-142**).

Temporal trends for composite target attainments were relatively flat over time, with a low proportion of around 20% for single target and slightly higher proportions at around 30% for either dual or triple targets (**Figure 4.7 on page 143**).

Other processes of care. Records of body mass index and smoking status at baseline showed similar trends with the key processes of care, peaking at around 70% and 65% respectively

during the first 5-6 years (**Figure 4.8A on page 143**). Serum creatinine testing, albuminuria testing and peripheral pulse check of lower extremities also shared a trend with peaks of around 75%, 60% and 58%, respectively (**Figures 4.8B and 4.9C on pages 143-144**). Treated albuminuria showed a positive trend with low proportions over time peaking at about 38% in year 5 onwards (**Figure 4.8B on page 143**), whilst neuropathy testing by ankle vibration sense test demonstrated a negative but low trend, starting at less than 40% (**Figure 4.9C on page 144**).

Diabetes treatment. About half of all incident T2D patients were not medically treated a year after diagnosis and although the proportion of untreated patients declined progressively thereafter, about 20% remained untreated by the end of the follow-up period (**Figure 4.9 on page 144**). Treatment with oral hypoglycaemic agents (OHAs) increased year-by-year with proportions of patients receiving more than one agent as part of a multi-drug regimen peaking at about 40% by the end of the follow-up period. Proportions receiving insulin in addition to OHAs also increased progressively peaking at about 25%.

Among patients who ever had their HbA1c measured in year 1, a third quarter achieved the target and of these, 45% were not on medications (**Figure 4.10 on page 144**). In comparison, the proportion was only 18% among those who did not achieve target. Subgroup analyses by EHR source further saw higher proportions over time of no diabetes treatment among HES-identified patients (**Appendix F, Figure F4.6 on page 347**).

Figure 4.4 Subgroup analyses for temporal trends in measurement and target attainment of HbA1c target in CALIBER's incident T2D cohort

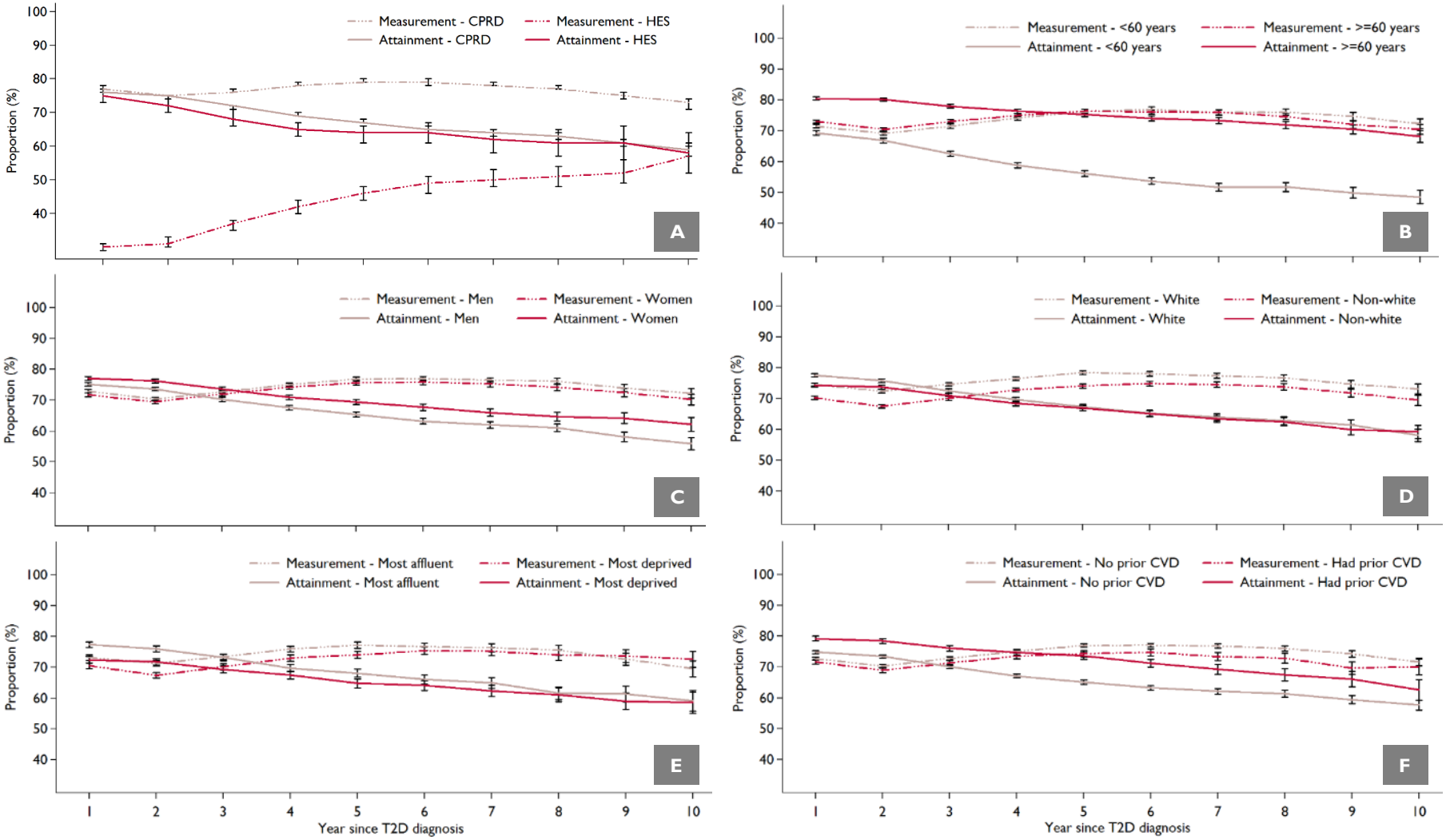


Figure 4.5 Subgroup analyses for temporal trends in measurement and target attainment of blood pressure target in CALIBER's incident T2D cohort

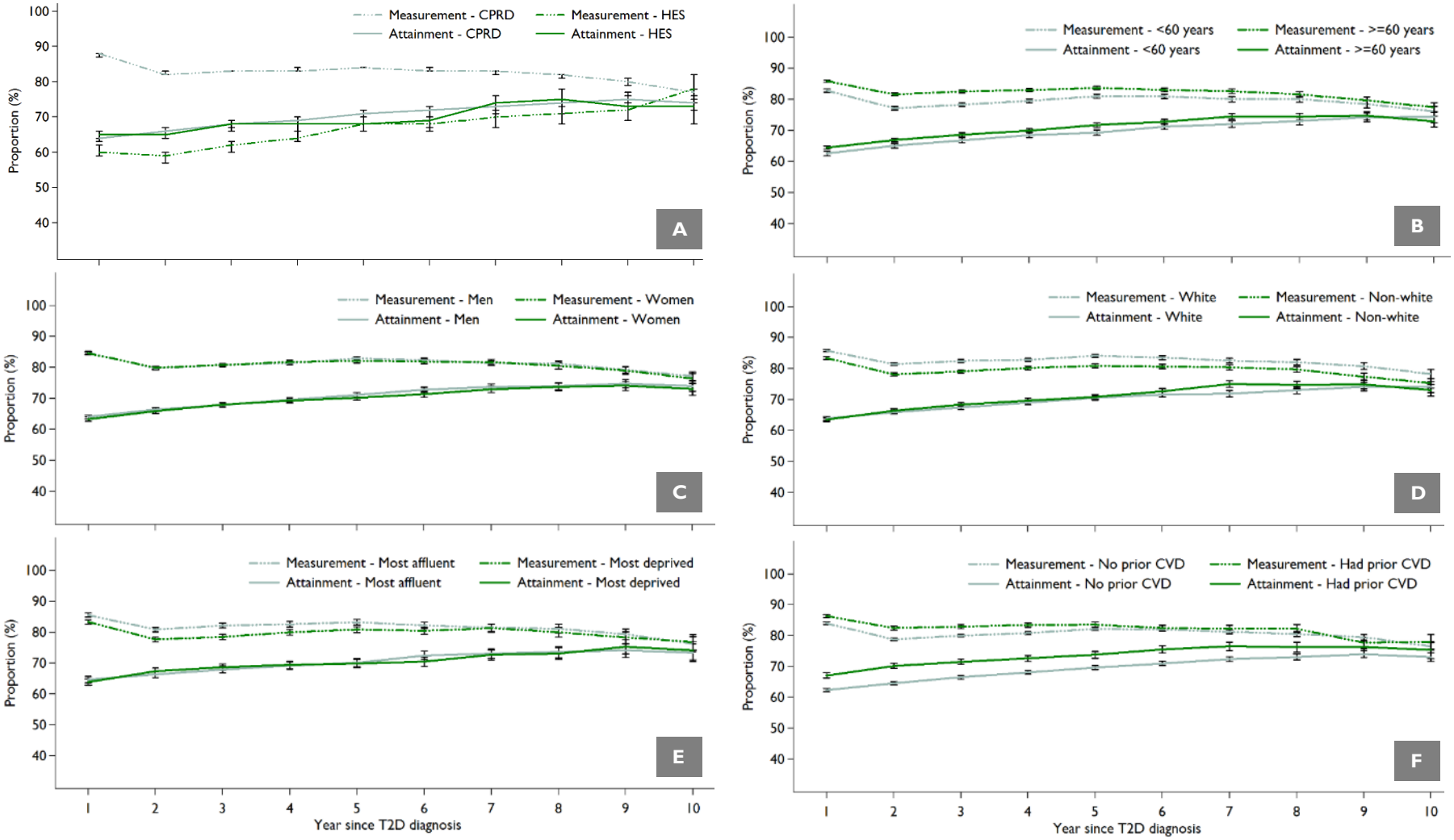


Figure 4.6 Subgroup analyses for temporal trends in measurement and target attainment of total cholesterol target in CALIBER's incident T2D cohort

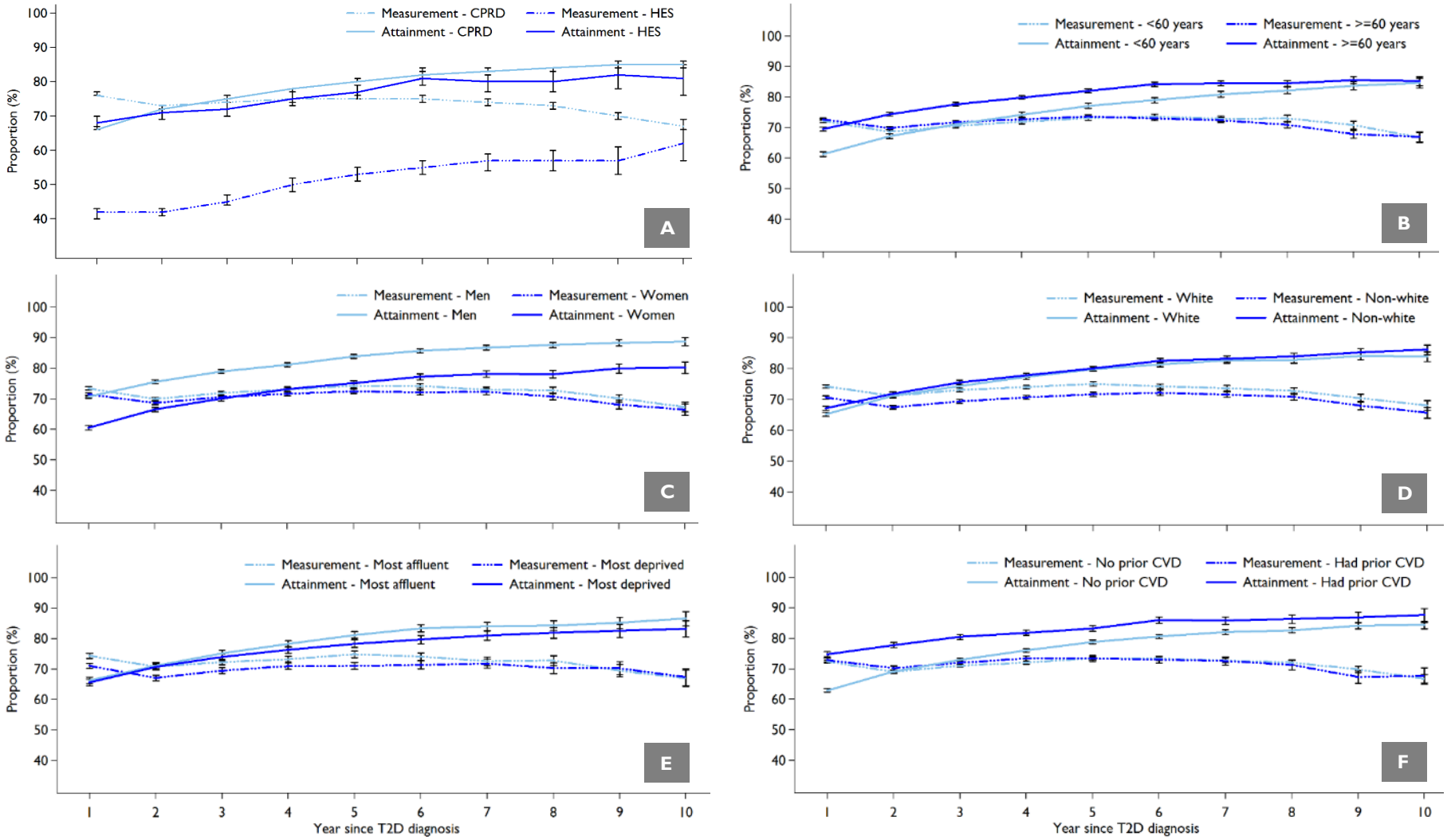


Figure 4.7 Patterns of composite measurements and target attainments over time in CALIBER's incident T2D cohort (N=52,379)

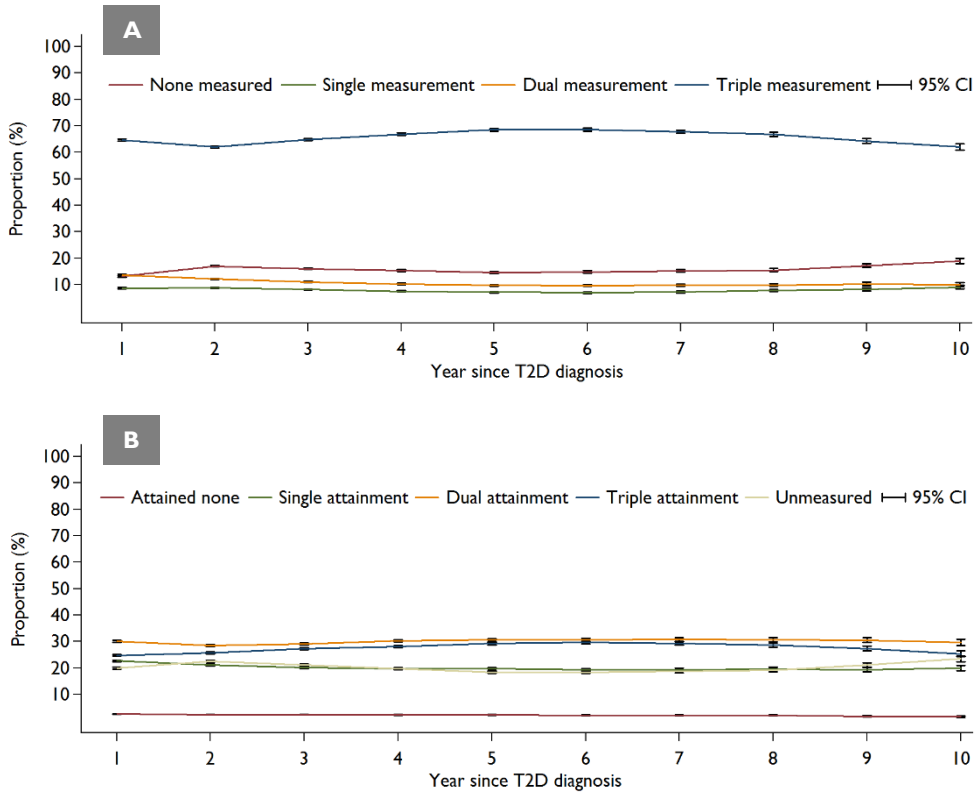
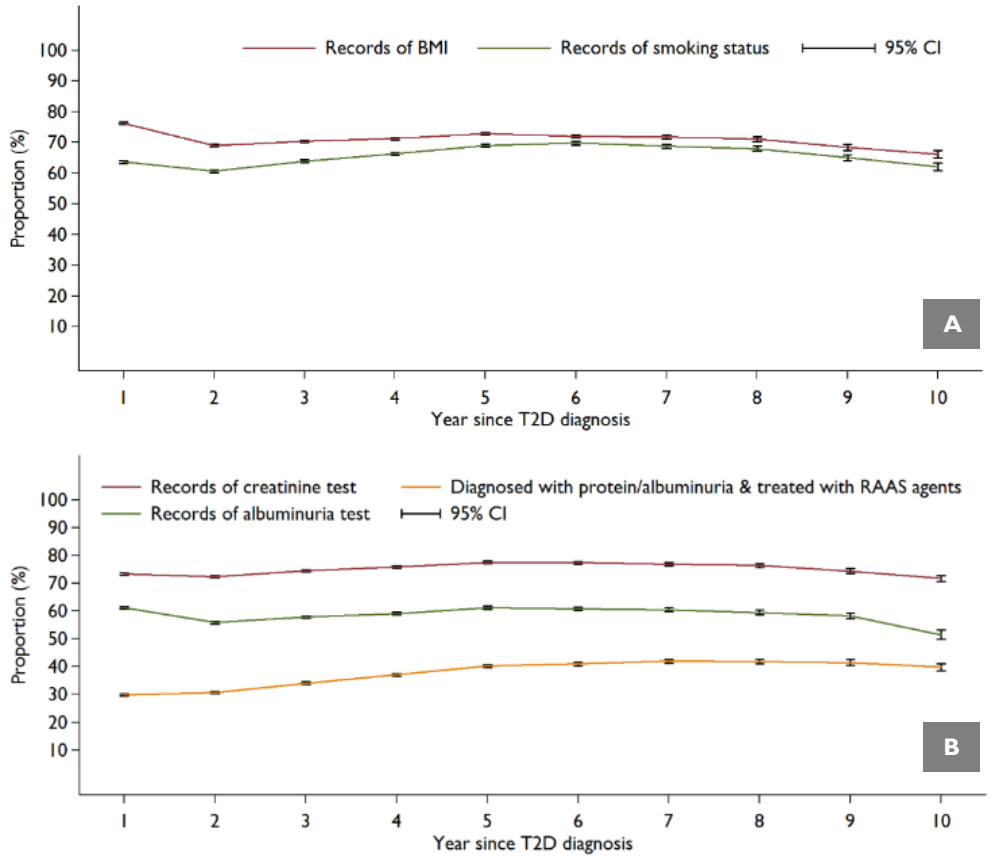


Figure 4.8 Attainment over time of additional care measures in CALIBER's incident T2D cohort



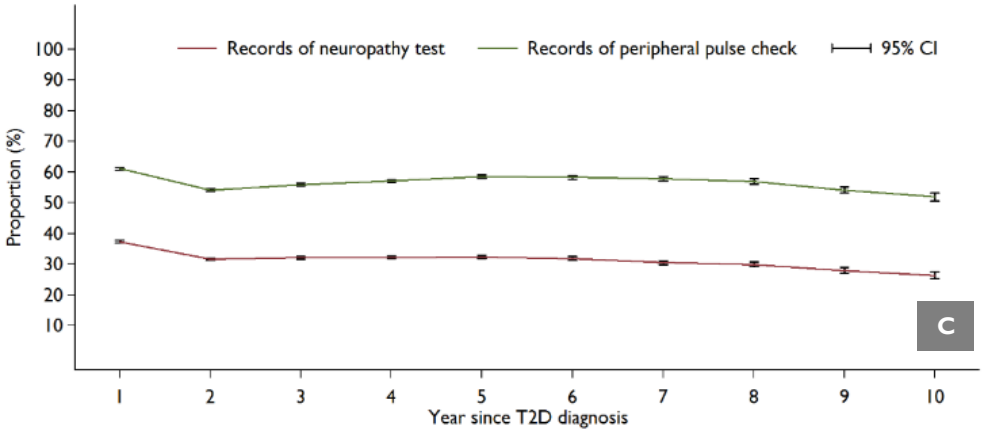


Figure 4.9 Patterns of diabetes treatment over time in CALIBER's incident T2D cohort

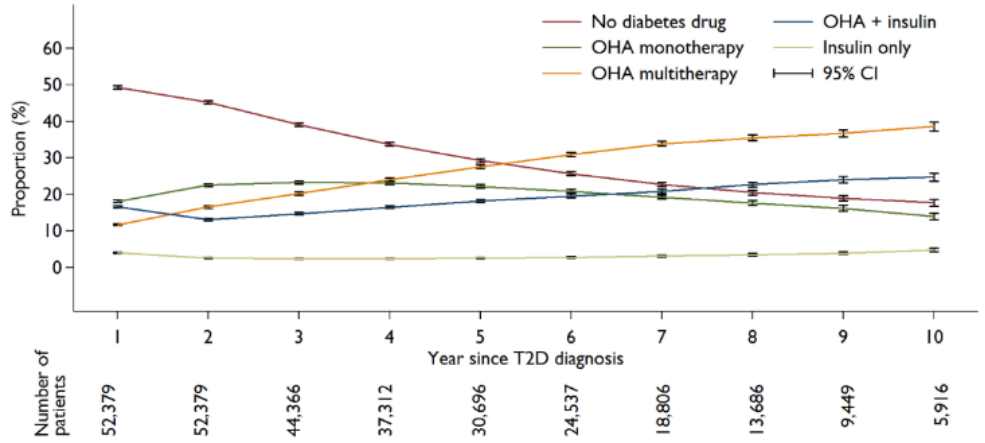
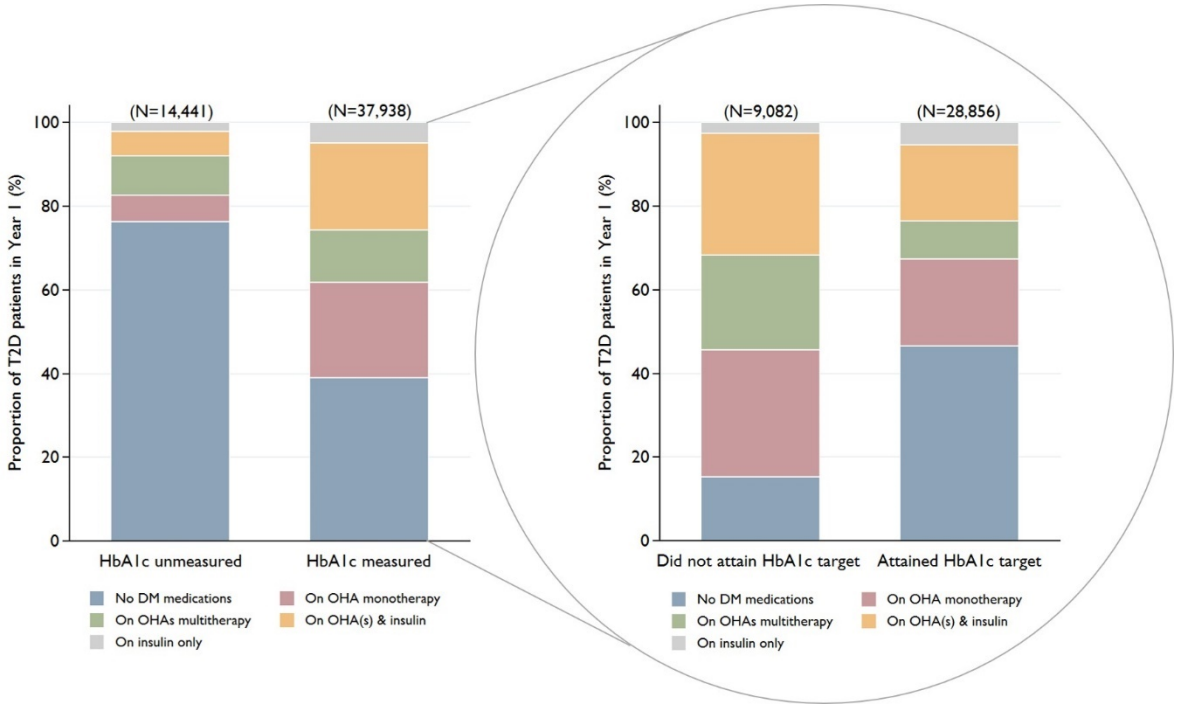


Figure 4.10 Proportion of incident T2D cases by diabetes treatment, receipt of HbA1c measurement and HbA1c target attainment within the first year since diagnosis



4.5.4 Sociodemographic factors and temporal trends in T2D care

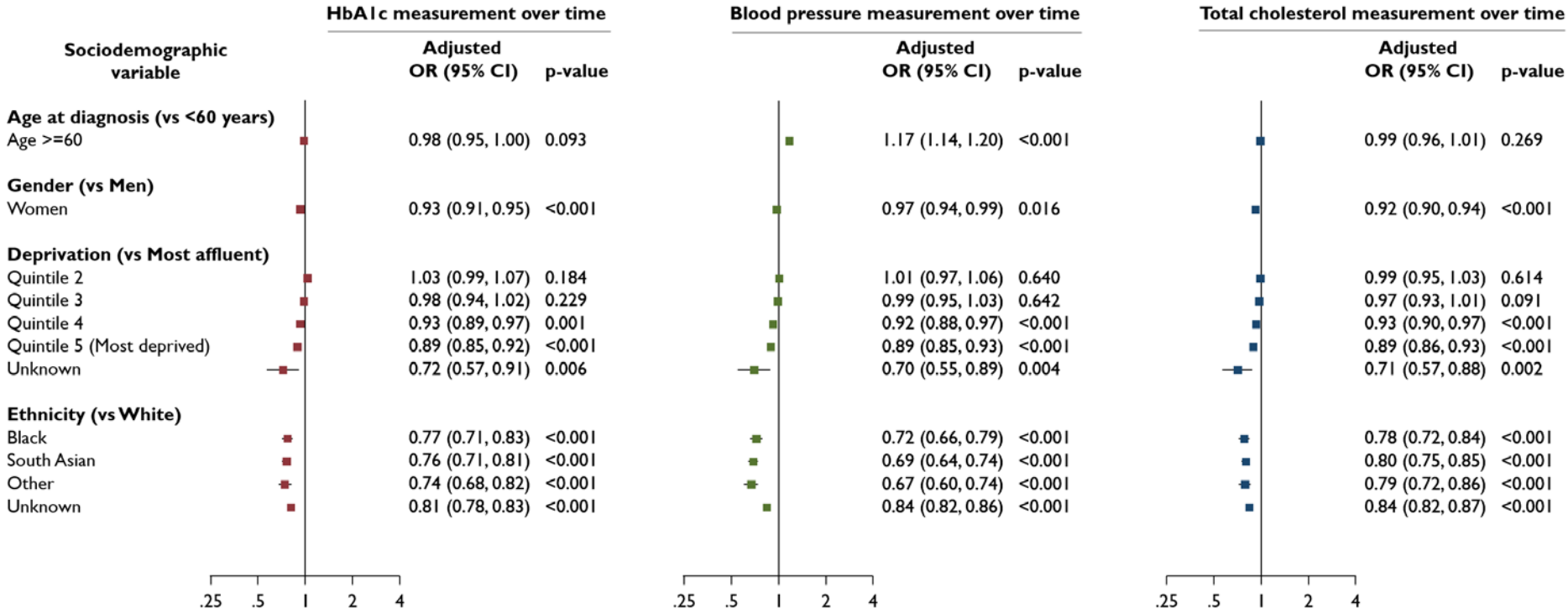
Process of care. **Figure 4.11 on page 146** demonstrated that the observed temporal gaps in care processes were associated with sociodemographic factors. Women, non-white ethnicities and being more deprived were shown to consistently relate to less probabilities in having HbA1c, blood pressure and total cholesterol measurements over time. Women had less than 10%, while black and South Asian ethnicities had about 20-30% lower probabilities to receive either of the key measurements. Probability to have blood pressure measurements over time was 17% greater with older age at diagnosis. All sociodemographic factors were further shown to have significant relationships with multiple measurements (**Figure 4.13 on page 148**).

Intermediate outcomes of care. Older age was significantly associated with higher probabilities for achieving the three targets, with up to 57% for HbA1c (**Figure 4.12 on page 147**). Women no longer had relationship with achieving HbA1c target over time, but the probability was higher (30%) than that of measurement for total cholesterol target. Ethnicity still played a role in target attainments, the probability for South Asian population remained to be lower (around 10%) to achieve blood pressure and total cholesterol targets. South Asian ethnicity did not correlate to achieving multiple targets over time (**Figure 4.14 on page 148**).

Diabetes treatment. Older age and women had lower probabilities (20% and 2%, respectively) to be pharmacologically treated over time (**Figure 4.15 on page 149**). In contrast, the most deprived population and black ethnicity had 5% higher probabilities to receive diabetes medications over time.

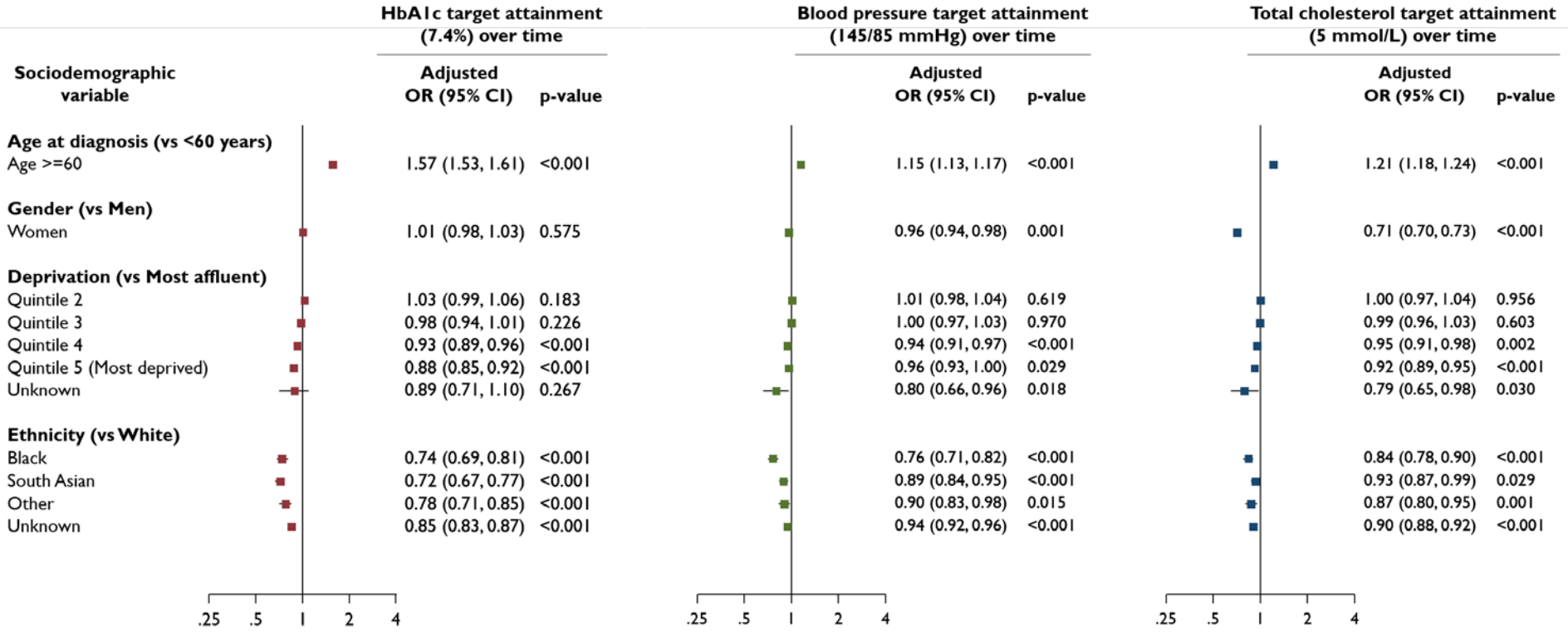
Correlations between sociodemographic factors. Additional analyses further showed that proportion of the most deprived population were significantly higher in black (57%) and South Asian (30%) ethnicities as compared to in white (20%). Both ethnicities also had higher proportions (60-70%) of younger population (<60 years at diagnosis) than white ethnicity (40%), whereas gender and prior CVD status were comparable by ethnicity.

Figure 4.11 Associations between sociodemographic factors and key processes of T2D care (measurements) over time*



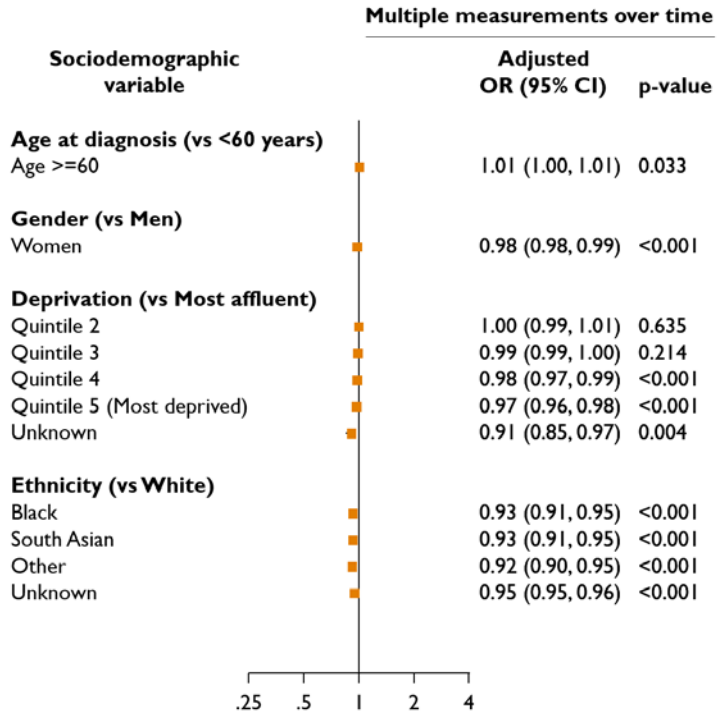
*Population-averaged estimates from generalised estimating equations logistic (n=52,379), within-patient correlations (r) = 0.289 (HbA1c), 0.269 (blood pressure) and 0.229 (total cholesterol).

Figure 4.12 Associations between sociodemographic factors and key intermediate outcomes of T2D care (target attainments) over time*



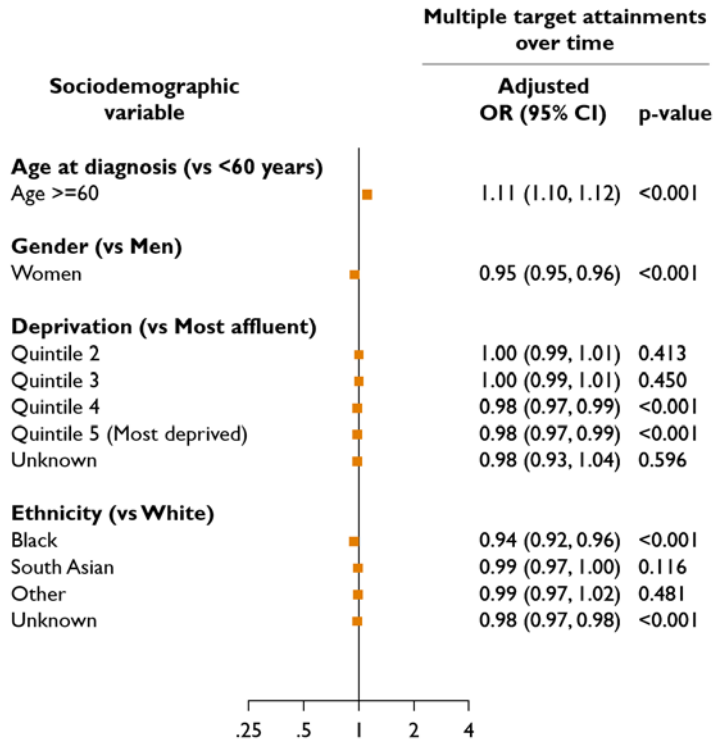
*Population-averaged estimates from generalised estimating equations logistic (n=52,379), within-patient correlations (r) = 0.300 (HbA1c), 0.199 (blood pressure) and 0.243 (total cholesterol).

Figure 4.13 Associations between sociodemographic factors and composite measurements over time*



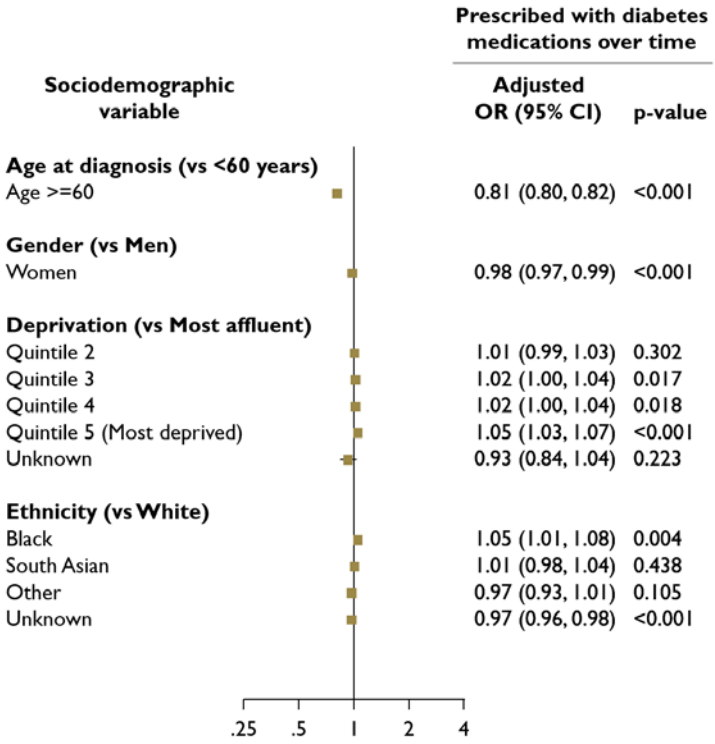
*Population-averaged estimates from generalised estimating equations Poisson (n=52,379), within-patient correlation (r) = 0.371.

Figure 4.14 Associations between sociodemographic factors and composite target attainments over time*



*Population-averaged estimates from generalised estimating equations Poisson (n=51,362, excluding patients who never had measurements over time), within-patient correlation (r) = 0.286.

Figure 4.15 Associations between sociodemographic factors and prescription of diabetes medications over time*



*Population-averaged estimates from generalised estimating equations logistic (n=52,379), within-patient correlation (r) = 0.520.

4.6 Discussion

4.6.1 Key findings

The linked primary and secondary care records within CALIBER provided a rich resource for development of the newly diagnosed T2D cohort with sufficient follow-up to analyse temporal trends in quality of diabetes care. The majority of cases were detected within CPRD by either obsolete, indicative code (i.e. NIDDM) or newer, specific code (i.e. T2D). A further 10.6% of cases were returned using NIDDM from the hospital record. All quality of care parameters were identified from the primary care record.

Despite the high number of uncertain diabetes (n=41,458, **Figure 4.1 on page 131**), I adhered to the phenotyping method from the previous CALIBER study on T2D.[4] Thus, I did not speculate to use relevant biomarkers or treatments to infer T2D diagnosis in the absence of overt diagnosis codes in order to avoid overdiagnosis or overclassification[245] (although at the expense of losing a potential considerable study size). Following the differing baseline characteristics of patients whose initial diagnosis was retrieved from HES (**Table 4.2 on pages 135-136**), further checks against CPRD and HES records showed that only 57.4% (n=3,171) have ever received HbA1c testing and/or diabetes medication following their diagnosis. The estimate was much higher than that of its CPRD-identified counterpart (98.7%, n=46,858). Admittedly, there may

be T2D miscoding, misdiagnosis or misclassification issues with the HES records as they were entered at admission by coding clerks with different levels of diagnosis. With HES-identified patients being older and having higher comorbidities (**Table 4.2 on pages 135-136**), the most cogent (mis)diagnosis, if existed, would be secondary T2D (to the underlying cause of hospitalisation). However, in the absence of HES data for HbA1c (and other glucose testing) in CALIBER, I could not rule out such patients as it could have led to false negative. Moreover, they contributed to only 4.5% of the total patients identified. In order to observe the impact of this issue, I performed several subgroup analyses, separating the study cohort by EHR source (discussed later on).

In general, this study has shown considerable suboptimal management of T2D in the early years after diagnosis with potentially adverse consequences for intermediate outcomes. There was a mismatch between proportions tested and proportions meeting the intermediate outcome targets, particularly for HbA1c and blood pressure. Thus while 70-76% of the cohort received HbA1c testing year-on-year after diagnosis of T2D, the proportion meeting the outcome target declined progressively to less than 60% after 10 years. This study was not intended to further explore whether the findings represented treatment failure, disease progression or both. Assessing treatment failure can introduce a new research domain which requires intricate analyses given the complexity of medication data (e.g. different agents and dosages prescribed, treatment changes, defining treatment failure). Finding from the UKPDS, however, indicates that glycaemic control in incident T2D tends to deteriorate with time either with or without treatment.[49] The extent to which target attainments relate to disease progression will be investigated later in this thesis (Studies 3-5).

Somewhat more encouraging finding was the cholesterol target which was met by an increasing proportion of patients with years after diagnosis. Yet a substantial proportion fell short in the early years for total cholesterol, and even ten years after diagnosis there remained about 15% who had not met the target. Other favourable findings were the high proportion of triple measurements over time (despite showing low for its target attainment) and the very low proportion of achieving none of the targets (**Figure 4.7 on page 143**), suggesting adequate efforts in care and, to a lesser extent, decent adoption of the clinical guidelines.

Additionally, this study also saw inequalities of care provision which, to some extent, might have led to the outcome gaps. These particularly held true, as supported by the longitudinal subgroup analyses (**Figures 4.11 and 4.12 on pages 146-147**), for HbA1c when scrutinised by deprivation, and for blood pressure when scrutinised by age at T2D diagnosis and prior CVD. The inequality of HbA1c testing by gender and prior CVD yielded reverse findings for meeting the target despite fewer measurements and less intensive diabetes treatment in women and those with prior CVD (**Figures F4.8 and F4.11 on pages 347 and 348**), yet result from subgroup analysis showed that women only had a modest, non-significant probabilities to meeting HbA1c target over time. These findings were similarly applicable to ethnicity where non-white patients were shown to comparably attain the key targets over time despite fewer measurements received; subgroup analyses were however not supportive of these, the possi-

bilities include the high proportion of patients with unknown ethnicities and cross-correlation with deprivation (**Section 4.5.4 on pages 145-149**). Completeness and quality of ethnicity records in CPRD have reportedly improved from 2006 onwards to be reliably used when assessing the continuum of care,[264] while this CALIBER study largely utilised data from before 2006 (**Figure 4.2 on page 131**). Nonetheless, the delay or failure in meeting intermediate outcome targets after T2D diagnosis represents a potentially important management failure for improving prognosis in this high risk population.

Other missed opportunities are indicated by temporal data on health behaviour with 30-40% of patients having their body mass index and smoking status unrecorded over time. These basic data should have been routinely checked in T2D, but were possibly overlooked by overemphasis on meeting the three key targets or once treatment commenced. Tests to anticipate foot and kidney complications also appeared to be underperformed (and undertreated) year-by-year. Prevention measures will work best when regularly conducted before complications occur, but in practice there remains a possibility that, when symptoms began to be palpable or reported by patients, the tests were scheduled and performed belatedly. While the well-known notion in T2D is that microvascular complications are typically found after initial diagnosis (as mentioned in **Section 1.2.4 on pages 40-42**),[119-121,265] more recent evidence reported that such complications are predictive of cardiovascular events.[266,267] Coupled with other studies reporting the presence of complications at T2D diagnosis,[118,268] the findings support the argument for microvascular symptoms preceding T2D. It remains a big challenge, however, to determine the true onset of T2D and the related vascular diseases, as to which one occurs earlier and affects the other, or whether both conditions can possibly coexist due to shared risk factors or intertwined pathomechanisms; more often than not, the processes transpire subclinically, thus rendering the issue on the natural course of T2D debatable. Apart from this issue, Study 1 underlines the need for improvement in performing tests to detect microvascular symptoms.

The observed trends in diabetes treatment (**Figure 4.9 on page 144**) indicate that in newly diagnosed patients, the disease management appeared to have followed the existing guidelines.[31-34] Within the first year since diagnosis, about half of the T2D patients have been managed with a non-pharmacological approach (**Figure 4.10 on page 144**). In fact, nearly half of patients who had HbA1c measurement was shown to be well-controlled, only those who did not attain target were more aggressively treated. Looking at the trends over time, however, medicalisation would be inevitable at some point. Moreover, modifying diet and lifestyle alone requires strong commitment and arduous endeavours which for many might be perceived as burdensome. The increasing multidrug treatment from year-to-year (i.e. 'treatment intensification') may reflect either disease worsening and/or drug resistance. The latter mention cannot be ascertained from this study, instead – with the complex interplay in T2D between patient lifestyle, healthcare factors and genetics – genotyping analyses can offer unbiased identification of such resistance to diabetes drugs.[269-271]

4.6.2 Comparison with other studies

Attainment of key process measures. As summarised in **Table 4.3 on page 153**, estimates for temporal trends in Study 1 are not directly comparable with previous research founded on prevalent cases (**Table 2.2 on pages 55-56**) owing to the differences in settings, study size, data source and assessment methods. This CALIBER study in a newly diagnosed T2D population – only outnumbered by an Italian study[142] – saw sigmoid-shaped trajectories for HbA1c, blood pressure and total cholesterol measurements which are distinct from the overall positive trends previously reported.[130,140-144] This study examined attainment of process measures year-by-year *after* diagnosis within a 12-year time frame (hence with different entry dates) while other studies appeared to generate their estimates from mixed cohorts of established and newly diagnosed cases accrued annually. However, the finding in this study that blood pressure measurement is the best recorded care indicator is consistent with other studies although proportions receiving blood pressure measurement were somewhat lower in the CALIBER cohort (77-84%) compared with other UK and Dutch studies (85-94%).[130,140,141] Differences for measurement of HbA1c measurement, peaking at 74%, and total cholesterol, peaking at 76%, were yet greater compared with about 90% of patients for whom these care indicators were recorded in other prevalent cohorts.[130,143]

Attainment of intermediate outcome targets. The negative trend with time in meeting the HbA1c target of ≤7.4% after diagnosis of T2D replicates the finding in an earlier UK study which also briefly analysed a subgroup of incident T2D, when a lower ≤6.4% target was chosen, not when the higher ≤7.5% target was chosen which saw a U-shaped trend.[140] The observed proportion reduction over time was however more apparent in Study 1, declining from 75% to 65%. Despite the decline, the estimates remained to be higher than those from the Italian and New Zealand studies reporting positive or U-shaped trends below 60%.[141,143] By forward referencing, I found another study documenting contradictive findings to my subgroup analysis. In a study with a large T2D population drawn from the EMIS web database (N=24,111), a positive trend was seen for glycaemic control across ethnic groups between 2004 and 2009. However, the study included prevalent T2D with South Asians being overrepresented (58%) and the improved glycaemic control never reached above 60% in all ethnicities.[272]

In contrast to HbA1c, the observed positive trends in meeting blood pressure (64-75%) and total cholesterol (66-85%) targets were relatively comparable with previous UK studies.[130,140] These findings combine to suggest a better outcomes of T2D care in the UK since other non-UK studies reported lower estimates.[141-144] Yet consistent to my findings were that proportion of target achievements in all previous studies also fell short of their respective measurements.[130,140-144]

Table 4.3 Comparison of Study 1 with existing studies*

Authors	Design	Study period (years)	N patients	Trends in process measurements				Intermediate outcome target set			Trends in outcome measurements			
				HbA1c	BP	Lipid	Other processes	HbA1c (%)	BP (mmHg)	Lipid (mmol/L)	HbA1c	BP	Lipid	Other outcomes
deLusignan† (2005)[140]	Longt'd (EHR)	7	13,173	▲	▲	▲	▲ BMI ▲ DM treatment	6.5 or 7.5	140/80 or 160/100	5	▼ (6.5)	▲	▲	
Taggart (2008)[144]	Serial CS (EHR)	9	3,358	n/a	n/a	n/a		7	130/80	4	△	△	△	
Calvert (2009)[130]	Longt'd (EHR)	6	42,032	▲	▲	▲	▲ (10 others)	7.5 & 10	145/85	5	▲	▲	▲	
Voorham (2010)[141]	Longt'd (EHR)	3	2,929	▲	▲	▲	■ DM treatment ■ BP treatment ▼ lipid treatment	7	140	5	□ ▲	△ ▲	△ ▲	
Tomlin (2013)[143]	Longt'd (EHR)	9	11,757	▲	▲	▲	▲ DM treatment ▲ BP treatment ▲ lipid treatment	7.2	130/80	4	△ ▲	△ ▲	△ ▲	▲ microvascular hospital admission ▼ macrovascular hospital admission
Rossi (2014)[142]	Longt'd (EHR)	7	532,651	▲	▲	▲	▲ (3 others) ▲ DM treatment ▲ BP treatment ▲ lipid treatment ▲ aspirin treatment	7	130/80	100 mg/dL (LDL)	△ ▲	△ ▲	△ ▲	▲ achievement of high QoC score
CALIBER‡	Longt'd (linked EHR)	12	52,379	■	■	■	▲ ■ ▼ (7 others) ▲ DM treatment (multi OHAs)	7.4	145/85	5	▼	▲	▲	

▲ Positive trends over time (proportion), ▼ Negative trends over time (proportion), ■ Non-linear trends over time (proportion)
△ Positive trends over time (mean reduction), □ Non-linear trends over time (mean reduction)
***As identified in Chapter 2 (**Table 2.2 on pages 55-56**)
†Includes patients with newly diagnosed T2D
‡Includes patients with newly diagnosed T2D only
BMI, body mass index; BP, blood pressure; CS, cross-sectional; DM, diabetes mellitus; OHA, oral hypoglycaemic agent.

Attainment of other process measures. The increasing trend for treated albuminuria is consistent with a previous study also using CPRD.[130] Other findings, however, did not match other studies reporting positive trends in care.[140,142-144] My analysis demonstrated a negative trend for neuropathy test and sigmoid-shaped trends for other processes of care.

Trends in diabetes treatment. This study saw temporal increases in the proportion of patients receiving diabetes treatment. A previous UK study also reported steady increases in the prevalence of pharmacologically treated T2D;[140] however, the findings may not be comparable as treatment groups were based on accrual rather than being mutually exclusive as they were in this study. Study 1 was not designed to pursue whether the longitudinal increases in treatment (which may be interpreted as treatment intensification) are related to glycaemic target attainment nor was it designed to seek trends in cardiovascular medications as explored in other studies.[141-143]

4.6.3 Strengths and limitations

The strengths of this study include a large cohort retrieved from linked EHRs, sufficient follow-up time to allow examination of the temporal trends in T2D care and examination according to demographic factors. T2D coding error is possible in clinical practice yet expected to be trivial since T2D requires several diagnostic tests before being established and/or specific medication (although women on metformin may have polycystic ovary syndrome). A validation study of the CPRD showed that recorded diagnoses in primary care are likely to be accurate.[216] The incident T2D cohort in this study was extracted using relevant diagnostic codes and prior diabetes medication, and not inferred from abnormal results of pre-diagnostic tests, to avoid overestimation. Proportion of HbA1c records at baseline was as low as 20% although other diagnostic tests such as fasting plasma glucose and oral glucose tolerance tests might have been taken (by a large number of different laboratories with different protocols) to confirm T2D. Consequently, this has left a large number of patients (over 40,000) with an uncertain status of diabetes. The cohort size, however, approximates to estimation in the previous CALIBER study.[4] Compared with previously identified studies, Study 1 has further explored the associations of sociodemographic factors with longitudinal T2D care following the main findings in temporal trends.

This study has some important limitations. Firstly, CPRD data were not from the entire UK population, but patients included were shown to be nationally representative (**Section 3.3.1 on pages 98-105**). Secondly, contributing practices in the CPRD might have better recorded disease events and supporting data, leading to potentially higher estimation relative to practices that do not contribute. The contributing practices are advised to follow recording guidelines and their data must meet standards of data completeness. Thirdly, I used the 2004 QOF indicators for diabetes to assess quality of care. The CALIBER cohort was extracted from its constituent data resources dating from 1998 to 2010 and the QOF was initially launched in 2004; therefore, it is considered the right point to assess the quality of care which covers the period before and after the implementation of the QOF in balance. The QOF has undergone continual revision annually and some indicators used differed from the lists in the newest version, including targeted intermediate outcomes. The 2016/17 QOF for diabetes sets the HbA1c target at 64 mmol/mol and

blood pressure at 140/80 mmHg and omits total cholesterol target. Fourthly, diet and physical activity, which are also central to T2D management, were not represented in the QOF indicators (which may explain why they are poorly recorded) and in this study accordingly. Lack of adherence to lifestyle modification (including smoking and alcohol intake) could lead to risk excess of cardiovascular complications.[273]

4.6.4 Clinical and research implications

Decline in temporal achievement of glycaemic targets and a long period to see high proportions of patients meeting blood pressure and cholesterol targets can be regarded as a failure, if not sub-optimal effort, in terms of secondary prevention of T2D. These results suggest that in new T2D cases, quality of care needs to be improved and, once achieved, to be maintained over time if the disease burden is to be reduced. The observed care inequalities by sociodemographic factors implies that healthcare providers should bear these factors in mind when delivering care to less advantaged groups in order to achieve optimal outcomes of care across communities.

With a substantial number of uncertain or possible diabetes being excluded from the study cohort, linkage of CALIBER with the diabetes national registry would be worth instigating for further disease ascertainment. In most settings, nearly 90% of diabetes cases are type 2, thus such initiative would help avoid considerable loss of potential T2D cases which, in turn, would improve accuracy in the analysis.

4.6.5 Conclusion

Encouraging findings on overall improved care from previous studies do not necessarily apply to newly diagnosed T2D cases. In the CALIBER cohort, the proportion of incident T2D in receipt of care processes over time are particularly lower than published estimates for prevalent cases. Proportions for meeting glycaemic and blood pressure targets – whilst higher than estimates from prevalent studies – fell short of the corresponding measurements. Additionally, sociodemographic disparities in quality of T2D care did exist.

4.7 Chapter summary

Study 1 casts light on the clinical journey of patients newly diagnosed with T2D in CALIBER as well as provides a base description and understanding of the continual quality of care. It particularly highlights the missed opportunity and inequality of care for primary prevention of vascular complications. The next chapter will investigate factors associated with early achievements of the key intermediate outcome targets.

Chapter 5

Study 2 – Factors associated with achieving intermediate outcome targets for glycaemia, blood pressure and lipid

The diabetic who knows the most lives the longest.
— Elliot Joslin

5.1 Chapter outline

This chapter presents CALIBER analyses conducted to identify factors associated with meeting intermediate outcome targets for HbA1c, blood pressure and total cholesterol, and to investigate whether intermediate outcomes of care are influenced by its process of care.

5.2 Abstract

Background. Observational studies have reported different factors influencing glycaemic, blood pressure and lipid targets in populations with established T2D. Recognition of those factors in newly diagnosed T2D populations is important to help improve quality of care from an early stage, yet studies addressing the issue are lacking.

Objectives. To identify factors, particularly processes of care, which may have a relationship with short-term achievement of intermediate outcome targets for HbA1c, blood pressure and total cholesterol in a newly diagnosed T2D population.

Methods. A cohort of newly diagnosed T2D patients aged 30 years or older with at least two years of follow-up was established from CALIBER. Patients were followed for achievement of glycaemic, blood pressure and total cholesterol targets in the second year after T2D diagnosis. Multivariate multinomial logistic regression was used to estimate the associations of baseline factors and processes of care within the first year from diagnosis with target achievement of intermediate outcomes.

Results. The cohort comprised 44,366 patients, 59.0% of whom achieved the HbA1c target of 7.4% (57.4 mmol/mol), 67.3% achieved the blood pressure target of 145/85 mmHg, 54.7% achieved the total cholesterol target of 5 mmol/L and 37.0% achieved all three targets. Median time needed was 15.6 months to achieve the glycaemic target, 15.8 months to achieve the blood pressure target and 16.2 months to achieve the total cholesterol target. Predictors for meeting the targets were variable across intermediate outcomes yet were consistent with older age at T2D diagnosis and baseline prescription of antiplatelet.

Conclusion. Factors associated with meeting the intermediate outcome target were dissimilar depending on how the intermediate outcome was defined and included demographic variables, cardiovascular risk factors, comorbidities, baseline prescription of cardiovascular medications and initial processes of care after diagnosis of T2D.

5.3 Introduction

Previous studies reported that achievement of glycaemic, blood pressure and lipid targets in prevalent T2D populations are determined by dissimilar factors, depending on the settings, data source and study methods. Whilst body mass index was shown to be consistently associated with achievement of HbA1c and blood pressure targets, studies reported conflicting or variable results for age, gender, deprivation, smoking status, presence of diabetes complications and medical treatments with the key targets.[132,135,146,147] In addition to the inconsistencies, little is known about whether target achievement is influenced by frequency of earlier measurement. Information on these factors or relationships is important to assess the extent of adoption into practice of recommended guidelines, and is particularly valuable in the context of the newly diagnosed T2D population, as it helps inform clinicians and health policy makers about priorities to be set in improving care from the time of diagnosis to prevent or delay progression of the disease.

In consideration of the limitations of previous studies, Study 2 sought to identify factors associated with the achievement of intermediate outcome targets during the second year from diagnosis of T2D in a large population-based cohort with incident T2D, with the particular aim of investigating how preceding processes of care might relate to the target achievement.

5.4 Methods

5.4.1 Study population, study period and inclusion criteria

This was an observational cohort study targeting newly diagnosed T2D in the CALIBER population who were followed prospectively from the first presentation until the 'exit date', defined as the date of transfer out of the practice, the last date of data collection in the practice or the date of death. Included were incident cases of T2D surviving at least two years after diagnosis. Other inclusion criteria are described in **Section 3.9 on pages 111-113.**

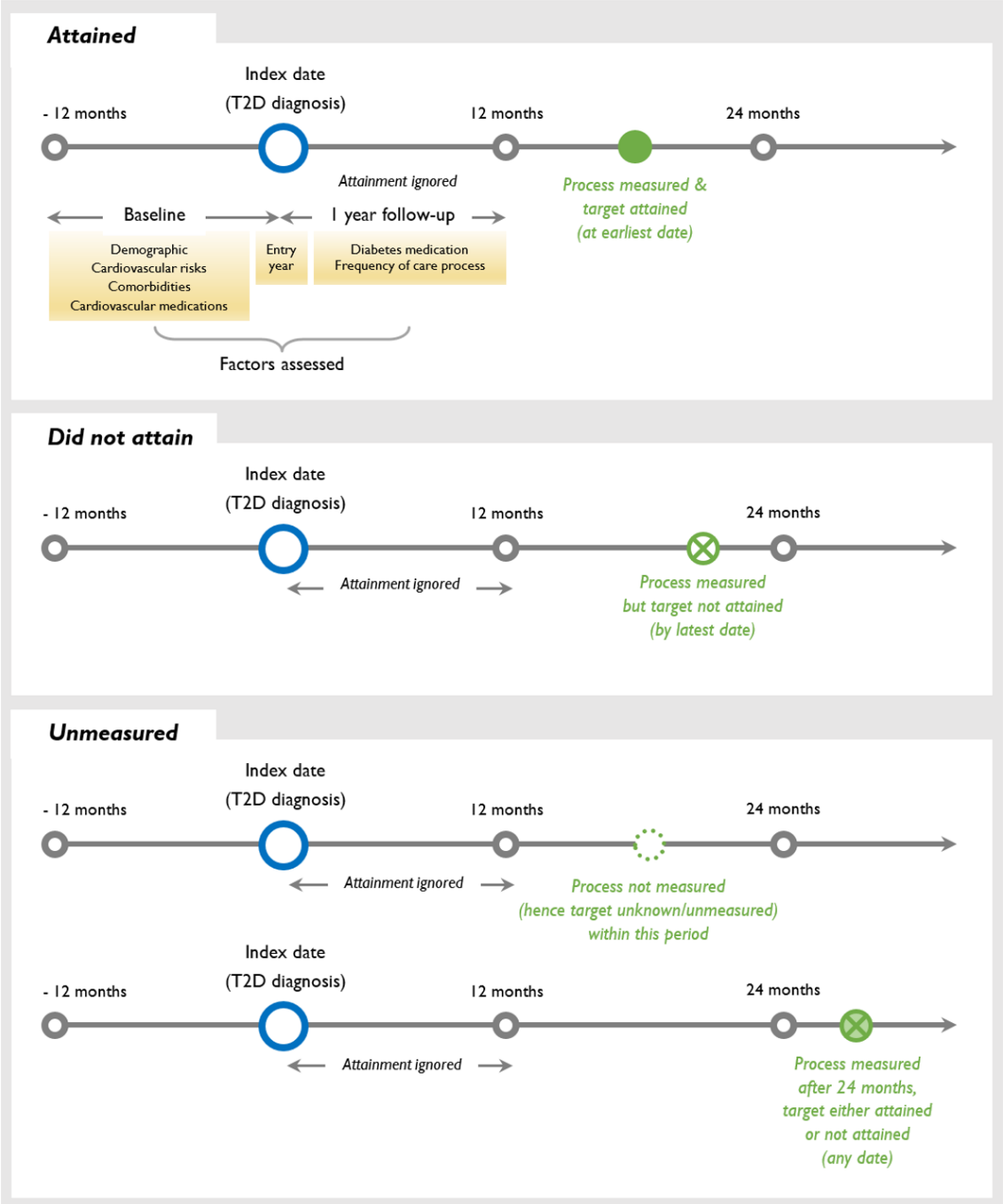
5.4.2 Covariates and endpoints

Prior CPRD records closest to the index date provided relevant covariates for Study 2, including demographic factors (age group, gender, ethnicity and deprivation status), year of diagnosis, baseline cardiovascular risk factors (smoking status, BMI), baseline treatment (blood pressure lowering medication, lipid lowering medication and antiplatelet), initial diabetes treatment and initial processes of care. Care processes of interest were frequency of HbA1c, blood pressure and total cholesterol measurement during the first 12 months after the index date.

The primary endpoints for Study 2 were intermediate outcome targets: HbA1c ≤7.4% (57.4 mmol/mol), blood pressure ≤145/85 mmHg and total cholesterol ≤5 mmol/L.[113] The target was defined as 'attained' or 'not attained' depending on whether or not it was achieved at any time between 12 and 24 months after the index date (**Figure 5.1 on page 159**). If an intermediate outcome was not recorded during the 12-24 months window period, target achievement was recorded as 'unmeasured'. Since one of the study objectives was to explore whether processes of care – among other factors – are predictive of care outcomes, intermediate outcome measurements made earlier than 12 months were ignored as being too early to have been affected by process of care, hence being put off instead until Year 2 to allow assessment of chronologically sensible associations. That said, assuming that most of patients would have been tested for HbA1c twice a year as per recommendation, for example, defining intermediate outcomes within the first year after diagnosis as 'attained' or 'not attained' at or after the first testing can lead to naïve inferences if there is any (e.g. a single HbA1c testing is associated with target attainment).

Also evaluated in this study was the influence of processes of care on a composite measure of intermediate outcome targets classified as unmeasured, none of targets achieved, single target achieved, two targets achieved and all three targets achieved.

Figure 5.1 Factors assessed and definition of attainment of glycaemic, blood pressure and total cholesterol targets (as main outcomes) in Study 2



5.4.3 Statistical analysis

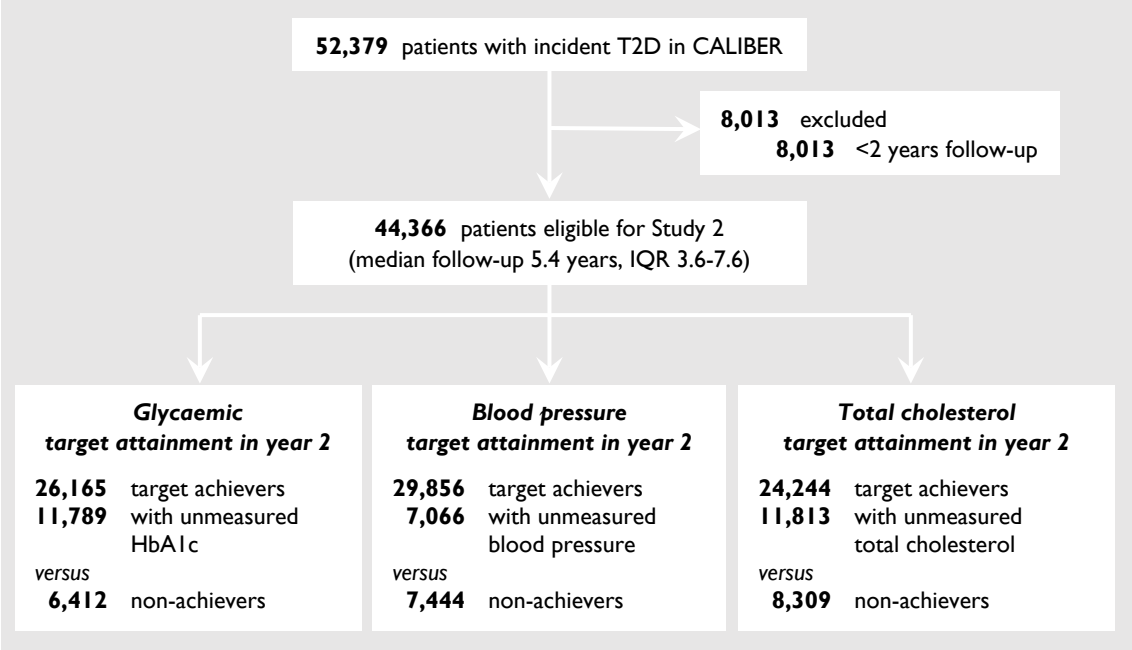
Descriptive results for continuous variables were summarised as means or medians, whereas categorical variables were summarised as proportions. Multivariate multinomial logistic regressions were used to examine factors contributing to attainment of each intermediate outcome target and composite target. The contributing factors were compared within each patient group by attainment of individual target relative to patients who 'did not attain (the relevant) target', or within

each patient group by attainment of composite target relative to patients with 'single target attainment'. Estimates were adjusted for baseline characteristics, initial diabetes treatment and HbA1c measurements, and stratified by GP practice to account for heterogeneity across practices. Interactions between age and sex and between diabetes medication and time to first prescription were investigated. Final models were fitted using Bayesian's information criterion.[274] Missing values were not imputed and missingness indicators were applied instead for all regression models. Analyses were conducted using Stata 13.0.

5.5 Results

Of the 52,379 patients newly diagnosed with T2D in CALIBER, 8,013 (15.3%) were excluded due to having less than two years follow-up, generating a total of 44,366 patients eligible for Study 2 (**Figure 5.2 below**). The median follow-up beyond analysis was 5.4 years (IQR 3.6-7.6).

Figure 5.2 Patient flow chart for Study 2

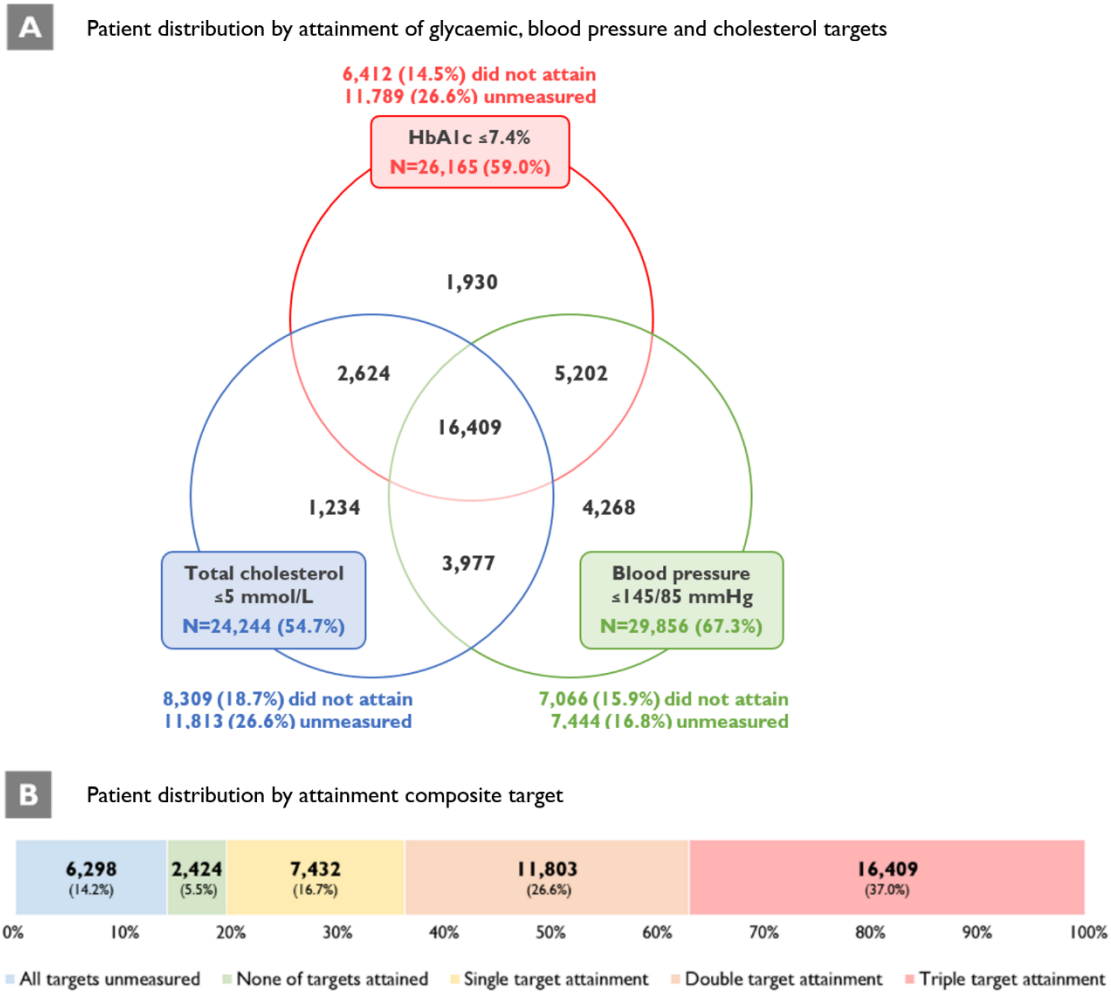


5.5.1 Attainment of intermediate outcome targets within second year after T2D diagnosis

Of the 44,366 total patients eligible for Study 2, 6,298 (14.2%) had none of the key intermediate outcomes measured during the second year after diagnosis and another 2,424 (5.5%) in whom measurements were made failed to meet any of the outcome targets. Patients meeting intermediate outcome targets were 26,165 (59.0%) for HbA1c, 29,856 (67.3%) for blood pressure and 24,244 (54.7%) for cholesterol, and the number of patients who had none of the intermediate outcomes measured were all higher than those failing to meet relevant targets (**Figure 5.3 on page**

161). A total of 7,432 patients (16.7%) met just one of the outcome targets, 11,803 (26.6%) met two and 16,409 (37.0%) met all three (**Figure 5.3 below**).

Figure 5.3 Patient distributions by attainment of intermediate outcome targets during the 2nd year of follow-up (N=44,366)



5.5.2 Baseline characteristics by attainment of intermediate outcome targets

Glycaemic target (HbA1c ≤7.4% or 57.4 mmol/mol). It took a median of 15.6 months (IQR 13.8-18.3) after diagnosis of T2D for patients to meet the HbA1c target. A greater proportion of patients diagnosed after 2004 met the target compared with patients diagnosed earlier. Patients who met the target were older, more likely of white ethnicity and non-smokers, had more frequent HbA1c measurements, had higher comorbidities for CHD, PAD and renal disease and were proportionately more likely to receive antiplatelet drugs and treatments to lower blood pressure and lipids compared to patients who failed to meet the target or had no measurements made (**Table 5.1 on pages 163-164**).

Blood pressure target (≤145/85 mmHg). Similarly to HbA1c, it took patients who met the blood pressure target a median of 15.8 months (IQR 13.7-18.8). Factors associated with meeting the target were also similar to HbA1c, with an additional factor being in receipt of hypoglycaemic treatment (**Table 5.1 on pages 163-164**).

Total cholesterol target (≤5 mmol/L). The median needed to meet the cholesterol target was slightly longer (16.2 months, IQR 14.0-19.3) and the associated factors with meeting the target were identical to those of blood pressure (**Table 5.1 on pages 163-164**).

Composite target. A median of 17.7 months (IQR 15.3-20.7) was needed to meet the triple target of HbA1c, blood pressure and cholesterol. Factors related to meeting the triple target remained the same as blood pressure, with addition of more frequent measurements of the three key care (**Table 5.2 on pages 165-166**).

Table 5.1 Baseline characteristics of incident T2D cohort in CALIBER by attainment of glycaemic, blood pressure and total cholesterol targets during the 2nd year of follow-up

Characteristics	HbA1c ≤7.4% (57.4 mmol/mol)						Blood pressure ≤145/85 mmHg						Total cholesterol ≤5 mmol/L					
	Attained (N=26,165)		Did not attain (N=6,412)		Unmeasured (N=11,789)		Attained (N=29,856)		Did not attain (N=7,444)		Unmeasured (N=7,066)		Attained (N=24,244)		Did not attain (N=8,309)		Unmeasured (N=11,813)	
Demographic																		
Duration of GP practice registration, median (IQR) years	11.9	(9.1-17.3)	11.4	(7.7-15.9)	8.1	(3.2-13.7)	11.6	(8.8-17.1)	12.3	(8.9-17.2)	4.8	(2.5-10.7)	11.7	(8.8-17.1)	11.8	(8.8-17.0)	8.1	(3.2-13.5)
Age, median (IQR) years	64.5	(55.6-73.1)	58.3	(48.9-68.4)	63.0	(51.7-74.0)	64.0	(54.8-72.7)	62.3	(52.3-72.4)	60.7	(49.4-73.0)	64.0	(55.1-72.3)	61.1	(51.6-71.5)	63.0	(51.7-74.7)
Age group, n (%)																		
<40	842	(3.2)	508	(7.9)	874	(7.4)	1,154	(3.9)	350	(5.0)	720	(9.7)	842	(3.5)	470	(5.7)	912	(7.7)
40-<50	2,884	(11.0)	1,239	(19.3)	1,696	(14.4)	3,557	(11.9)	1,043	(14.8)	1,219	(16.4)	2,813	(11.6)	1,340	(16.1)	1,666	(14.1)
50-<60	5,883	(22.5)	1,768	(27.6)	2,587	(21.9)	6,830	(22.9)	1,705	(24.1)	1,703	(22.9)	5,571	(23.0)	2,089	(25.1)	2,578	(21.8)
60-<70	7,690	(29.4)	1,516	(23.6)	2,658	(22.6)	8,562	(28.7)	1,791	(25.4)	1,511	(20.3)	7,316	(30.2)	2,019	(24.3)	2,529	(21.4)
70-<80	6,370	(24.4)	1,016	(15.9)	2,394	(20.3)	6,963	(23.3)	1,478	(20.9)	1,339	(18.0)	5,727	(23.6)	1,593	(19.2)	2,460	(20.8)
>80	2,496	(9.5)	365	(5.7)	1,580	(13.4)	2,790	(9.3)	699	(9.9)	952	(12.8)	1,975	(8.2)	798	(9.6)	1,668	(14.1)
Women, n (%)	11,900	(45.5)	2,690	(42.0)	5,426	(46.0)	13,573	(45.5)	3,104	(43.9)	3,339	(44.9)	10,160	(41.9)	4,367	(52.6)	5,489	(46.5)
Social deprivation, n (%)*																		
1 (most affluent)	5,437	(20.8)	1,278	(19.9)	2,230	(18.9)	6,083	(20.4)	1,461	(20.7)	1,401	(18.8)	4,998	(20.6)	1,692	(20.4)	2,255	(19.1)
5 (most deprived)	4,764	(18.2)	1,407	(21.9)	2,580	(21.9)	5,776	(19.4)	1,328	(18.8)	1,647	(22.1)	4,568	(18.8)	1,658	(20.0)	2,525	(21.4)
Ethnicity, n (%)*																		
White	13,969	(53.4)	3,126	(48.8)	5,488	(46.6)	15,569	(52.2)	3,564	(50.4)	3,450	(46.4)	12,572	(51.9)	4,370	(52.6)	5,641	(47.8)
Black	466	(1.8)	199	(3.1)	344	(2.9)	586	(2.0)	160	(2.3)	263	(3.5)	486	(2.0)	183	(2.2)	340	(2.9)
South Asian	650	(2.5)	254	(4.0)	451	(3.8)	826	(2.8)	170	(2.4)	359	(4.8)	671	(2.8)	236	(2.8)	448	(3.8)
Other	362	(1.4)	108	(1.7)	238	(2.0)	436	(1.5)	85	(1.2)	187	(2.5)	339	(1.4)	138	(1.7)	231	(2.0)
Diabetes diagnosis																		
Year of diagnosis																		
1998-2003	10,700	(40.9)	3,183	(49.6)	8,079	(68.5)	12,617	(42.3)	4,175	(59.1)	5,170	(69.5)	9,160	(37.8)	4,887	(58.8)	7,915	(67.0)
2004-2006	11,233	(42.9)	2,284	(35.6)	2,899	(24.6)	12,475	(41.8)	2,103	(29.8)	1,838	(24.7)	10,933	(45.1)	2,426	(29.2)	3,057	(25.9)
2007-2009	4,232	(16.2)	945	(14.7)	811	(6.9)	4,764	(16.0)	788	(11.2)	436	(5.9)	4,151	(17.1)	996	(12.0)	841	(7.1)
HbA1c, mean (SD) mmol/mol*	58.7	(21.1)	76.2	(22.7)	58.8	(20.1)	61.5	(22.2)	62.0	(22.0)	60.6	(12.3)	60.2	(21.1)	61.9	(22.5)	61.3	(21.7)
Time needed to achieve target, median (IQR) months	15.6	(13.8-18.3)	–		–		15.8	(13.7-18.8)	–		–		16.2	(14.0-19.3)	–		–	
Cardiovascular risks																		
Smoking, n (%)*																		
Current	2,262	(8.7)	650	(10.1)	512	(4.3)	2,670	(8.9)	496	(7.0)	258	(3.5)	2,289	(9.4)	612	(7.4)	523	(4.4)
Ex	4,335	(16.6)	784	(12.2)	637	(5.4)	4,806	(16.1)	729	(10.3)	221	(3.0)	4,261	(17.6)	855	(10.3)	640	(5.4)
Never	4,900	(18.7)	886	(13.8)	883	(7.5)	5,285	(17.7)	1,005	(14.2)	379	(5.1)	4,620	(19.1)	1,166	(14.0)	883	(7.5)

Blood pressure*																	
Systolic, mean (SD) mmHg	145.9	(19.3)	145.4	(20.4)	145.9	(20.4)	144.1	(18.9)	154.6	(20.7)	143.7	(20.1)	145.1	(19.2)	147.5	(20.0)	147.0	(20.9)
Diastolic, mean (SD) mmHg	83.4	(10.9)	85.3	(11.4)	83.8	(11.6)	82.7	(10.7)	88.2	(11.6)	84.3	(11.9)	83.1	(11.0)	85.2	(11.0)	84.4	(11.6)
Hypertension, n (%)*	4,815	(18.4)	929	(14.5)	927	(7.9)	4,844	(16.2)	1,585	(22.4)	242	(3.3)	4,264	(17.6)	1,471	(17.7)	936	(7.9)
Total cholesterol, mean (SD) mmol/L*	5.4	(1.3)	5.7	(1.5)	5.5	(1.3)	5.5	(1.3)	5.7	(1.4)	5.7	(1.4)	5.8	(1.3)	6.5	(1.3)	5.8	(1.3)
LDL cholesterol, mean (SD) mmol/L*	3.2	(1.1)	3.3	(1.1)	3.3	(1.1)	3.2	(1.1)	3.4	(1.0)	3.4	(1.1)	3.1	(1.1)	3.8	(1.0)	3.2	(1.1)
HDL cholesterol, mean (SD) mmol/L*	1.2	(0.4)	1.2	(0.3)	1.3	(0.4)	1.2	(0.4)	1.2	(0.4)	1.2	(0.4)	1.2	(0.3)	1.3	(0.4)	1.2	(0.4)
Triglycerides, mean (SD) mmol/L	2.4	(2.1)	3.0	(3.0)	2.4	(2.1)	2.5	(2.2)	2.6	(2.4)	2.6	(2.5)	2.4	(2.1)	2.8	(2.7)	2.5	(2.4)
Serum creatinine, mean (SD) µmol/L*	91.6	(26.0)	88.0	(25.8)	95.2	(46.6)	91.6	(29.7)	90.7	(27.2)	91.8	(28.5)	91.6	(28.0)	89.1	(21.4)	94.2	(42.3)
BMI, mean (SD) kg/m^2*	31.7	(6.3)	32.7	(6.7)	31.1	(7.1)	31.6	(6.3)	32.6	(6.9)	31.3	(7.4)	31.8	(6.4)	32.0	(6.5)	31.3	(6.9)
BMI category, n (%)*																		
Underweight (<18.5)	41	(0.2)	8	(0.1)	29	(0.3)	49	(0.2)	15	(0.2)	12	(0.2)	37	(0.2)	17	(0.2)	22	(0.2)
Normal weight (18.5-24.9)	1,172	(4.5)	252	(3.9)	361	(3.1)	1,399	(4.7)	234	(3.3)	152	(2.0)	1,138	(4.7)	315	(3.8)	332	(2.8)
Overweight (25.0-29.9)	3,508	(13.4)	593	(9.3)	676	(5.7)	3,789	(12.7)	735	(10.4)	253	(3.4)	3,241	(13.4)	904	(10.9)	632	(5.4)
Obese class I (30.0-34.9)	3,236	(12.4)	691	(10.8)	553	(4.7)	3,568	(12.0)	716	(10.1)	196	(2.6)	3,051	(12.6)	863	(10.4)	566	(4.8)
Obese class II (35.0-39.9)	1,573	(6.0)	418	(6.5)	303	(2.6)	1,749	(5.9)	413	(5.8)	132	(1.8)	1,494	(6.2)	493	(5.9)	307	(2.6)
Obese class III (≥40)	1,071	(4.1)	304	(4.7)	231	(2.0)	1,171	(3.9)	333	(4.7)	102	(1.4)	1,064	(4.4)	309	(3.7)	233	(2.0)
Medications prescribed																		
Blood pressure lowering drug, n (%)	13,632	(52.1)	2,378	(37.1)	3,137	(26.6)	14,988	(50.2)	3,241	(45.9)	918	(12.3)	12,562	(51.8)	3,549	(42.7)	3,036	(25.7)
Lipid lowering drug, n (%)	5,714	(21.8)	932	(14.5)	970	(8.2)	6,415	(21.5)	922	(13.1)	279	(3.8)	5,862	(24.2)	983	(11.8)	771	(6.5)
Antiplatelet, n (%)	5,286	(20.2)	805	(12.6)	1,261	(10.7)	5,233	(21.2)	1,720	(14.0)	399	(5.4)	5,228	(21.6)	990	(11.9)	1,134	(9.6)
Comorbidities																		
Coronary heart disease	4,908	(18.8)	970	(15.1)	2,013	(17.1)	5,939	(19.9)	1,014	(14.4)	938	(12.6)	5,113	(21.1)	1,043	(12.6)	1,735	(14.7)
Cerebrovascular disease	1,472	(5.6)	283	(4.4)	748	(6.3)	1,765	(5.9)	332	(4.7)	406	(5.5)	1,444	(6.0)	354	(4.3)	705	(6.0)
Peripheral arterial disease	864	(3.3)	165	(2.6)	337	(2.9)	985	(3.3)	220	(3.1)	161	(2.2)	858	(3.5)	208	(2.5)	300	(2.5)
Renal disease	532	(2.0)	102	(1.6)	167	(1.4)	591	(2.4)	148	(1.2)	62	(0.8)	543	(2.2)	117	(1.4)	141	(1.2)
Initial care processes†																		
Diabetes medication, n (%)	14,643	(56.0)	4,598	(71.7)	2,958	(25.1)	16,916	(56.7)	3,764	(53.3)	1,519	(20.4)	14,249	(58.8)	4,388	(52.8)	3,562	(30.2)
Frequency of HbA1c measurement, median (IQR)	2	(2-3)	2	(1-3)	2	(1-2)	2	(2-3)	2	(1-3)	2	(1-2)	2	(2-3)	2	(1-3)	2	(1-3)
Frequency of blood pressure measurement, median (IQR)	4	(2-6)	3	(2-5)	3	(1-4)	4	(2-6)	4	(2-6)	2	(1-3)	4	(2-6)	3	(2-5)	3	(2-5)
Frequency of total cholesterol measurement, median (IQR)	2	(1-2)	2	(1-2)	1	(1-2)	2	(1-2)	2	(1-2)	1	(1-2)	2	(1-2)	2	(1-2)	1	(1-2)

Baseline was defined as 365 days before the index date (T2D diagnosis). *Proportion of non-missing baseline data was 99.7% for deprivation, 57.8% for ethnicity, 35.7% for smoking status, for 33.9% BMI, 20.8% for HbA1c, for 63.3% blood pressure, for 15.3% total cholesterol, for 29.1% LDL-C, 37.7% for HDL-C, 12.4% for triglyceride and 18.3% for serum creatinine. †Within 12 month window since the index date.

Table 5.2 Baseline characteristics of incident T2D cohort in CALIBER by attainment of composite target during the 2nd year of follow-up

Characteristics	Unmeasured (N=6,298)		Attained none of targets (N=2,424)		Single target attainment (N=7,432)		Double target attainment (N=11,803)		Triple target attainment (N=16,409)	
Demographic										
Duration of GP practice registration, median (IQR) years	4.1	(2.3-9.4)	11.9	(7.9-16.6)	11.6	(8.0-16.8)	11.6	(8.7-16.9)	11.9	(9.1-17.4)
Age in years, median (IQR)	61.0	(49.6-73.3)	60.5	(50.0-72.0)	61.6	(51.3-72.8)	63.0	(53.6-72.3)	65.0	(56.4-72.9)
Age group, n (%)										
<40	614	(9.8)	185	(7.6)	451	(6.1)	535	(4.5)	439	(2.7)
40-<50	1,010	(16.0)	416	(17.2)	1,193	(16.1)	1,539	(13.0)	1,661	(10.1)
50-<60	1,421	(22.6)	588	(24.3)	1,760	(23.7)	2,883	(24.4)	3,586	(21.9)
60-<70	1,284	(20.4)	526	(23.0)	1,710	(23.0)	3,174	(26.9)	5,170	(31.5)
70-<80	1,147	(18.2)	460	(19.8)	1,470	(19.8)	2,519	(21.3)	4,184	(25.5)
>80	822	(13.1)	249	(11.4)	848	(11.4)	1,153	(9.8)	1,369	(8.3)
Women, n (%)	2,840	(45.09)	1,118	(46.1)	3,564	(48.0)	5,413	(45.9)	7,081	(43.2)
Social deprivation, n (%)*										
1 (most affluent)	1,165	(18.5)	453	(18.7)	1,506	(20.3)	2,451	(20.8)	3,370	(20.5)
5 (most deprived)	1,415	(22.5)	537	(22.2)	1,499	(20.2)	2,291	(19.4)	3,009	(18.3)
Ethnicity, n (%)*										
White	2,891	(45.9)	1,208	(49.8)	3,640	(49.0)	6,062	(51.4)	8,782	(53.5)
Black	233	(3.7)	54	(2.2)	180	(2.4)	268	(2.3)	274	(1.7)
South Asian	309	(4.9)	65	(2.7)	225	(3.0)	346	(2.9)	410	(2.5)
Other	163	(2.6)	21	(0.9)	121	(1.6)	193	(1.6)	210	(1.3)
Diabetes diagnosis										
Year of diagnosis										
1998-2003	4,510	(71.6)	1,734	(71.5)	4,524	(60.9)	5,629	(47.7)	5,565	(33.9)
2004-2006	1,502	(23.9)	520	(21.5)	2,092	(28.2)	4,357	(36.9)	7,945	(48.4)
2007-2009	286	(4.5)	170	(7.0)	816	(11.0)	1,817	(15.4)	2,899	(17.7)
HbA1c, mean (SD) mmol/mol*	66.9	(23.3)	73.9	(25.1)	70.5	(25.6)	68.7	(24.8)	64.8	(23.2)
Time needed to achieve target in months, median (IQR)	–		–		16.3	(14.0-19.2)	20.7	(18.0-22.6)	17.7	(15.3-20.7)
Cardiovascular risks										
Smoking, n (%)*										
Current	178	(2.8)	133	(5.5)	532	(7.2)	1,054	(8.9)	1,527	(9.3)
Ex	126	(2.0)	149	(6.2)	718	(9.7)	1,605	(13.6)	3,158	(19.3)
Never	271	(4.3)	243	(10.0)	866	(11.7)	1,928	(16.3)	3,361	(20.5)
Blood pressure*										
Systolic, mean (SD) mmHg	145.0	(20.4)	153.7	(20.5)	147.6	(21.0)	146.6	(20.1)	144.0	(18.4)
Diastolic, mean (SD) mmHg	84.7	(11.9)	88.4	(11.6)	85.3	(11.6)	84.2	(11.0)	82.4	(10.7)

Hypertension, n (%)*	178	(2.8)	403	(16.6)	1,152	(15.5)	2,043	(17.3)	2,895	(17.6)
Total cholesterol, mean (SD) mmol/L*	5.6	(1.4)	6.1	(1.3)	5.9	(1.5)	5.6	(1.3)	5.3	(1.2)
LDL cholesterol, mean (SD) mmol/L*	3.4	(1.1)	3.7	(1.1)	3.5	(1.1)	3.3	(1.1)	3.1	(1.1)
HDL cholesterol, mean (SD) mmol/L*	1.2	(0.4)	1.2	(0.4)	1.3	(0.4)	1.2	(0.4)	1.2	(0.3)
Triglycerides, mean (SD) mmol/L*	2.5	(2.6)	3.0	(2.7)	2.8	(2.6)	2.6	(2.4)	2.3	(1.9)
Serum creatinine, mean (SD) µmol/L*	93.1	(27.9)	91.3	(40.3)	90.8	(36.9)	90.7	(25.7)	92.0	(27.9)
BMI, mean (SD) kg/m^2*	31.4	(7.5)	32.5	(7.2)	31.9	(6.7)	31.9	(6.6)	31.6	(6.2)
BMI category, n (%)*										
Underweight (<18.5)	9	(0.1)	5	(0.2)	21	(0.3)	17	(0.1)	24	(0.2)
Normal weight (18.5-24.9)	102	(1.6)	73	(3.0)	298	(4.0)	525	(4.5)	787	(4.8)
Overweight (25.0-29.9)	167	(2.7)	191	(7.9)	689	(9.3)	1,341	(11.4)	2,389	(14.6)
Obese class I (30.0-34.9)	126	(2.0)	178	(7.3)	663	(8.9)	1,347	(11.4)	2,166	(13.2)
Obese class II (35.0-39.9)	86	(1.4)	117	(4.8)	403	(5.4)	651	(5.5)	1,037	(6.3)
Obese class III (≥40)	72	(1.1)	92	(3.8)	259	(3.5)	502	(4.3)	681	(4.2)
Medications prescribed										
Blood pressure lowering agent, n (%)	651	(10.3)	899	(37.1)	3,043	(40.9)	5,523	(46.8)	9,031	(55.0)
Lipid lowering drug, n (%)	155	(2.5)	188	(7.8)	858	(11.5)	2,112	(17.9)	4,303	(26.2)
Antiplatelet, n (%)	271	(4.3)	224	(9.2)	1,021	(13.7)	2,017	(17.1)	3,819	(23.3)
Comorbidities										
Coronary heart disease	793	(12.6)	279	(11.5)	1,192	(16.0)	2,113	(17.9)	3,514	(21.4)
Cerebrovascular disease	353	(5.6)	106	(4.4)	414	(5.6)	623	(5.3)	1,007	(6.1)
Peripheral arterial disease	123	(2.0)	65	(2.7)	237	(3.2)	353	(3.0)	588	(3.6)
Renal disease	49	(0.8)	20	(0.8)	120	(1.6)	216	(1.8)	396	(2.4)
Initial care processes†										
Diabetes medication, n (%)	934	(14.8)	1,117	(46.1)	3,939	(53.0)	6,758	(57.3)	9,451	(57.6)
Frequency of HbA1c measurement, median (IQR)	1	(1-2)	2	(1-2)	2	(1-3)	2	(1-3)	2	(2-3)
Frequency of blood pressure measurement, median (IQR)	2	(1-3)	3	(2-5)	3	(2-5)	4	(2-6)	4	(3-6)
Frequency of total cholesterol measurement, median (IQR)	1	(1-2)	1	(1-2)	1	(1-2)	2	(1-2)	2	(1-3)

Baseline was defined as 365 days before the index date (T2D diagnosis).

*Proportion of non-missing baseline data was 99.7% for deprivation, 57.8% for ethnicity, 35.7% for smoking status, for 33.9% BMI, 20.8% for HbA1c, for 63.3% blood pressure, for 15.3% total cholesterol, for 29.1% LDL-C, 37.7% for HDL-C, 12.4% for triglyceride and 18.3% for serum creatinine.

†Within 12 month window since the index date.

5.5.3 Factors associated with attainment of intermediate outcome targets for HbA1c, blood pressure and total cholesterol

In multivariate regressions, factors associated with meeting the individual intermediate outcome target were variable, yet positive findings were consistently observed for the year of T2D diagnosis, treatment with antiplatelet at baseline and frequency of intermediate outcome measurements. With an exception for frequency of blood pressure and total cholesterol measurements, these factors continued to show positive associations with all the three targets being met when compared with meeting a single target only. Details on the factors associated with meeting individual and composite targets are summarised below.

Glycaemic target (HbA1c ≤7.4% or 57.4 mmol/mol). The likelihood of meeting the glycaemic target rather than failing to meet the target were significantly higher for patients who were older at T2D diagnosis or diagnosed from 2004 onwards. In particular, for an additional HbA1c measurement within the first year, the likelihood of meeting the target during the second year relative to not meeting the target increased by 15% (RRR 1.15, 95% CI 1.12-1.19). Treatment with blood pressure lowering medication and antiplatelet were also positively associated with meeting the glycaemic target. In contrast, blacks and South Asians, being a current smoker, prior CHD, renal disease and diabetes treatment reduced the likelihood of meeting the glycaemic target (**Figure 5.4 on page 169**).

Older age at diagnosis was associated with a smaller increased likelihood of having no HbA1c measurement relative to not meeting the target. Women and most deprived patients also had a higher likelihood of not having their HbA1c measured. Diabetes treatment in the first year was associated with either reduced likelihood of meeting the target or having HbA1c unmeasured, suggesting that the highest risk was for failing to meet glycaemic target in the second year despite the initial treatment. Stroke, PAD and BMI were not associated with the attainment category for glycaemic target.

Blood pressure target (≤145/85 mmHg). The likelihood of meeting the blood pressure target rather than failing to meet the target were significantly higher for women, South Asian patients and patients who were older at T2D diagnosis or diagnosed from 2004 onwards. For an additional blood pressure measurement within the first year, the likelihood of meeting the target during the second year relative to not meeting the target increased marginally by 2% (RRR 1.02, 95% CI 1.01-1.03). Being an ex-smoker, prior CHD or renal disease, treatment with antiplatelet, lipid lowering and diabetes medications were also positively associated with meeting the blood pressure target. In contrast, prior PAD and blood pressure treatment reduced the likelihood of meeting the blood pressure target (**Figure 5.5 on page 170**).

Besides being associated with an increased likelihood of meeting the blood pressure target, women, South Asians and prior CHD were also associated with an increased likelihood of having no blood pressure measurements made over failing to meet the target. With multinomial

logistic regressions, the RRR of 1.16 for meeting blood pressure target and of 1.38 for having blood pressure unmeasured for South Asians translate to the meaning that the relative probability to meet blood pressure target over not meeting the target is slightly larger than to have no blood pressure measurement over not meeting the target.

Blacks and those of other ethnicity, being more deprived, a current smoker and having a prior stroke also had a higher likelihood of having no blood pressure measurement over not meeting the target. Treatment for high blood pressure was associated with either reduced likelihood of meeting the target or having no blood pressure measured. In other words, patients who received blood pressure treatment did have less probability to meet the target (RRR 0.90), but also less probability to get their blood pressure unmeasured (0.40) over failing to meet BP target. These indicate that: (1) blood pressure treatment did not guarantee success in meeting target, and (2) receipt of blood pressure treatment is possible without having the blood pressure measured, but still those receiving treatment will mostly fail to meet target than to get no measurement.

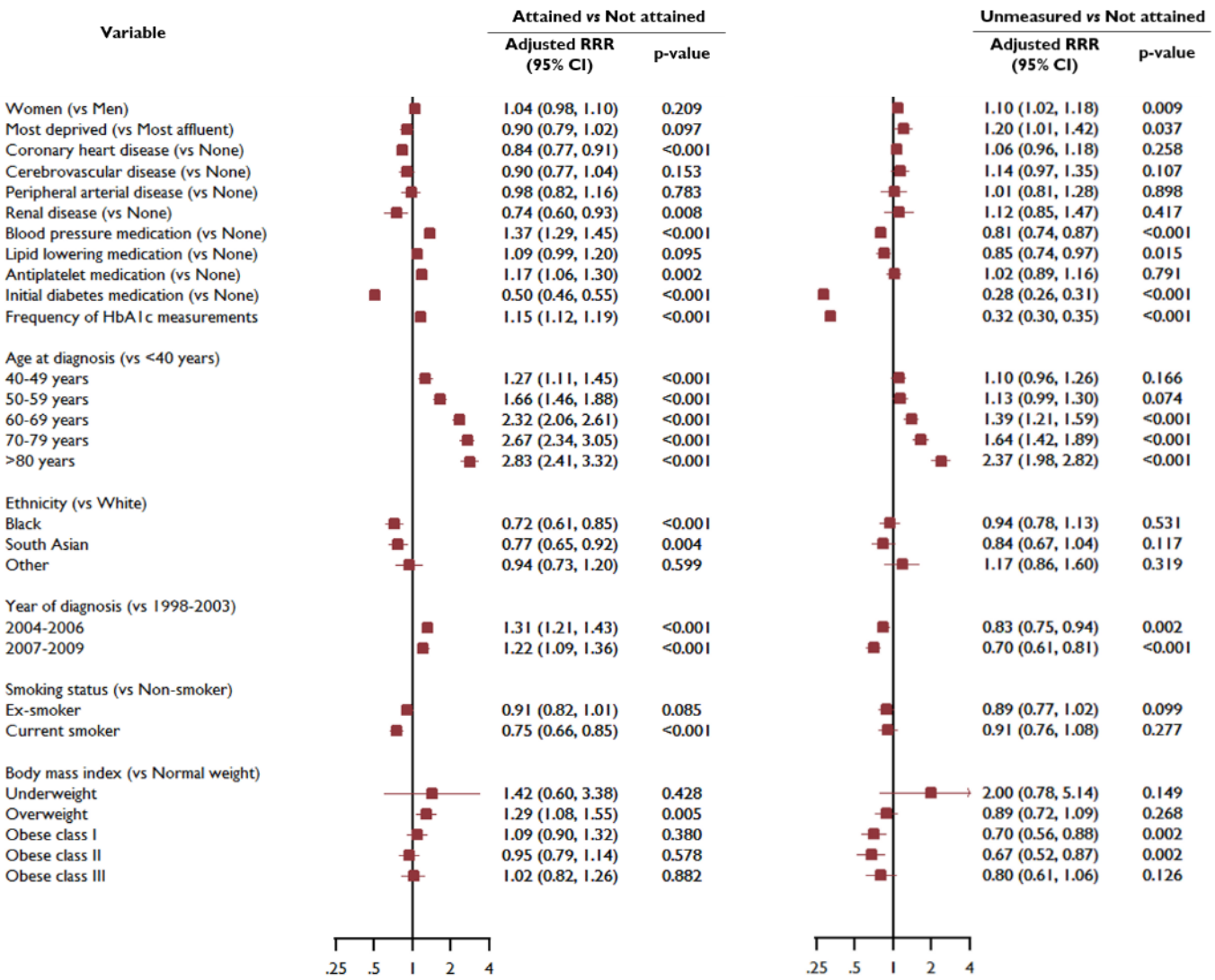
Total cholesterol target (≤5 mmol/L). The likelihood of meeting total cholesterol target rather than failing to meet the target were significantly higher for patients who were older at T2D diagnosis, diagnosed from 2004 onwards, had prior CHD and had been treated with antiplatelet, lipid lowering and diabetes medications. For every additional total cholesterol measurement within the first year, the likelihood of meeting the target during the second year relative to not meeting the target increased by 19% (RRR 1.19, 95% CI 1.16-1.23). Female gender was the only factor significantly associated with reduced likelihood of meeting the total cholesterol target (**Figure 5.6 on page 171**).

Blacks and patients who had prior CHD or stroke had a higher likelihood of having total cholesterol unmeasured over not meeting the target. Conversely, blood pressure medication and BMI outside the normal range were associated with reduced likelihood of having total cholesterol unmeasured. Women, who had reduced likelihood of meeting the target, were also significantly associated with reduced likelihood of having total cholesterol unmeasured.

Composite target attainment. Being older at T2D diagnosis, diagnosed from 2004 onwards, treatment with lipid lowering medication, prior CHD and stroke were all positively associated with meeting double or triple intermediate outcome targets relative to patients who met any single target (**Figure 5.7 on pages 172-173**). An additional HbA1c measurement was associated with an increased likelihood of meeting double targets by 30% (RRR 1.30 95% CI 1.25-1.36) and meeting triple targets by 56% (RRR 1.56, 95% CI 1.47-1.66). Black ethnicity also had a higher likelihood of meeting double but not triple targets. Being overweight and treated with blood pressure medication or antiplatelet were positively associated with meeting triple but not double targets.

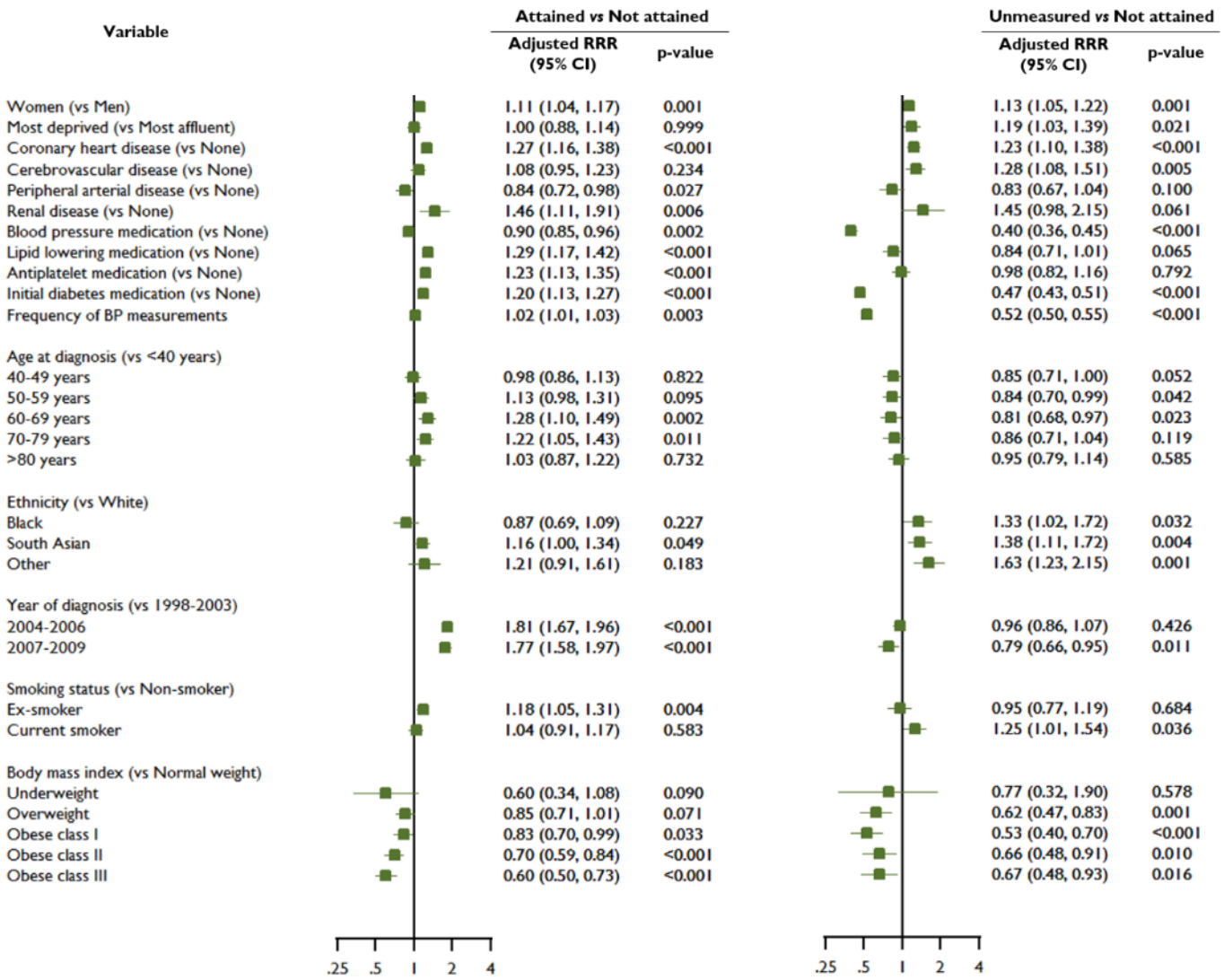
Female gender and frequency of blood pressure measurements significantly reduced the likelihood of meeting double or triple targets, whereas being a current smoker reduced the likelihood of meeting triple targets only.

Figure 5.4 Factors associated with attainment of glycaemic target during the 2nd year of follow-up



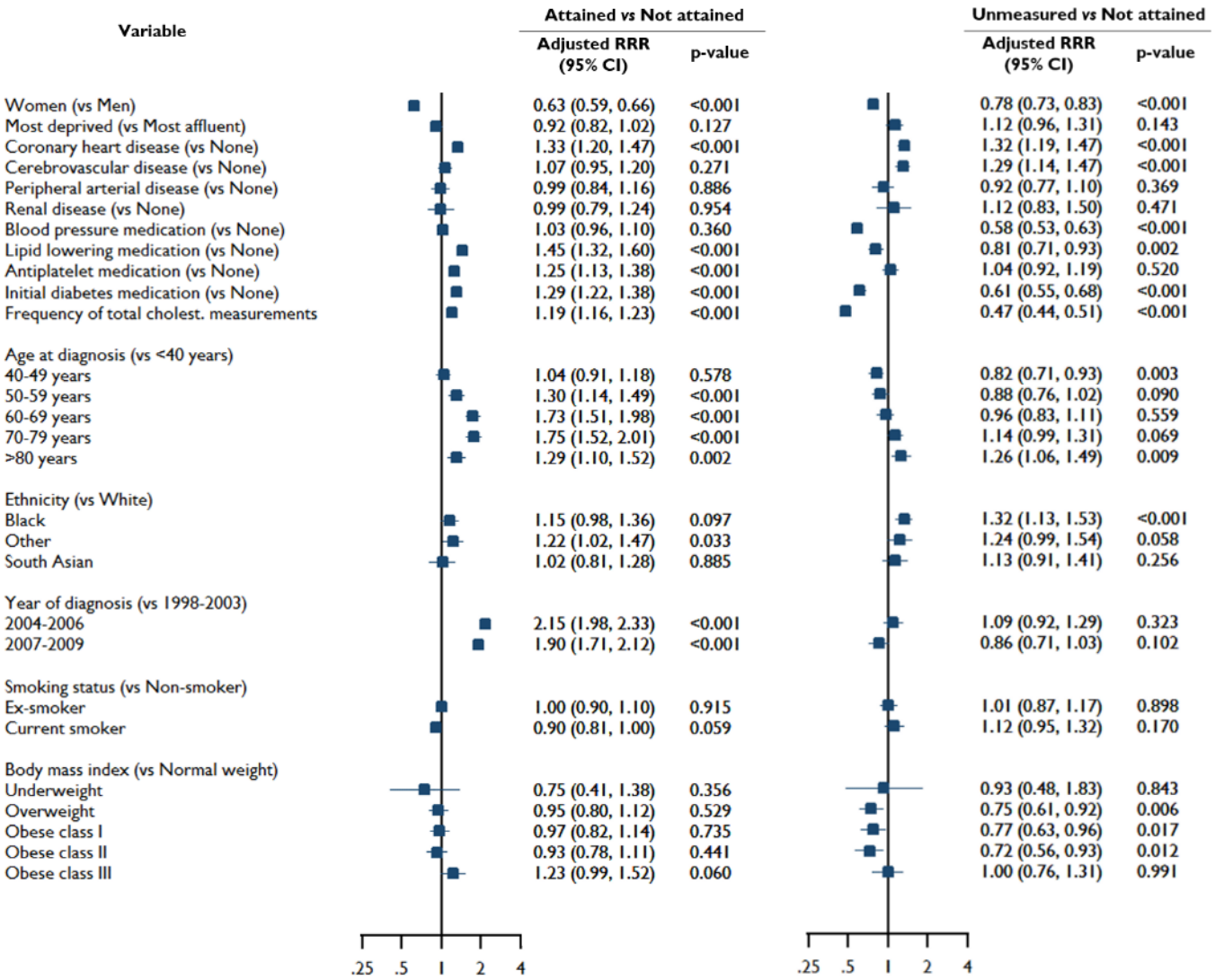
Multivariate regression models were stratified by GP practice. Control group was 'Target not attained'. Abbreviations: CI, confidence interval; RRR, relative risk ratio.

Figure 5.5 Factors associated with attainment of blood pressure target during the 2nd year of follow-up



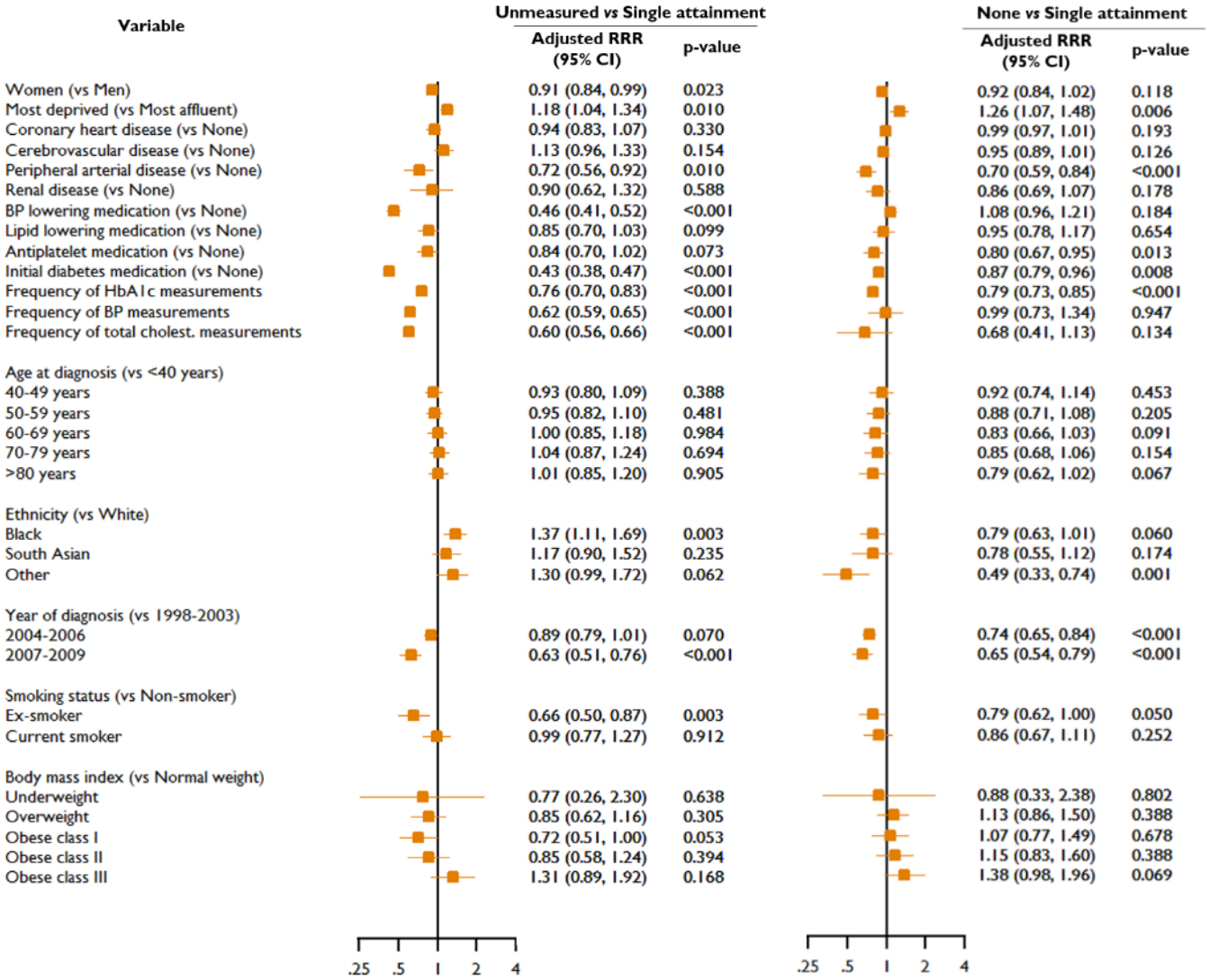
Multivariate regression models were stratified by GP practice. Control group was 'Target not attained'. Abbreviations: CI, confidence interval; RRR, relative risk ratio.

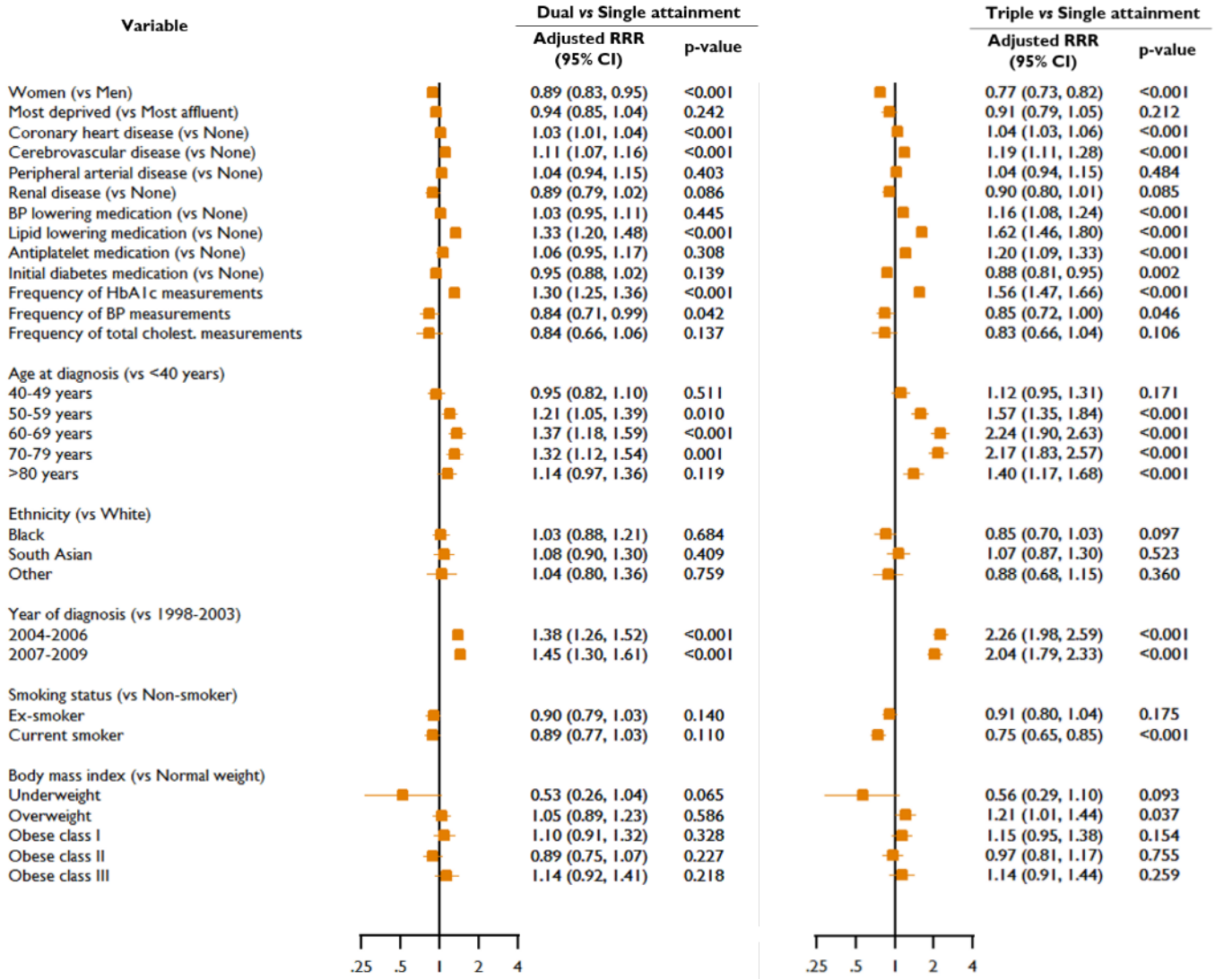
Figure 5.6 Factors associated with attainment of total cholesterol target during the 2nd year of follow-up



Multivariate regression models were stratified by GP practice. Control group was 'Target not attained'. Abbreviations: CI, confidence interval; RRR, relative risk ratio.

Figure 5.7 Factors associated with attainment of composite target during the 2nd year of follow-up





Multivariate regression models were stratified by GP practice. Control group was 'Single target attainment'. Abbreviations: CI, confidence interval; RRR, relative risk ratio.

5.6 Discussion

5.6.1 Key findings

The longitudinal nature of EHR data from which the CALIBER cohort was established allowed reconstruction of the patient journey from initial T2D presentation through the care pathway. Study 2 demonstrated how multiple factors combine to influence achievement of intermediate outcome targets in the second year of follow-up. Demographic factors were important predictors of target attainment, suggesting that health inequality issues remained existent despite continuing efforts to improve processes of care. It was a novel finding that quality of care factors were important drivers for meeting intermediate outcome targets in newly diagnosed T2D. Thus, patients already started on antiplatelets and lipid lowering drugs, and patients who received more frequent intermediate outcome measurements were generally more likely to meet the individual target. Contrary to HbA1c, however, more frequent blood pressure and total cholesterol measurements were negatively associated with meeting the triple target over meeting an individual target, indicating that HbA1c measurement was the most important key care factor for meeting all targets. Initial diabetes treatment was shown to only relate to meeting total cholesterol target. This study further demonstrated that more recent diagnosis of T2D – i.e. after 2004 when the QOF was introduced – had a positive association with meeting the key targets, hence providing additional evidence to suggest the positive impact of the policy implementation to incentivise high quality care.

The estimates for meeting intermediate outcome targets were calculated in this study relative to patients not meeting targets. Despite a smaller proportion of patients, this failure-of-care group was considered an appropriate comparator group over patients who had no measurements for at least two reasons: (1) it facilitates result comparison with most other studies which generally compared target achievers against non-achievers when evaluating quality of care, and (2) as a 'middle endpoint', it allowed the estimation of the best (target achieved) and worst outcomes (no intermediate outcome measurement) at a time. To enable further comparison with patients meeting multiple targets, patients with any single target attained was chosen as the referent group in the composite target analysis over those without measurement or failing to meet any target.

5.6.2 Comparison with other studies

Overall, my study showed that among newly diagnosed patients, the key targets within 12-24 months period after diagnosis were more likely to be met by patients who were older at diagnosis and received antiplatelets (**Table 5.3 on page 176**). Other sociodemographic and traditional risk factors showed mixed associations. Patients of white ethnicity were more likely to meet glycaemic target, while non-whites were more likely to meet blood pressure and total cholesterol targets. Being most deprived was significantly associated with a higher likelihood to meet none of the targets. Overweight patients (but not obese) were more likely to meet glycaemic and triple targets despite receiving less intensive diabetes treatment (data not shown), whereas obese patients were less likely to meet blood pressure control. In contrast, women were more likely to meet the blood pressure target, whilst men to meet total cholesterol and triple targets. The most distinctive finding in my study in comparison

with previous studies was the substantial effect of care process measures, particularly relevant treatments and measurements, on meeting intermediate outcome targets.

Glycaemic target. In the previous literature review, I found only one study of process measures in which no diabetes treatment showed positive association with meeting glycaemic targets,[132] consistent with my finding. Also in line with my finding were studies showing a positive association of age, non-smoker and no renal disease with meeting glycaemic targets.[132,146,147] Negative association observed for ethnicity and deprivation was also documented in another study.[272] However, BMI association in previous studies[132,146-149] was contradictory to my finding.

Blood pressure target attainment. The findings in my study were consistent with previous studies as regards the positive associations of increasing age, female gender, lower BMI, macrovascular disease and no blood pressure treatment with meeting blood pressure targets,[132,146,149] although the positive association shown for microvascular disease contradicts result from one study.[132] Negative association for black ethnicity was also reported in another study.[275]

Total cholesterol target attainment. The association of increasing age, male gender, obesity and lipid lowering treatment with meeting cholesterol target is consistent with previous studies.[132,146]

Composite target attainment. The associations of increasing age, male gender and lipid lowering treatment with composite target achievement in the present study are consistent with previous studies although one of the studies showed contradictory results for BMI, macrovascular disease and blood pressure treatment.[132]

5.6.3 Strengths and limitations

The strengths of Study 2 include the large cohort size and novel finding on the important association between key processes of care and its targeted outcomes. A key limitation of this study is the considerable missing data on several covariates. I used missingness indicators for categorical variables to maintain sample size and precision of estimates in the multivariate analyses. I did not include other quantitative data such as blood pressure, HbA1c, lipid profiles and creatinine in the analyses due to the varying degree of missing values, but I assumed that these can be represented, to some extent, by data on prescription of diabetes, blood pressure lowering and lipid lowering medications and renal disease. Completeness of diet and physical activity records, which are not less important to target attainment, were previously shown in **Chapter 4** to be poorer so that they could not be included in the analysis. Another limitation is that, unlike other reviewed studies, this study defined achievement of intermediate outcome targets within a relatively short period of time while target achievement may not always be sustained over the years of follow-up. However, the restricted time window for target attainment ensures an equal follow-up period for all patients and should have minimised immortal-time bias. In other studies using prevalent cohort, such bias might be introduced since patients with a longer onset of T2D potentially had a greater chance of being classified as meeting the targets, likely due to more intensive treatment.

Table 5.3 Comparison of Study 2 with existing studies*

Authors	Design	Study period (years)	N patients	Positive predictor of meeting intermediate outcome targets: Younger age	Older age	Male	Female	Least deprived	Most deprived	White	Non-white	Lower BMI	Higher BMI/obesity	Ex- or non-smoker	Smoker	Macrovascular dis	No macrovasc dis	Microvascular dis	No microvasc dis	Shorter onset	Longer onset	DM treatment	No DM treatment	BP treatment	No BP treatment	Lipid treatment	No lipid treatment	Antiplatelet	No antiplatelet	Initial A1c measure	Initial BP measure	Initial lipid measure
Nilsson (2005)[149]	Longt'd (EHR)	6	1,759	2			②					2		②				2		②												
Tomlin (2007)[148]	Longt'd (EHR)	5	9,988	1		①						1		①						1		1										
Guthrie† (2009)[146]	CS (EHR)	1	10,161		1 ① 2 ② 3 ③ 4 ④	1 ① 2 ② 3 ③ 4 ④		1 ② 3 ④				1 2 4	3																				
Wong (2012)[147]	CS (EHR)	4 mo	1,970	②	1 ③	1 ② ③						1 ②	3							1	② ③											
Stone (2013)[132]	CS (Mixed)	21 mo	7,597		1 ② 3 ④	1 2 3 4	2					1 2 4	3	1 ③	2 ④	2 3 4	①		1 2 ④	1 4	2 ③		1 ④		2 4	3 4						
CALIBER	Longt'd (linked EHR)	2 (for analysis)	44,366		1 2 3 4		1 2	1 ② 3 4		1	2 3 4	2	1 ③ 4	1 2 ③ 4		2 3 4	1	2	1 3 4		2 3	1	1 ④	1	2 ④	1 ② 3 4		1 2 3 4		1	2	3

Authors	Design	Study period (years)	N patients	Positive predictor of having no intermediate outcome measurements: Younger age	Older age	Male	Female	Least deprived	Most deprived	White	Non-white	Lower BMI	Higher BMI/obesity	Ex- or non-smoker	Smoker	Macrovascular dis	No macrovasc dis	Microvascular dis	No microvasc dis	Shorter onset	Longer onset	DM treatment	No DM treatment	BP treatment	No BP treatment	Lipid treatment	No lipid treatment	Antiplatelet	No antiplatelet	Initial A1c measure	Initial BP measure	Initial lipid measure
CALIBER	Longt'd (linked EHR)	2 (for analysis)	44,366	2 3	1 ④	3 4	1 2		1 2 3 4	①	2 3 4	1 2 3	④	① 4	2 3	1 2 3 4		1 ② 3					1 2 3 4	1 2 3 4		1 ② 3 4	1 3	②	2				

Significant predictors for: 1 HbA1c target, 2 Blood pressure target, 3 Lipid target, 4 Composite (dual/triple) target.
Non-significant predictors for: ① HbA1c target, ② Blood pressure target, ③ Lipid target, ④ Composite (dual/triple) target.
*As identified in Chapter 2 **(Table 2.3 on pages 59-60)**. †Composite target included quit smoking. BP, blood pressure; CS, cross sectional; EHR, electronic health record.

5.6.4 Clinical and research implications

The findings of Study 2 leave no doubt that quality of care, as reflected by treatment and investigation, is critical in delivering guideline recommended targets for glycaemic, blood pressure and lipid control in newly diagnosed T2D. Identification of factors associated with the achievement of intermediate outcome target provides some insights into which groups or areas should receive priority for improved care outcomes. Recording information on diet and physical activity should be encouraged more as these are equally important as other measurements and treatments in T2D. Implementation of EHR with obesity intake protocol form for prompt assessment by clinician has been shown to improve behaviour management through enhanced counselling for weight loss.[276] Furthermore, cardiovascular risks in general population (not necessarily having diabetes) were reportedly higher when lifestyle modification (diet, physical activity, smoking and alcohol intake) was not maintained.[273]

More observational research on quality of care in incident T2D cases should be conducted to allow comparison of the study findings, in terms of whether they are also replicated in other settings. Limitation of EHR-based studies arising from missing data should be dealt with contemporary techniques made possible by advances in statistical software, otherwise the findings should be cautiously interpreted.

5.6.5 Conclusion

This study found that factors associated with attainment of intermediate outcome targets in the incident T2D cohort varied depending on how the intermediate outcome is defined, yet older patients and those who were prescribed antiplatelet at baseline are consistently more likely to meet the targets. Those of male gender, non-white ethnicity, who are obese, non-smokers, have no comorbidities and are on other cardiovascular medication are also inclined to achieve more. Importantly, this study underscores the strong associations between more frequent measurements within the first year from T2D diagnosis and the likelihood of meeting intermediate outcome targets.

5.7 Chapter summary

This chapter identified contributing factors for the achievement of key intermediate outcome targets in a newly diagnosed T2D population from CALIBER. The next chapter will investigate whether early achievement of intermediate outcome targets may relate to the onset of CVDs.

Chapter 6

Study 3 – Attainment of intermediate outcome targets and initial presentations of cardiovascular diseases

Simple can be harder than complex;
you have to work hard to get your thinking clean to make it simple.
But it's worth it in the end because once you get there, you can move mountains.
— Steve Jobs

6.1 Chapter outline

This chapter presents the results of CALIBER analyses conducted to examine the relationship between attainment of intermediate outcome targets following diagnosis of T2D and initial presentations of a wide range of CVDs.

6.2 Abstract

Background. Observational studies and clinical trials have demonstrated that glycaemic, blood pressure and lipid controls reduce the risks of CHD, stroke and heart failure. Whether the protective effect also applies to more contemporary cardiovascular phenotypes has not previously been investigated in large population-based studies.

Objectives. To investigate the associations between meeting glycaemic, blood pressure and total cholesterol targets within the first year after T2D diagnosis and the initial presentations of twelve CVDs.

Methods. A cohort of newly diagnosed T2D patients aged at least 30 years and without prior CVD was established from CALIBER data. Patients were followed for the first presentation of stable angina, unstable angina, myocardial infarction, unheralded coronary death, heart failure, arrhythmia/sudden cardiac death, TIA, ischaemic stroke, subarachnoid haemorrhage, intracerebral haemorrhage, PAD and AAA. Cox models were used to estimate cause-specific hazard ratios.

Results. The cohort consisted of 36,149 patients with a median follow-up of 4.4 years (IQR 2.5-6.8), 5,300 of whom experienced an initial presentation of CVD. Relative to patients who failed to meet the HbA1c target (≤7.4%), patients meeting the target had reduced risk of heart failure and PAD. The risk reductions were extended to myocardial infarction and ischaemic stroke in patients who met the blood pressure target (≤145/85 mmHg) compared with those who fail to meet the target. Meeting the total cholesterol target (≤5 mmol/L) was associated with reduced risk of myocardial infarction and TIA. Meeting double or triple intermediate outcome targets was strongly associated with reduced risk of stable angina, myocardial infarction, heart failure, PAD and mortality.

Conclusion. Achievement of an individual intermediate outcome target showed heterogeneous associations with a wide range of CVDs. Achievement of composite targets showed additive protective effects against contemporary CVDs and mortality.

6.3 Introduction

A previous CALIBER study has investigated the association between T2D and initial presentations of cardiovascular phenotype.[4] However, this study was not designed to assess the quality of diabetes care and identified T2D status at baseline, ensuring that many new cases that emerged during follow-up were missed. The concept of a legacy effect emerged from the UKPDS trial suggesting that early care intervention following T2D presentation is critical in the management of the disease as it offers long-term cardiovascular benefits.[50] Two studies founded on prevalent T2D population further revealed that poor quality of care – reflected by undermeasurement and unmet targets for intermediate outcomes – is associated with higher incidence of conventional, aggregated CVDs.[137,150] Yet assessing quality of care with a composite metric, as used in the latter studies, may obscure the individual effect of intermediate outcome of care on CVDs.

Further, the extent to which specific CVDs may be associated with quality of diabetes care is worthy of investigation because despite declining trend in the prevalence of overall CVD, some contemporary subtypes showed the contrary and they will need different treatment approach due to different underlying pathomechanism. For a notable example, the absolute prevalence of heart failure – a known CVD related to diabetes complications – has reportedly increased within the last decade[277] and certain medications should not be prescribed for the condition.[278] Antidiabetes medications such as thiazolidinediones can exacerbate heart failure as they lead to fluid retention and weight gain.[279-281] Dipeptidyl peptidase-4 inhibitors are also contraindicated for an unknown yet mechanism,[282] likewise metformin in unstable or hospitalised heart failure due to the increased potential for lactic acidosis.[31-34,71,72] Hypoglycaemia resulting from intensive diabetes treatment can further induce arrhythmia – another CVD subtype being increasingly found in T2D patients[283] – by provoking abnormal electrical activity.[73,80] Calcium channel blockers, while commonly prescribed for angina or arrhythmia, should also be avoided in heart failure owing to the negative inotropic and vasodilating effects that the transmembrane influx of calcium ions into cardiac and vascular smooth muscles are blocked.[284] Similarly, cilostazol – a vasodilator and antiplatelet – can only be prescribed in PAD in the absence of heart failure.[285]

By harnessing the CALIBER research platform which allow measurements of T2D care since diagnosis and detailed CVD phenotyping, Study 3 seeks to address the limitations of the previous studies, aiming to examine the associations between achievement of either individual or composite intermediate outcome targets and initial presentation of contemporary CVDs in a large population of those newly diagnosed with T2D.

6.4 Methods

6.4.1 Study population and inclusion criteria

This was an observational cohort study of incident T2D in the CALIBER population. Patients were followed prospectively from the first T2D presentation (the index date) to the first occurrence of a cardiovascular endpoint or to the date of transfer out of the practice, the last date of data collection in the practice or the date of death, whichever occurred first. Inclusion criteria, in addition to incident T2D, are described in **Section 3.9 on pages 111-113**. Patients with prior CVD on the index date were excluded from this study.

6.4.2 Exposures, covariates and endpoints

Exposures were attainment of intermediate outcome targets (HbA1c ≤7.4% or 57.4 mmol/mol, blood pressure ≤145/85 mmHg, total cholesterol ≤5 mmol/L, and a composite of these) in their associations with first recorded CVD from any of the data sources. Processes of care were not considered in Study 3 based on the assumption that they have been adequately reflected by intermediate target achievement. Achievement of intermediate outcome targets was confined to up to 12 months after the index date; patients were, therefore, classified as 'attained' or 'did not attain' the targets. Patients without records on the targets during the 12-month window were allocated

to the 'unmeasured' category (**Figure 6.1 on page 182**). The reference group was patients who did not attain target values.

Relevant covariates included demographic factors (age group at diagnosis, gender, ethnicity and deprivation status), baseline cardiovascular risk factors (smoking status, body mass index, HbA1c, systolic blood pressure, total cholesterol and HDL cholesterol), prior renal disease and baseline treatment (blood pressure lowering medication, lipid lowering medication and antiplatelet) retrieved from prior CPRD records closest to the index date. Initial diabetes treatment was also considered referring to class of drug initially prescribed (or 'no treatment' if records on prescription were not found) within the first year of follow-up. Since diabetes treatment can be in the causal pathway between meeting (or not meeting) the intermediate outcome target and cardiovascular endpoint, it was treated as a time-varying covariate. Thus, patients who were prescribed diabetes medication after the date of meeting (or not meeting) the target was classified into the 'no treatment' category.

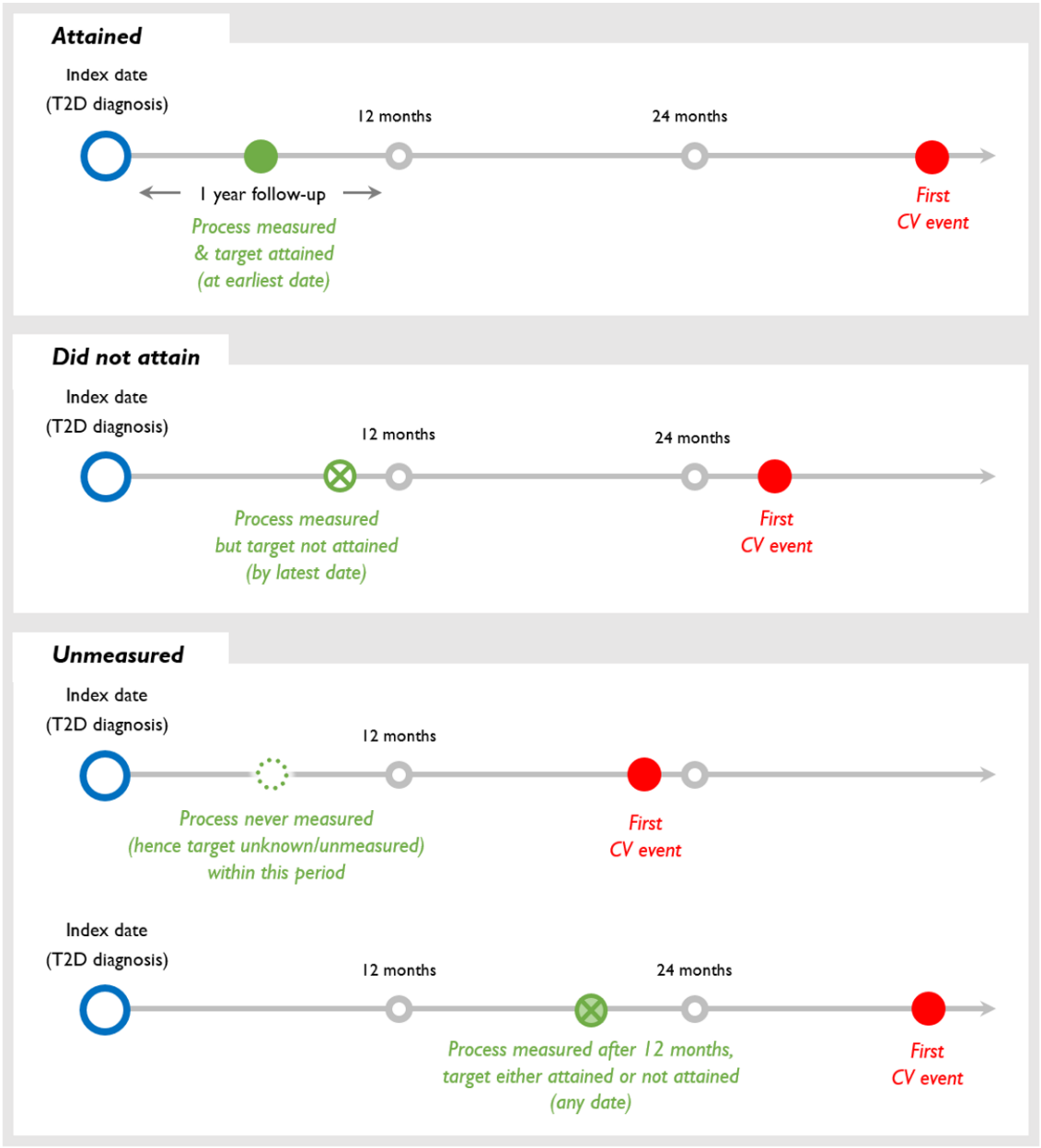
The primary endpoints for Study 3 were initial presentations of twelve specific CVDs (excluding unspecified CHD and stroke), defined as any first cardiovascular event occurring after 12 months of follow-up. A unique endpoint was selected according to the following hierarchy if multiple cardiovascular events were recorded on the same day:

- Arrhythmia/sudden cardiac death
- Heart failure
- Unheralded coronary death
- Non-fatal myocardial infarction
- Unstable angina
- Stable angina
- Unspecified CHD
- AAA
- PAD
- Intracerebral haemorrhage
- Subarachnoid haemorrhage
- Ischaemic stroke
- Unspecified stroke
- TIA

The hierarchy has been formulated and adjudicated by a panel of clinical experts for the CALIBER project (**Section 3.5 on pages 106-107**). The cardiovascular events were sorted by CVD type first followed by severity within the type, thus creating a 'subtype hierarchy'. The hierarchy has been exercised on the CALIBER's published works and consistency across similar studies (i.e. initial presentation of CVD) is therefore expected.

Secondary endpoints were cardiovascular mortality and non-cardiovascular mortality. All other endpoints were censored when an endpoint had been met.

Figure 6.1 Definition of attainment of glycaemic, blood pressure and total cholesterol targets (as main exposures) in Study 3



6.4.3 Statistical analysis

Descriptive results for continuous variables were summarised as means or medians, and categorical variables were summarised as proportions. Cumulative incidence function by target attainment was plotted for each cardiovascular endpoint and used study follow-up year as the timescale accounting for competing risk events.[274]

Multiple Cox regression models were used to estimate the effect of meeting each intermediate outcome target and composite target on each cardiovascular endpoint. The reference group for analysis of individual target was 'did not attain (the relevant) target', while the refer-

ence group for analysis of the composite target was 'attained none of the targets'. GP practice heterogeneity was accounted for using stratification. Models were firstly adjusted for age and sex, and further for cardiovascular risk factors and treatment. Interactions between age and gender were investigated. Proportional hazards assumptions were verified by goodness-of-fit test and plotting Schoenfeld residuals.[286] No imputations were generated for missing values; missingness indicators were applied instead for all regression models. Analyses were conducted using Stata 13.0.

6.4.4 Sensitivity analysis

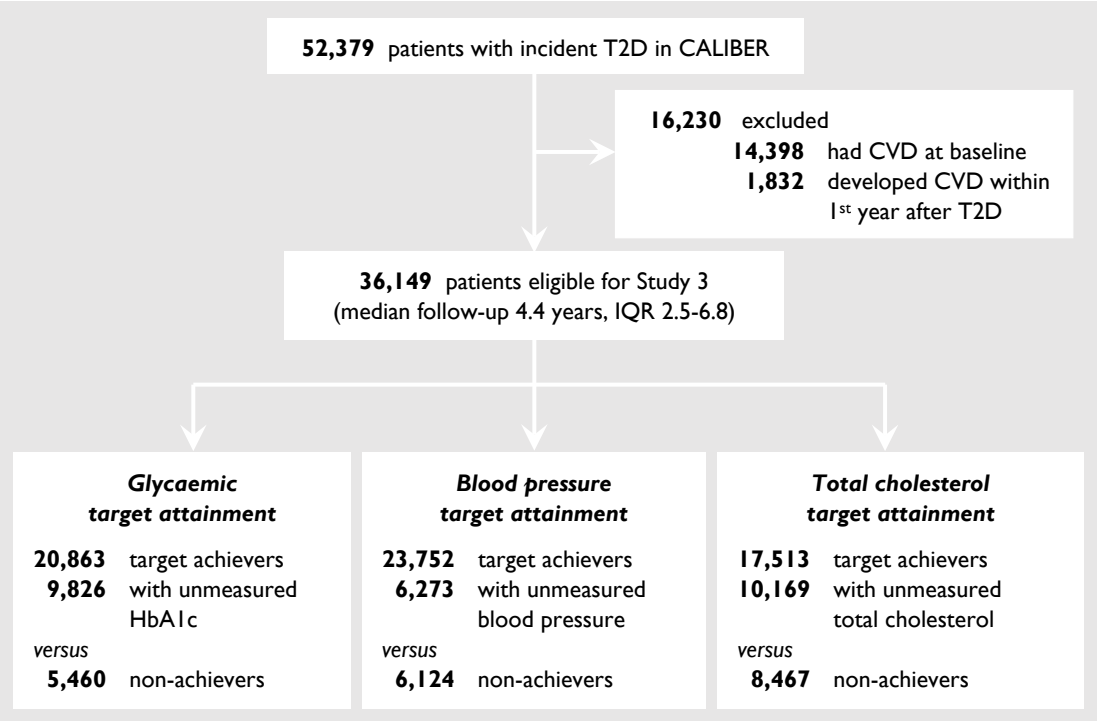
Sensitivity analyses for Study 3 were performed by restricting to patients entering on or after 1 January 2004 when the QOF was first implemented, and by using more stringent thresholds for blood glucose <7%, blood pressure <140/80 mmHg and total cholesterol <4 mmol/L.

6.5 Results

6.5.1 Characteristics of eligible patients

Of the 52,379 patients with incident T2D, 16,230 (31.0%) were excluded due to not meeting inclusion criteria (**Figure 6.2 below**). Baseline characteristics of excluded and eligible patients in Study 3 were compared in **Table 6.1 on pages 184-185**. Eligible patients were younger at T2D diagnosis, more likely to be women and hypertensive, less commonly prescribed with cardiovascular medication, and had higher HbA1c values at baseline. Their lipid profiles and body mass index were also higher, but their serum creatinine levels were lower relative to excluded patients.

Figure 6.2 Patient flow chart for Study 3



6.5.2 Attainment of intermediate outcome targets within first year after T2D diagnosis

Despite the different time window for achievement of intermediate outcome targets, the distribution of eligible patients in Study 3 according to the achievement (**Figure 6.3 on page 186**) was closely similar to that in Study 2 (**Figure 5.3 on page 161**). Of the 36,149 total patients eligible for Study 3, 14.3% had none of the key intermediate outcomes measured during the first year after diagnosis, 6.8% failed to meet any of the targets, 18.6% met just one target, 27.7% met two and 32.6% met all three. Patients meeting intermediate outcome targets were 57.7% for HbA1c, 65.7% for blood pressure and 48.5% for total cholesterol, and proportion of those without measurement were all higher than that of failing to meet the corresponding target.

Table 6.1 Baseline characteristics of excluded versus eligible patients in Study 3

Characteristics	non-missing (%)	Excluded patients (N=16,230)		non-missing (%)	Eligible patients (N=36,149)	
Demographic						
Age in years, median (IQR)	100	70.7	(62.2-78.3)	100	59.7	(50.2-69.1)
Age group, n (%)	100			100		
<40		121	(0.7)		2,452	(6.8)
40-<50		706	(4.4)		6,147	(17.0)
50-<60		2,379	(14.7)		9,483	(26.2)
60-<70		4,500	(27.7)		9,374	(25.9)
70-<80		5,276	(32.5)		6,234	(17.3)
>=80		3,248	(20.0)		2,459	(6.8)
Duration of registration in years, median (IQR)	100	11.4	(7.6-16.5)	99.7	10.9	(6.4-15.7)
Women, n (%)	100	6,907	(42.6)	100	16,693	(46.2)
Social deprivation, n (%)	99.7			99.7		
Quintile 1 (most affluent)		2,946	(18.2)		7,534	(20.8)
Quintile 5 (most deprived)		3,417	(21.1)		7,023	(19.4)
Ethnicity, n (%)	40.3			54.9		
White		6,120	(37.7)		20,422	(56.5)
South Asian		206	(1.3)		1,351	(3.7)
Black		125	(0.8)		1,069	(3.0)
Other		96	(0.6)		764	(2.1)
Diabetes diagnosis						
Year of diagnosis	100			100		
1998-2003		7,033	(43.3)		15,808	(43.7)
2004-2006		5,531	(34.1)		11,866	(32.8)
2007-2009		3,666	(22.6)		8,475	(23.4)
HbA1c, mean (SD) mmol/L	20.4	58.0	(19.9)	22.6	62.8	(22.9)
Cardiovascular risks						
Smoking status, n (%)	44.3			36.7		
Never		2,412	(14.9)		5,965	(16.5)
Ex		3,325	(20.5)		4,243	(11.7)
Current		1,448	(8.9)		3,041	(8.4)
Blood pressure	73.5			61.3		
Systolic, mean (SD) mmHg		142.8	(20.5)		143.3	(20.2)
Diastolic, mean (SD) mmHg		80.6	(11.4)		84.0	(11.2)

Hypertension, n (%)	73.5	2,212	(13.6)	61.3	5,459	(15.1)
Total cholesterol, mean (SD) mmol/L	58.6	5.1	(1.3)	48.8	5.6	(1.3)
LDL cholesterol, mean (SD) mmol/L	35.0	2.8	(1.1)	30.4	3.1	(1.1)
HDL cholesterol, mean (SD) mmol/L	44.8	1.2	(0.0)	38.7	1.2	(0.5)
Triglycerides, mean (SD) mmol/L	47.0	2.2	(1.8)	41.4	2.4	(2.3)
Serum creatinine, mean (SD) µmol/L	62.7	98.6	(35.4)	55.0	87.3	(36.0)
BMI, mean (SD) kg/m^2	38.7	29.7	(5.8)	34.3	30.8	(6.4)
BMI category, n (%)	38.7			34.3		
Underweight (<18.5)		48	(0.3)		68	(0.2)
Normal weight (18.5-24.9)		861	(5.3)		1,361	(3.8)
Overweight (25.0-29.9)		2,192	(13.5)		3,678	(10.2)
Obese class I (30.0-34.9)		1,860	(11.5)		3,678	(10.2)
Obese class II (35.0-39.9)		833	(5.1)		2,065	(5.7)
Obese class III (≥40)		489	(3.0)		1,535	(4.2)
Medications prescribed						
Blood pressure lowering agent, n (%)	100	10,778	(66.4)	100	12,403	(34.3)
Lipid lowering drug, n (%)	100	6,556	(40.4)	100	3,306	(9.2)
Antiplatelet, n (%)	100	7,243	(44.6)	100	1,891	(5.2)
Comorbidities						
Coronary heart disease, n (%)	100	9,451	(58.2)		-	
Cerebrovascular disease, n (%)	100	3,067	(18.9)		-	
Peripheral arterial disease, n (%)	100	1,704	(10.5)		-	
Renal disease, n (%)	100	700	(4.3)	100	481	(1.3)

Baseline was defined as 365 days before the index date (first T2D diagnosis).

6.5.3 Initial presentations of CVD

During a median follow-up of 4.4 years (IQR 2.5-6.8), 5,300 cardiovascular events occurred in 36,149 patients free from CVD at baseline. Heart failure was the most common initial presentation of cardiovascular events in 961 (18.1%) patients, followed by stable angina in 926 (17.5%) patients and PAD in 641 (12.1%) patients (**Figure 6.4 on page 186**). Stratification by attainment of intermediate outcome targets did not change the ranking of these cardiovascular presentations (**Figure 6.5 on page 187**) but cumulative incidence curves for the events showed differences according to whether targets were met (**Figures 6.6 to 6.9 on pages 188-191**). Compared with patients who met or failed to meet their intermediate outcome targets, patients who had none of the intermediate outcome targets measured tended to have the highest incidence of CVD despite longer time needed for the event to occur after T2D diagnosis (**Table 6.2 on pages 192-193**).

Figure 6.3 Distribution of eligible patients for Study 3 (N=36,149) by attainment of intermediate outcome targets within 1st year of follow-up

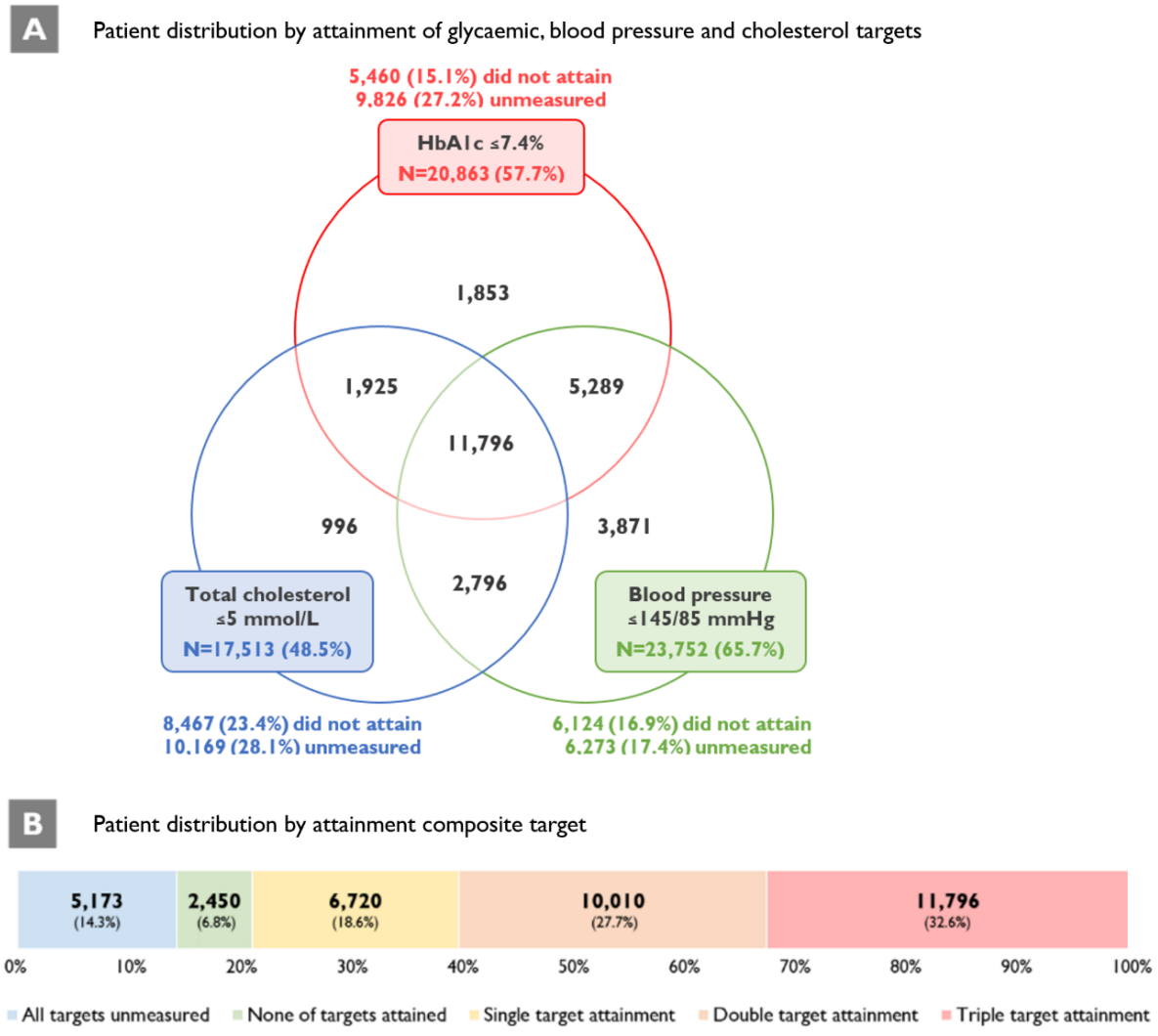


Figure 6.4 Initial presentation of CVD in CALIBER's incident T2D cohort (N=36,149)

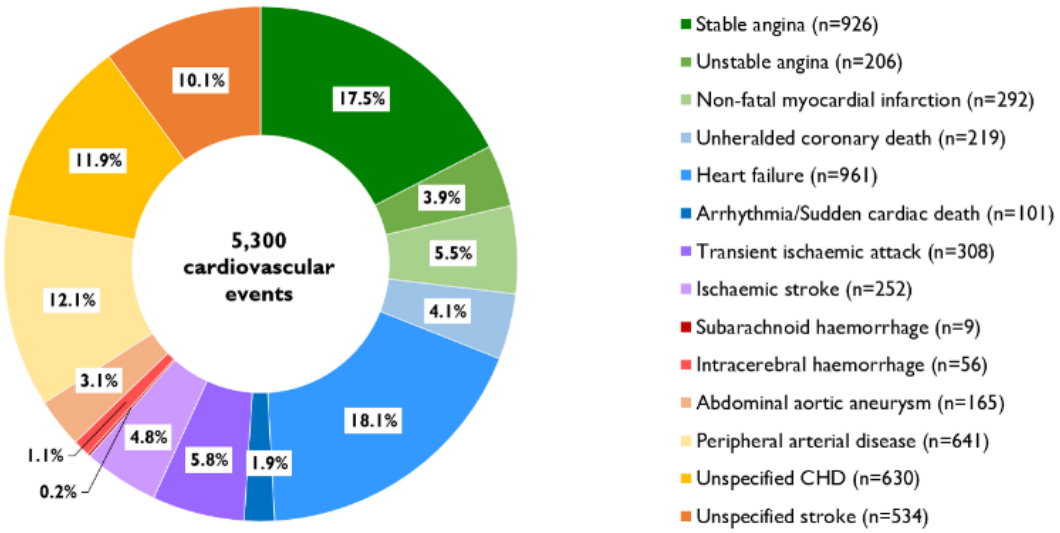


Figure 6.5 Initial presentation of CVDs (n=5,300 events) in CALIBERS's incident T2D cohort by attainment of intermediate outcome targets

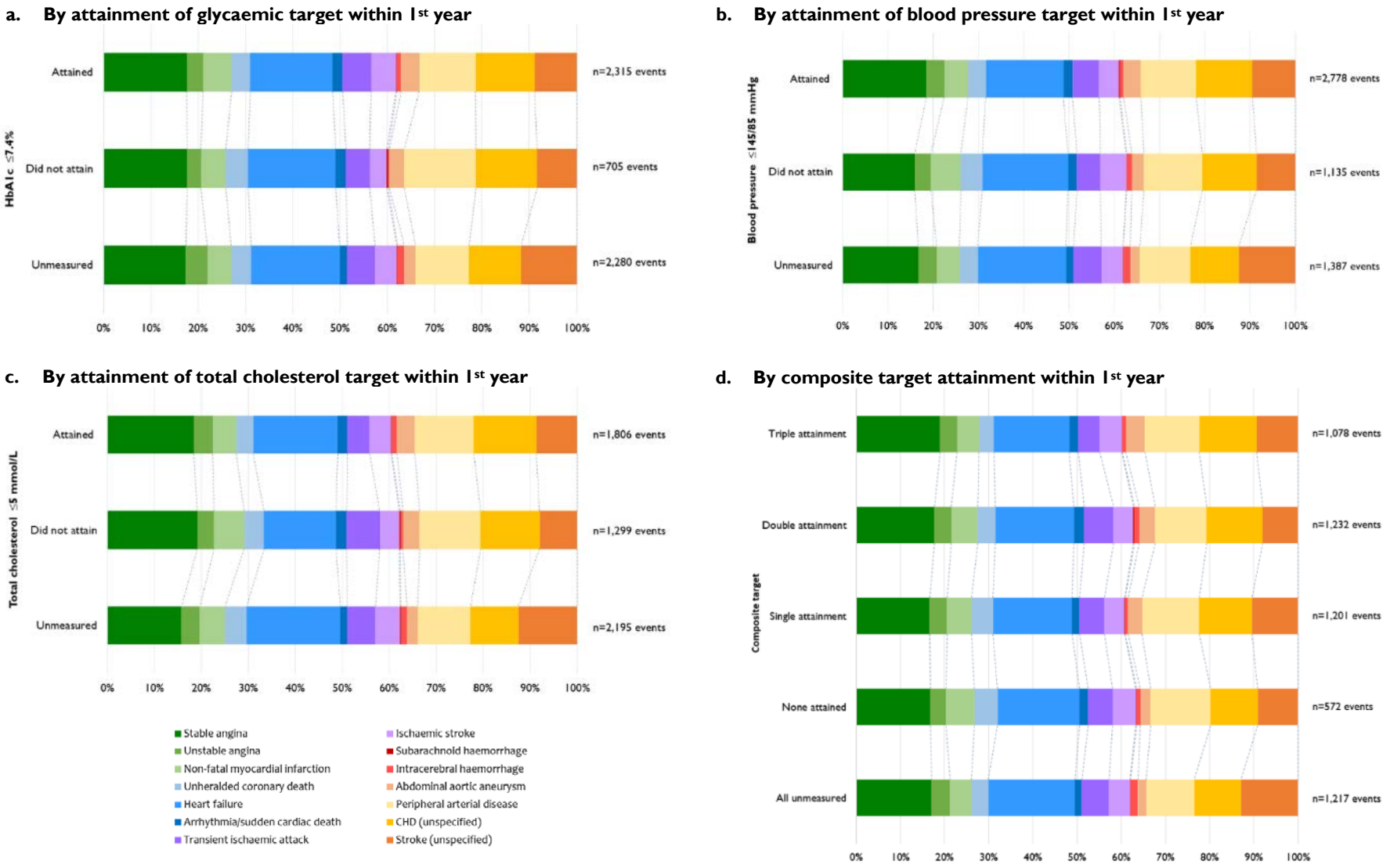


Figure 6.6 Cumulative incidence curves for initial presentation of specific CVD by attainment of glycaemic target

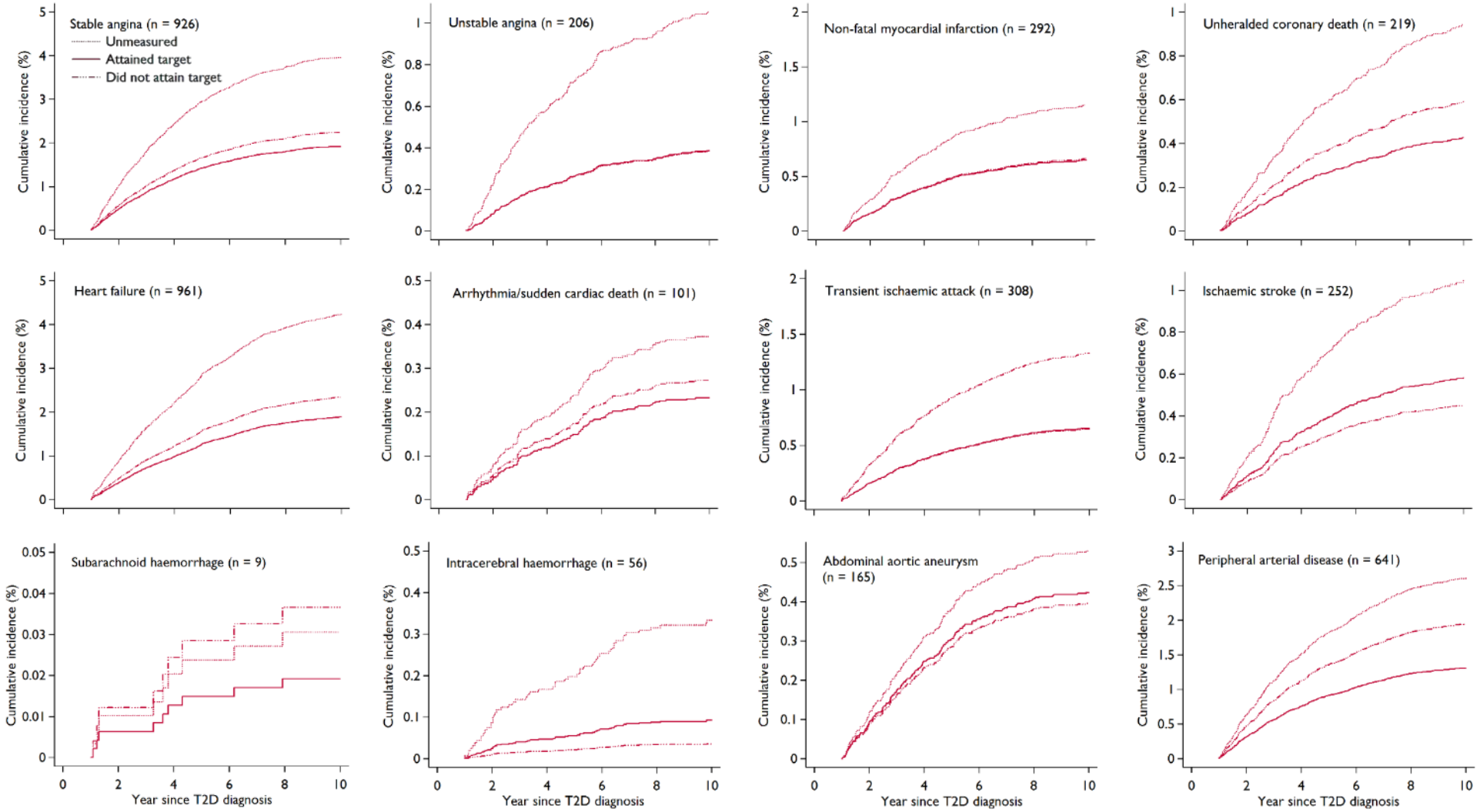


Figure 6.7 Cumulative incidence curves for initial presentation of specific CVD by attainment of blood pressure target

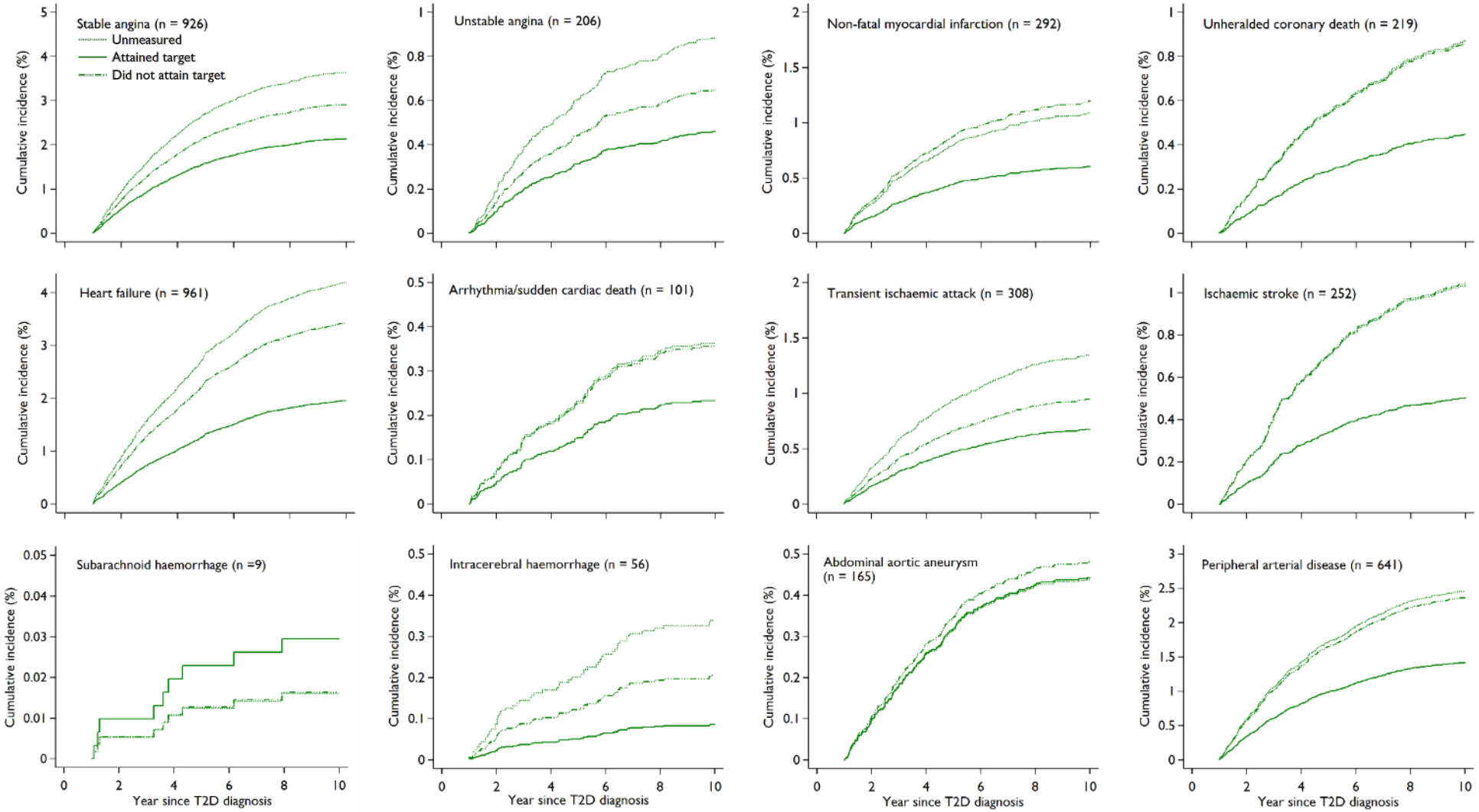


Figure 6.8 Cumulative incidence curves for initial presentation of specific CVD by attainment of total cholesterol target

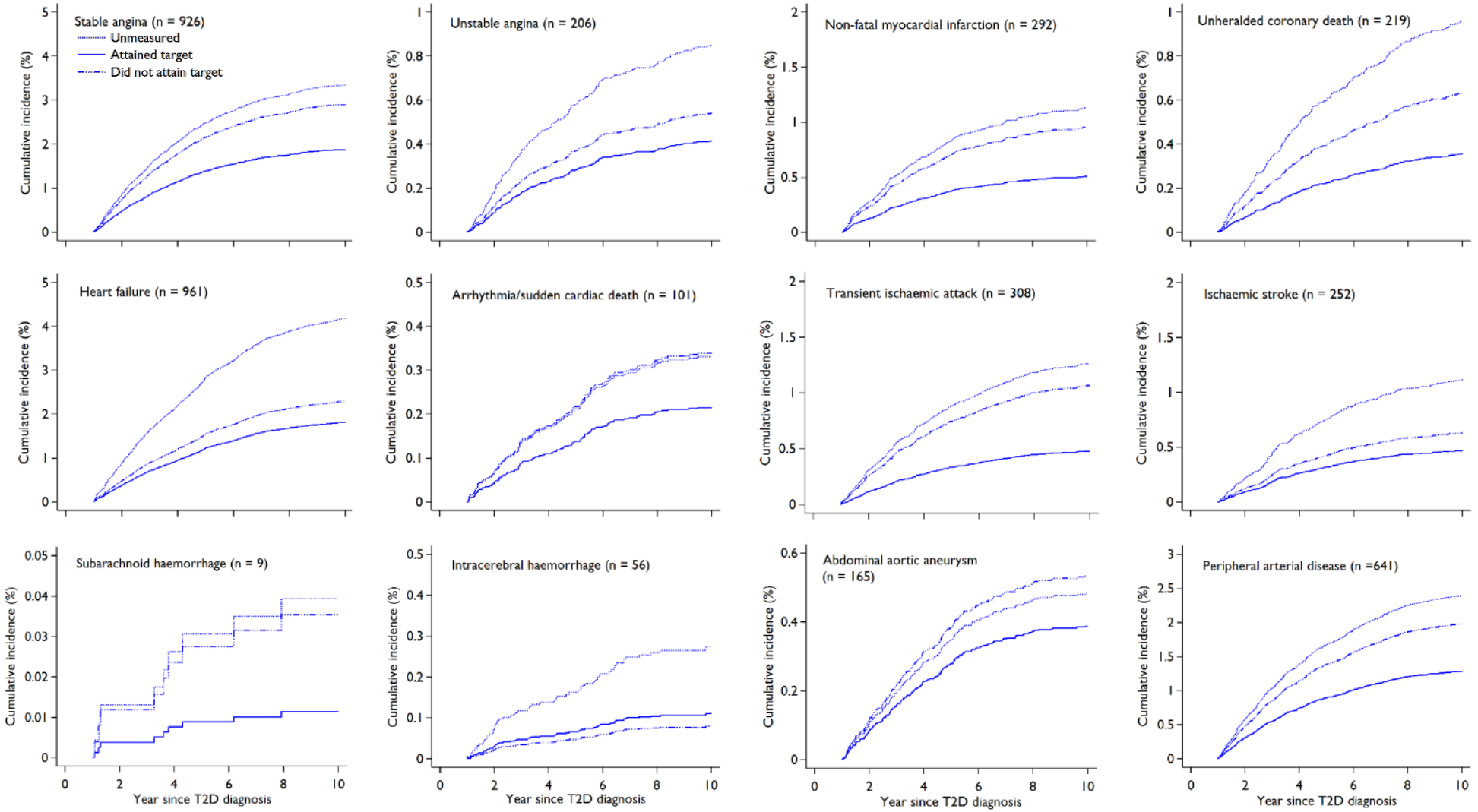


Figure 6.9 Cumulative incidence curves for initial presentation of specific CVD by attainment of composite target

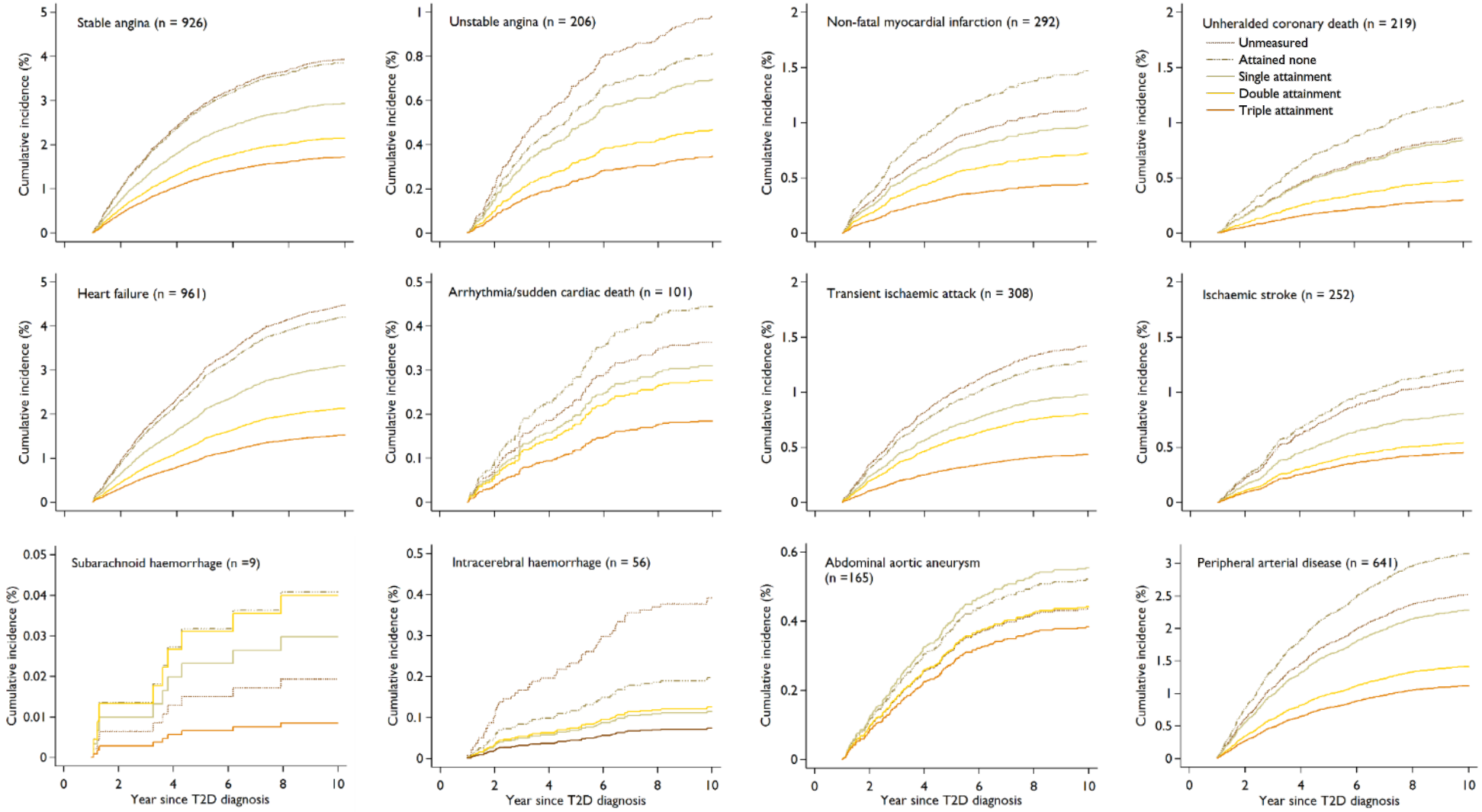


Table 6.2 Distribution of event, median time to event (years) and median age at event (years) for specific CVD (n=4,136 events*) in CALIBER's incident T2D cohort by attainment of glycaemic, blood pressure, total cholesterol and composite targets

a. HbA1c ≤7.4%

Cardiovascular event	Attained			Did not attain			Unmeasured		
	n	Age at event	Time to event	n	Age at event	Time to event	n	Age at event	Time to event
Stable angina	406	67.3	2.9	124	64.6	3.0	396	66.6	4.0
Unstable angina	81	63.7	3.0	21	54.5	3.0	104	65.4	4.4
Non-fatal myocardial infarction	139	70.4	3.5	37	72.4	3.3	116	69.9	3.4
Unheralded coronary death	91	76.1	3.8	33	72.8	4.0	95	74.8	4.4
Heart failure	403	76.8	3.3	131	71.7	3.7	427	76.8	4.7
Arrhythmia/sudden cardiac death	49	72.6	4.1	15	66.2	2.9	37	70.1	4.6
Transient ischaemic attack	139	74.1	3.3	36	69.5	3.1	133	77.4	4.0
Ischaemic stroke	123	75.2	3.2	25	71.0	3.3	104	76.8	4.2
Subarachnoid haemorraghe	4	64.9	3.8	2	52.1	3.7	3	68.9	1.2
Intracerebral haemorraghe	20	72.8	3.9	2	56.1	2.2	34	66.2	4.9
Abdominal aortic aneurysm	90	70.9	3.5	22	62.0	2.6	53	69.7	4.4
Peripheral arterial disease	275	71.9	3.1	107	67.3	3.1	259	69.8	4.2
Overall	1,820	71.4	3.2	555	67.6	3.2	1,761	71.6	4.1

b. Blood pressure ≤145/85 mmHg

Cardiovascular event	Attained			Did not attain			Unmeasured		
	n	Age at event	Time to event	n	Age at event	Time to event	n	Age at event	Time to event
Stable angina	513	66.7	3.0	181	67.4	3.7	232	65.8	4.2
Unstable angina	110	64.5	3.5	40	62.0	3.1	56	64.0	4.5
Non-fatal myocardial infarction	147	75.2	3.5	75	70.3	3.0	70	64.0	3.5
Unheralded coronary death	109	74.1	3.8	54	73.7	4.3	56	79.2	4.3
Heart failure	476	76.0	3.5	215	76.4	4.1	270	76.5	4.6
Arrhythmia/sudden cardiac death	56	71.9	4.1	22	71.7	4.3	23	69.9	3.0
Transient ischaemic attack	163	73.3	3.1	59	72.5	3.2	86	78.7	4.2
Ischaemic stroke	121	75.2	3.3	65	74.2	3.8	66	76.1	3.9
Subarachnoid haemorraghe	7	64.4	3.8	1	54.1	3.6	1	80.1	1.2
Intracerebral haemorraghe	21	69.8	3.7	13	69.2	4.8	22	63.2	3.1
Abdominal aortic aneurysm	107	67.7	3.5	30	68.5	2.9	28	69.6	4.0
Peripheral arterial disease	339	70.3	3.1	146	72.1	3.8	156	69.3	4.4
Overall	2,169	70.6	3.2	901	71.5	3.7	1,066	71.7	4.2

c. Total cholesterol ≤5 mmol/L

Cardiovascular event	Attained			Did not attain			Unmeasured		
	n	Age at event	Time to event	n	Age at event	Time to event	n	Age at event	Time to event
Stable angina	332	66.6	2.9	249	65.8	3.2	345	67.4	3.9
Unstable angina	73	65.8	3.2	46	62.4	3.1	87	64.7	4.2
Non-fatal myocardial infarction	91	72.1	2.7	83	68.7	3.7	118	71.1	3.5
Unheralded coronary death	64	73.4	3.3	55	75.0	5.5	100	77.0	4.3
Heart failure	325	75.4	3.3	199	74.8	3.7	437	77.2	4.5
Arrhythmia/sudden cardiac death	38	72.2	3.8	29	73.1	4.6	34	68.1	3.4
Transient ischaemic attack	85	69.5	2.9	92	74.2	3.7	131	78.4	3.9
Ischaemic stroke	83	75.2	3.0	54	72.4	3.7	115	78.6	4.4
Subarachnoid haemorraghe	2	56.3	3.5	3	67.4	4.3	4	66.6	2.4
Intracerebral haemorraghe	20	68.6	3.2	7	76.7	5.7	29	65.2	4.8
Abdominal aortic aneurysm	69	70.9	3.0	46	65.1	4.2	50	70.1	4.0
Peripheral arterial disease	226	70.6	2.9	169	69.8	3.6	246	71.0	3.9
Overall	1,408	70.2	3.1	1,032	69.9	3.6	1,696	72.7	4.0

d. Composite target

Cardiovascular event	Unmeasured			Attained none			Single attainment			Double attainment			Triple attainment		
	n	Age at event	Time to event	n	Age at event	Time to event	n	Age at event	Time to event	n	Age at event	Time to event	n	Age at event	Time to event
Stable angina	207	66.6	4.4	96	66.9	3.8	200	66.6	3.5	218	66.0	2.8	205	67.4	2.9
Unstable angina	51	64.2	4.3	20	61.2	3.7	47	65.4	4.0	47	62.0	3.4	41	68.1	3.2
Non-fatal myocardial infarction	60	63.3	3.1	37	74.1	3.6	67	71.0	3.5	74	74.5	3.9	54	69.8	2.6
Unheralded coronary death	46	78.2	4.4	30	73.4	4.6	58	75.6	4.7	49	76.1	3.4	36	72.5	3.5
Heart failure	238	76.8	4.7	106	74.5	4.5	214	76.0	4.1	219	76.9	3.6	184	75.6	2.9
Arrhythmia/sudden cardiac death	19	69.9	3.0	11	69.1	4.3	21	70.3	4.6	28	72.4	4.2	22	72.2	3.6
Transient ischaemic attack	75	79.6	4.4	32	75.3	3.1	67	70.7	3.2	82	73.8	3.7	52	70.2	2.8
Ischaemic stroke	58	75.8	4.4	30	78.9	3.5	55	74.4	3.8	55	74.8	4.1	54	75.5	3.0
Subarachnoid haemorraghe	1	80.1	1.2	1	54.1	3.6	2	66.6	4.5	4	64.2	4.1	1	62.4	3.3
Intracerebral haemorraghe	21	64.4	2.9	5	70.8	4.8	8	70.5	6.1	13	68.3	2.8	9	69.8	3.7
Abdominal aortic aneurysm	23	72.1	3.9	13	64.4	2.7	38	64.6	3.9	45	70.6	3.8	46	71.1	3.1
Peripheral arterial disease	132	69.3	4.4	78	71.3	3.4	155	70.4	4.0	143	70.4	3.2	133	71.4	2.6
Overall	931	71.8	4.2	459	70.9	3.8	932	71.0	3.8	977	70.8	3.2	837	70.6	3.0

*Excluding unspecified CHD and unspecified stroke.

6.5.4 Effect of meeting intermediate outcome targets on cardiovascular events

Glycaemic target (HbA1c ≤7.4%). Patients who met the HbA1c target during the first year after diagnosis of T2D had reduced incidence of heart failure (HR 0.73, 95% CI 0.59-0.90, p=0.003) and PAD (HR 0.67, 95% CI 0.53-0.86, p=0.001) compared with patients who failed to meet the target (**Figure 6.10 on page 195**). In patients in whom HbA1c was not measured, an increased risk of unstable angina was observed (HR 1.88, 95% CI 1.10-3.24, p=0.022). A similar finding was also seen for intracerebral haemorrhage but the excess risk, although profound, was marginally significant, apparently due to being represented by a small number of events (HR 4.77, 95% CI 1.03-22.1, p=0.046). Other cardiovascular presentations were unaffected across achievement of the HbA1c target category. In terms of mortality, significant risk reduction in patients meeting the HbA1c target was observed for cardiovascular death (HR 0.69, 95% 0.55-0.86, p=0.001) and non-cardiovascular death (HR 0.81, 95% CI 0.70-0.93, p=0.003) (**Figure 6.14 on page 199**). Increased risk of non-cardiovascular death was documented in patients in whom HbA1c measurements were not made (HR 1.20, 95% 1.03-1.40, p=0.021).

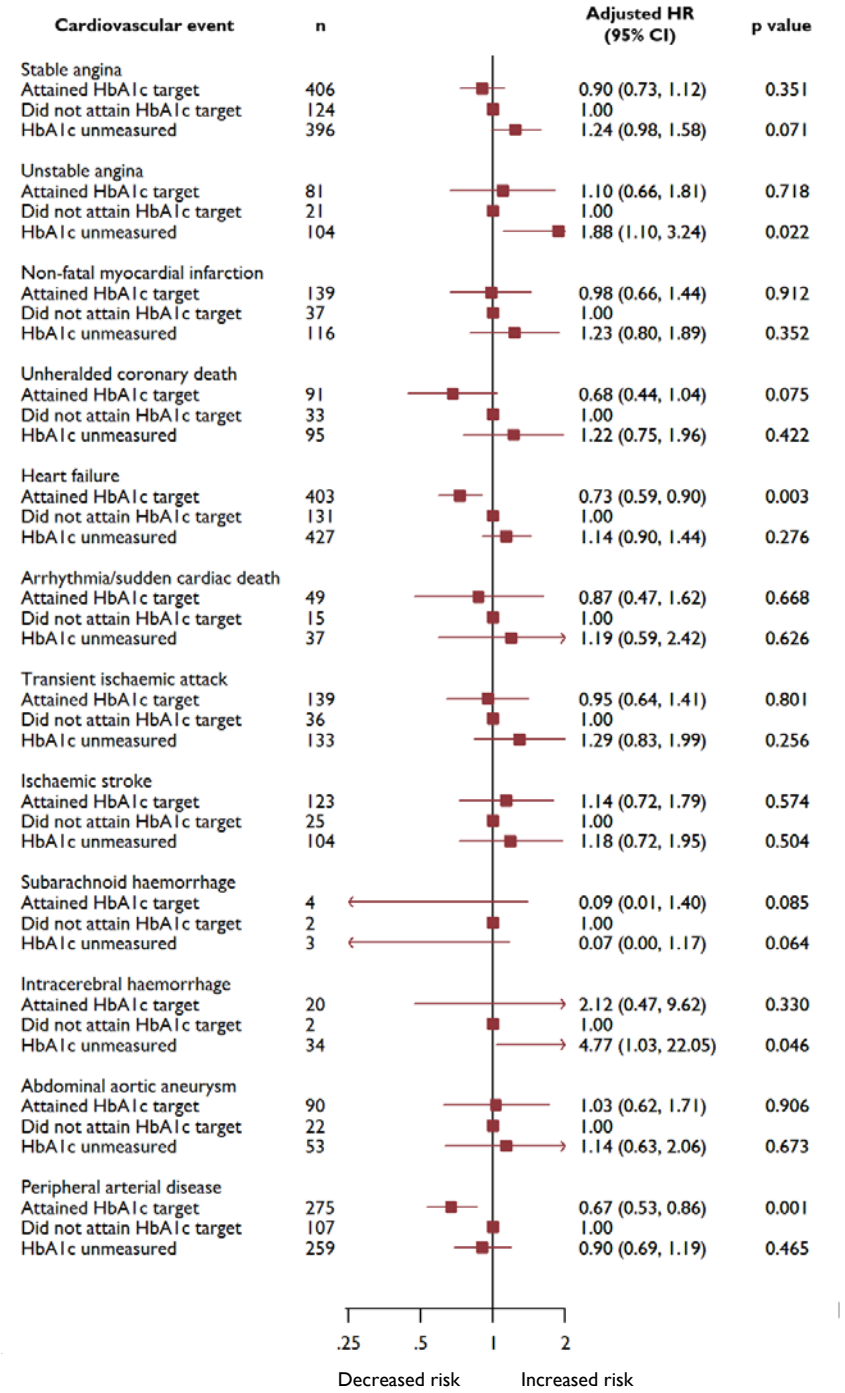
Blood pressure target (≤145/85 mmHg). Patients who met the blood pressure target during the first year after diagnosis of T2D had reduced incidence of several CVDs compared with patients who failed to meet the target. Greatest risk reductions were equally observed for non-fatal myocardial infarction (HR 0.69, 95% CI 0.51-0.93, p=0.015) and ischaemic stroke (HR 0.69, 95% CI 0.50-0.96, p=0.027), followed by heart failure (HR 0.80, 95% CI 0.67-0.95, p=0.011), and PAD (HR 0.81, 95% CI 0.66-0.99, p=0.042) (**Figure 6.11 on page 196**). Significant risk reductions in patients meeting the blood pressure target were also documented for cardiovascular and non-cardiovascular death (**Figure 6.14 on page 199**). Patients in whom blood pressure was not measured had increased risk of heart failure (HR 1.31, 95% CI 1.05-1.63, p=0.015) and non-cardiovascular death (HR 1.17, 95% CI 1.01-1.35, p=0.034).

Total cholesterol target (≤5 mmol/L). Compared with patients who failed to meet total cholesterol target during the first year after diagnosis of T2D, patients who met the target had reduced incidence of non-fatal myocardial infarction (HR 0.69, 95% CI 0.50-0.94, p=0.019) and TIA (HR 0.58, 95% CI 0.43-0.80, p=0.001) (**Figure 6.12 on page 197**). No protective effect of meeting cholesterol target was found for mortality (**Figure 6.14 on page 199**). In patients in whom total cholesterol was not measured, increased risks were observed for heart failure (HR 1.49, 95% CI 1.23-1.80, p<0.001), cardiovascular death (HR 1.52, 95% CI 1.26-1.84, p<0.001) and non-cardiovascular death (HR 1.52, 95% CI 1.34-1.71, p<0.001). Marginal excess risks were also documented for ischaemic stroke (HR 1.44, 95% CI 1.00-2.08, p=0.049) and unheralded coronary death (HR 1.47, 95% CI 1.01-2.15, p=0.045).

Composite target attainment. Compared with patients who achieved none of the intermediate outcome targets, meeting a combination of any two or all three targets lowered the risks of mortality and most CVDs. Greatest risk reduction due to meeting the triple target was seen for unheralded coronary death (HR 0.36, 95% 0.21-0.62, p<0.001), while the least reduction was for stable angina (HR 0.75, 95% CI 0.58-0.98, p=0.038) (**Figure 6.13 on page 198**). Greatest risk re-

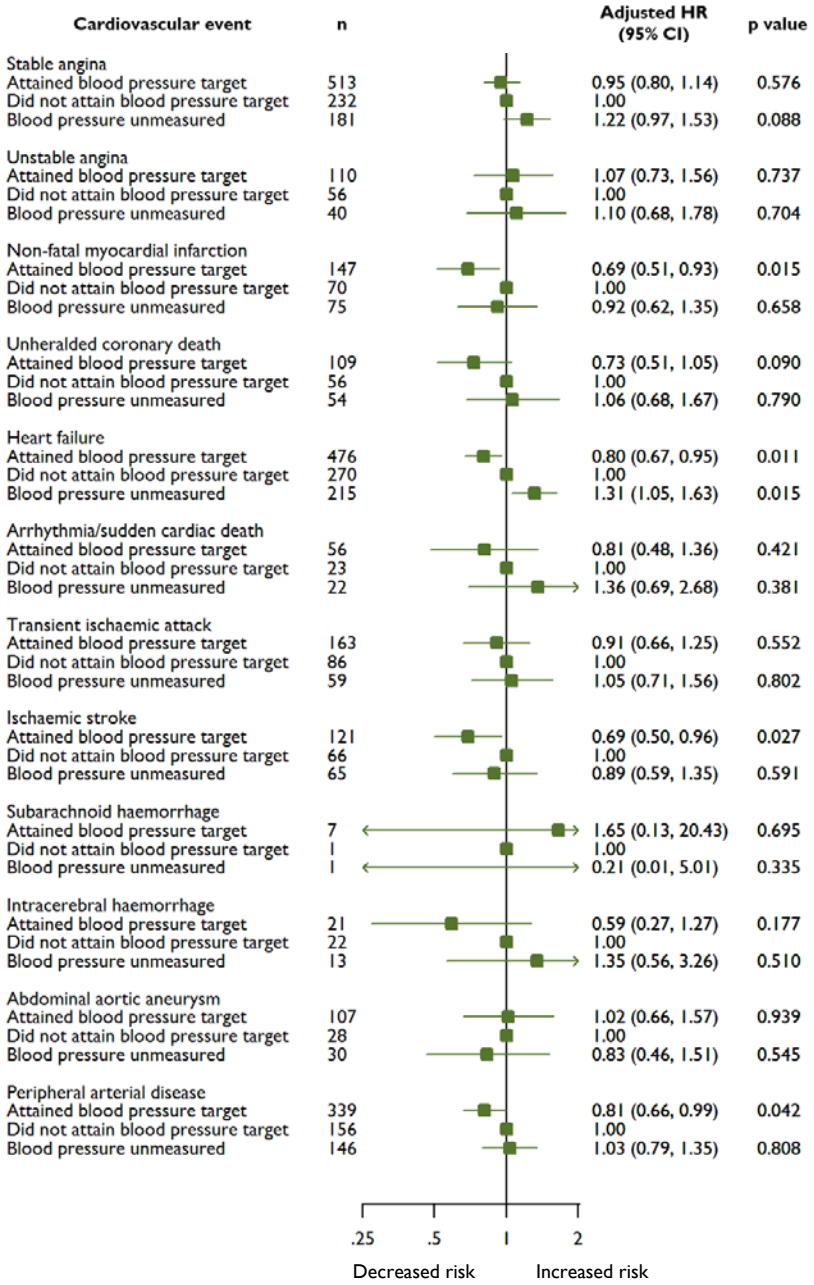
duction due to meeting the double target was also seen for unheralded coronary death (HR 0.46, 95% 0.28-0.76, p=0.002), while the least reduction was for heart failure (HR 0.68, 95% CI 0.53-0.88, p=0.003). No excess risk for mortality was documented in patients in whom none of the intermediate outcomes were measured when compared with patients who achieved none of the targets (**Figure 6.14 on page 199**).

Figure 6.10 Association between attainment of glycaemic target and CVD in CALIBERS's incident T2D cohort



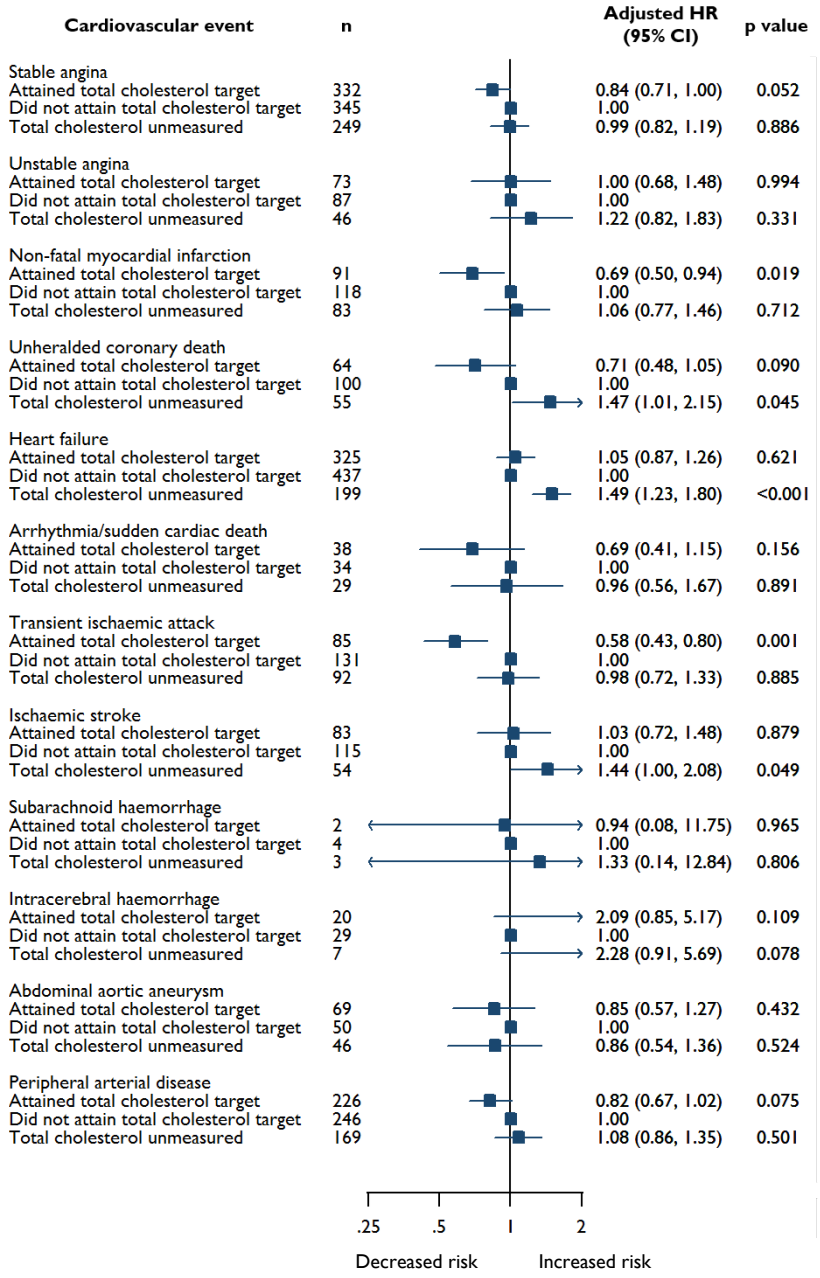
Risk estimates were adjusted for baseline factors (age, sex, social deprivation, ethnicity, body mass index category, smoking status, systolic blood pressure category, total cholesterol category, HDL cholesterol category, renal disease, blood pressure lowering medication, lipid lowering medication and antiplatelet) and initial diabetes treatment, and stratified by GP practice.

Figure 6.11 Association between attainment of blood pressure target and CVD in CALIBERS's incident T2D cohort



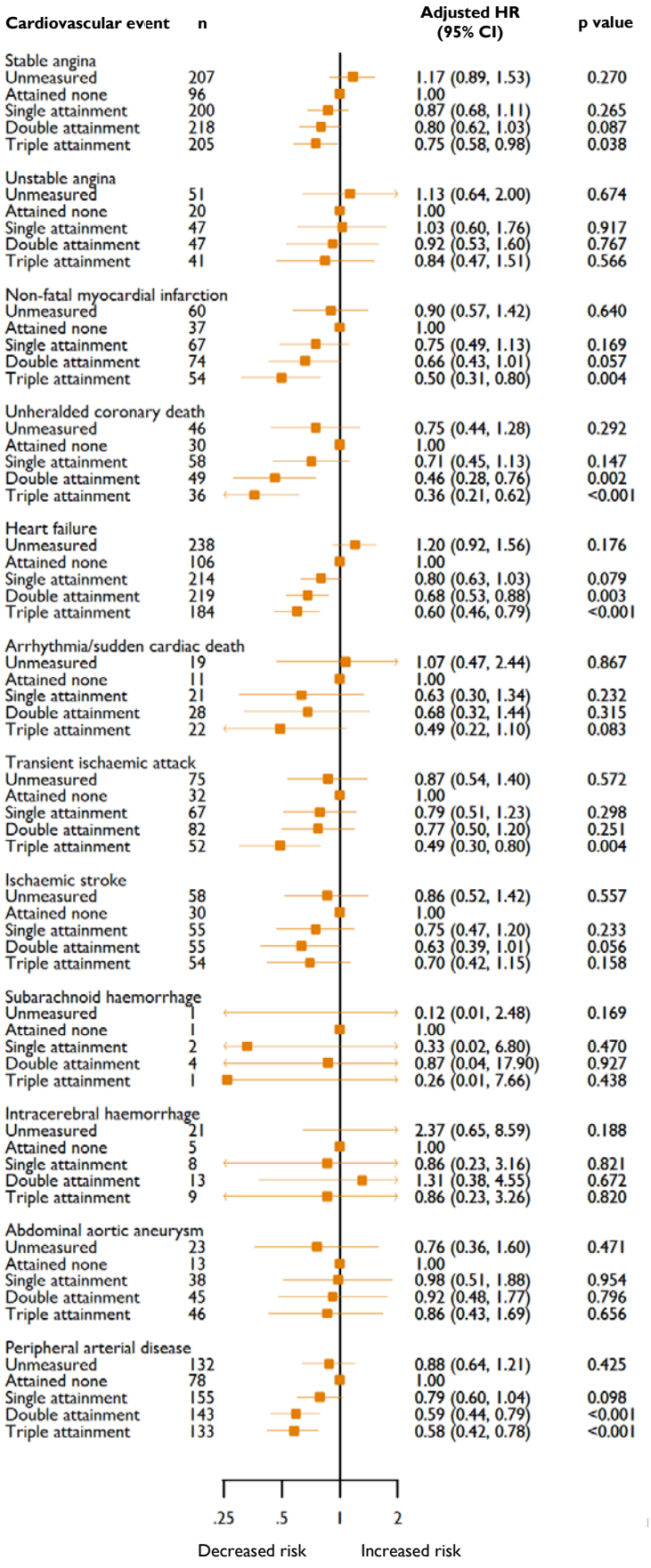
Risk estimates were adjusted for baseline factors (age, sex, social deprivation, ethnicity, body mass index category, smoking status, systolic blood pressure category, total cholesterol category, HDL cholesterol category, renal disease, blood pressure lowering medication, lipid lowering medication and antiplatelet) and initial diabetes treatment, and stratified by GP practice.

Figure 6.12 Association between attainment of total cholesterol target and CVD in CALIBERS's incident T2D cohort



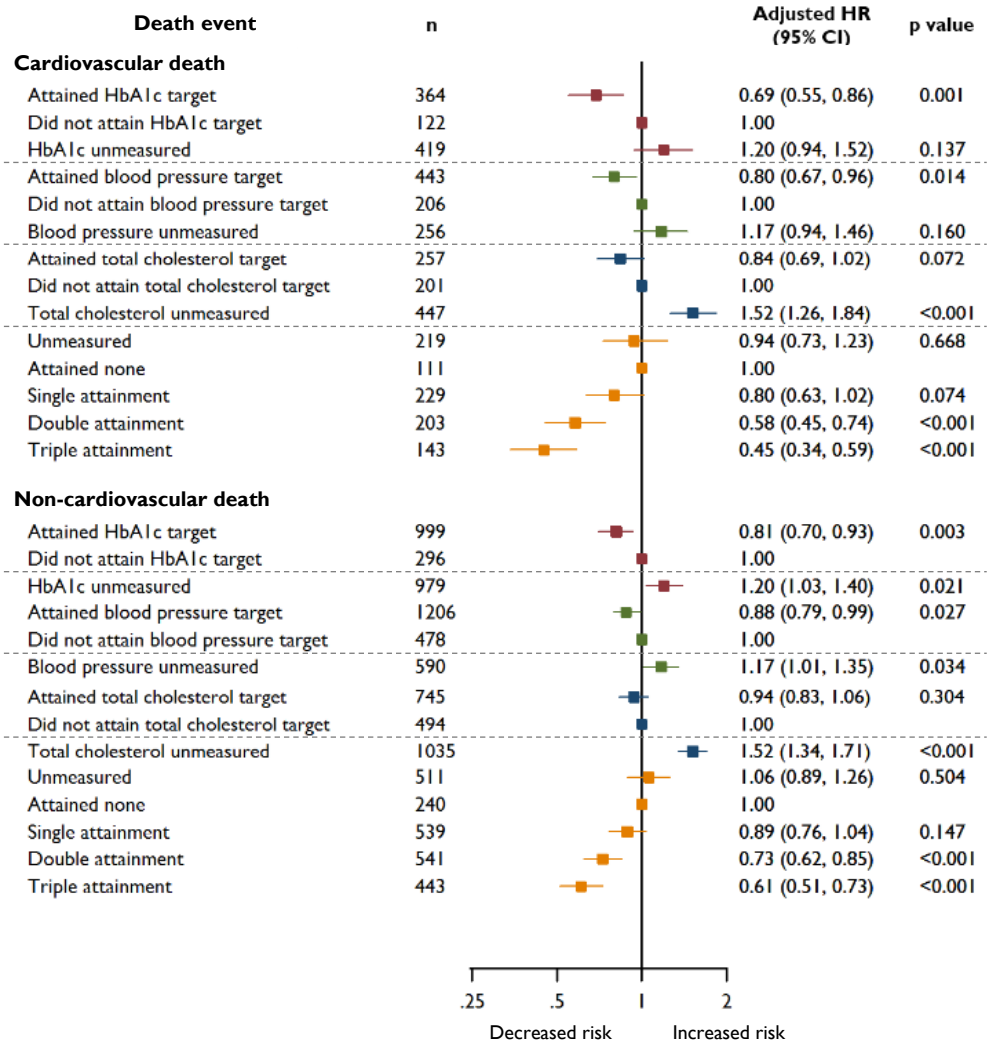
Risk estimates were adjusted for baseline factors (age, sex, social deprivation, ethnicity, body mass index category, smoking status, systolic blood pressure category, total cholesterol category, HDL cholesterol category, renal disease, blood pressure lowering medication, lipid lowering medication and antiplatelet) and initial diabetes treatment, and stratified by GP practice.

Figure 6.13
Association between attainment of composite target and CVD in CALIBERS's incident T2D cohort



Risk estimates were adjusted for baseline factors (age, sex, social deprivation, ethnicity, body mass index category, smoking status, systolic blood pressure category, total cholesterol category, HDL cholesterol category, renal disease, blood pressure lowering medication, lipid lowering medication and antiplatelet) and initial diabetes treatment, and stratified by GP practice.

Figure 6.14 Association between attainment of intermediate outcome targets and mortality in CALIBERS's incident T2D cohort



Risk estimates were adjusted for baseline factors (age, sex, social deprivation, ethnicity, body mass index category, smoking status, systolic blood pressure category, total cholesterol category, HDL cholesterol category, renal disease, blood pressure lowering medication, lipid lowering medication and antiplatelet) and initial diabetes treatment, and stratified by GP practice.

6.5.5 Sensitivity analyses

Applying tighter threshold for intermediate outcome targets. Compared with the main analysis, the protective effects with application of tighter HbA1c target (≤7%) were lost for heart failure but became substantial for unheralded coronary death (**Appendix F, Figure F6.1 on page 350**). The protective effects of application of a tighter blood pressure target (≤140/80 mmHg) were only sustained for non-fatal myocardial infarction and became substantial for stable angina (**Figure F6.2 on page 351**). Similar changes were observed on application of tighter total cholesterol target (≤4 mmol/L) with an additional protective effect for heart failure (**Figure F6.3 on page 352**). In contrast, the excess risks in patients in whom the intermediate outcomes were not measured remained unchanged – compared with the main analysis – for all the CVDs; the exception was heart failure, the risk of which became substantial in patients without HbA1c measurement but

was lost in those without total cholesterol measurement (**Figures F6.1 to F6.3 on pages 350-352**). Meeting two or three of the tighter targets was associated with comparable effects on the risk of CVDs compared with the main analysis, only PAD being attenuated (**Figure F6.4 on page 353**).

Restricting analyses to patients diagnosed with T2D after 1 January 2004. In the sub-cohort diagnosed during or after 2004, the protective effect of meeting the glycaemic target compared with patients who failed to meet the target was only observed for AAA – this was never observed in the main analysis (**Figure F6.5 on page 354**). Meeting the blood pressure target in the sub-cohort showed protections against heart failure, ischaemic stroke, non-fatal myocardial infarction and unheralded coronary death (**Figure F6.6 on page 355**). No beneficial effect was seen in the sub-cohort for meeting total cholesterol target; however, the risk for unheralded coronary death increased by sixfold in patients in whom total cholesterol was not measured compared with patients who failed to meet the target (**Figure F6.7 on page 356**). A smaller excess risk for unheralded coronary death was also found in patients in whom HbA1c was not measured compared with patients who failed to meet the glycaemic target (**Figure F6.5 on page 354**). The associations of meeting double or triple intermediate outcome targets – compared with patients who achieved none of the targets – were directionally similar to the main analysis with protective effects being documented for non-fatal myocardial infarction, unheralded coronary death, heart failure and PAD (**Figure F6.8 on page 357**).

6.6 Discussion

6.6.1 Key findings

The most common cardiovascular presentations in CALIBER's newly diagnosed T2D cohort were heart failure (18.1%), stable angina (17.5%) and PAD (12.1%), and the study was large enough to identify subarachnoid haemorrhage, the least common cardiovascular outcome (0.2%). These estimates are similar to those quantified in a previous CALIBER study on T2D.[4] Study 3 has provided a novel insight into how attainment of intermediate outcome targets taken individually and together is associated with a broad range of incident CVD presentations in incident T2D. The data showed clearly that in patients who met intermediate outcome targets, the risk of many CVDs was reduced. However, associations were heterogeneous and, for different CVDs, differed in magnitude but also in direction. Achievement of triple target, for example, related to the reduced risks of acute myocardial infarction, unheralded coronary death and TIA by at least 50% but of stable angina, heart failure and PAD by 25-40%, while having no relation on the risks of unstable angina, arrhythmia, stroke and AAA. Similar heterogeneity was observed in the effects of glycaemia, blood pressure and cholesterol targets on different cardiovascular presentations. Achieving HbA1c or blood pressure target related to risk reductions for heart failure and PAD, although the estimates were greater for HbA1c. Yet achieving blood pressure was also associated with equal risk reductions for myocardial infarction and ischaemic stroke. Achieving total cholesterol target was asso-

ciated with myocardial infarction and TIA risk reductions. Blood pressure or total cholesterol also had a comparable risk excess for heart failure when they were not measured.

Furthermore, significant risk reductions for cardiovascular and non-cardiovascular death were only observed in those meeting HbA1c and blood pressure targets. Having no total cholesterol measured was significantly associated with increased risk of both cardiovascular and non-cardiovascular deaths, whereas having no HbA1c or blood pressure measured was associated with non-cardiovascular death only. The extent to which these findings are a direct effect of intermediate outcomes on CVD or reflect, at least in part, the inherent biases in a study of this type will be discussed later. Yet assuming that target achievement played a significant role, this study emphasises the critical longitudinal associations between quality of care in those newly diagnosed with T2D and the later development of CVDs. This study highlights missed opportunities for care that, if addressed, might have salutary effects on prognosis by reducing the risk of many CVDs that complicate T2D.

6.6.2 Comparison with other studies

Attainment of intermediate outcome targets. Unlike previous studies,[137,150] Study 3 did not consider initial process measures. These had already been shown to influence target achievement in Study 2 and were, therefore, implicitly incorporated within my analysis of intermediate targets as they affect cardiovascular outcomes. Poor quality of care measures in T2D have been associated with myocardial infarction and aggregated cardiovascular events in a small underpowered study.[150] However, there is very little information about the broader range of CVDs. My finding of heterogeneous associations for intermediate outcome targets – and by implication initial process measures – with different cardiovascular presentations represents a novel observation that has not been previously reported. Thus, while achievement of glycaemic, blood pressure and cholesterol targets appeared to protect against different CVDs, endpoints rarely considered in previous studies such as sudden cardiac death, subarachnoid haemorrhage and AAA were unaffected. I found no significant risk reduction for sudden cardiac death with meeting glycaemic target, apparently due to the relatively small cohort size preventing detection of more events. Existing evidence demonstrated that poor glycaemic control is associated with spontaneous ventricular tachycardia[287] and intensive treatment targeting HbA1c <6.5% may protect against CAN.[288] QT interval prolongation, diabetic cardiomyopathy, hypercoagulable state and impaired respiratory response to hypoxia and hypercapnia are predisposing factors to arrhythmic death in hyperglycaemic individuals.[288] My finding neither supported the epidemiological observation which show that diabetes protects against AAA.[4,289,290] Again, it seems that a larger cohort size is needed to adequately capture such a rare event. It should also be recognised that only patients with incident T2D were enrolled in this study and the comparator group in my assessment of AAA risk was not non-diabetic patients but diabetic patients who failed to meet the targets.

Additional heterogeneity was evident in myocardial infarction risk which was reduced equally by blood pressure control and cholesterol control but was unaffected by glycaemic control (**Table 6.3 on page 203**). Likewise, risk of heart failure, PAD and cardiovascular death were

reduced by glycaemic and blood pressure control but unaffected by lipid control. As for stable angina and unheralded coronary death, the risk reduction was only observed for triple target achievement.

Composite target attainment. I performed additional analyses by composite target attainment to improve comparability with previous studies that have used a summary score in analysing the effects of intermediate outcomes on cardiovascular risk.[137,150] Risk reductions due to attainment of either two or all three targets were most pronounced for unheralded coronary death, myocardial infarction and TIA but extended to heart failure, PAD and stable angina. It was a key strength of this study, distinguishing it from previous studies, that these effects on individual cardiovascular presentation could be differentiated.

Comparison with cardiovascular outcomes in trials targeting glycaemic control. Most identified trials (**Section 2.7.3.3 on pages 65-71**) did not include contemporary cardiovascular endpoints as this study did, allowing indirect comparison for a few findings only. Substantial risk reduction for PAD and cardiovascular death observed in this study by meeting glycaemic target were not documented by existing trials (**Table 6.4 on pages 204-205**). However, non-significant excess risk of angina and stroke were reported by other trials. Other cardioprotective effects were largely not observed despite achieved HbA1c target at ≤7.5% in most trials.

Comparison with cardiovascular outcomes in trials targeting blood pressure control. Protective effects from meeting blood pressure target for cardiovascular death, myocardial infarction, heart failure, ischaemic stroke and PAD were also documented by several trials in which achieved systolic blood pressure was below 145 mmHg (**Table 6.5 on page 206**).

Comparison with cardiovascular outcomes in trials targeting lipid control. Substantial risk reduction for non-fatal myocardial infarction, but not TIA, following achievement of a total cholesterol level below 5 mmol/L was previously reported in other trials (**Table 6.6 on page 207**).

My study differs from randomised trials in many ways; therefore, comparisons made must be cautiously interpreted. Nevertheless, documentation of the timing of relationships between baseline factors, intermediate outcomes and cardiovascular outcomes in newly diagnosed T2D provides useful information for developing prevention strategies and designing trials. Study 3 shows that the cardiovascular burden in T2D is not confined to myocardial infarction, stroke and cardiovascular death, and other common cardiovascular outcomes such as heart failure, PAD and stable angina that require different treatment strategies now merit consideration as primary endpoints in trials.

Table 6.3 Comparison of Study 3 with existing observational studies

Authors	Design	Median follow-up	N patients	Excess risk for cardiovascular events													
				Total cardio-vascular events	Major cardio-vascular events	Myocardial infarction				Cardiac revascularisation		Stroke				Limb complication	
Berardis (2008)[150]	Longitudinal (EHR)	5 years (3.3-5.4)	3,235	● ●	● ●	● ●				●		●				●	
Rossi (2011)[137]	Longitudinal (EHR)	28 months (24-31)	5,181	●												●	

Authors	Design	Median follow-up	N patients	Excess risk for cardiovascular events (due to intermediate outcomes being unmeasured)													
				Cardiovascular death	Stable angina	Unstable angina	Non-fatal MI	Coronary death	Heart failure	Arrhythmia / SCD	Transient ischaemic attack	Ischaemic stroke	Subarachnoid haemorrhage	Intracerebral haemorrhage	Peripheral arterial disease	Abdominal aortic aneurysm	Non-cardio-vascular death
CALIBER	Longitudinal (linked EHR)	4.4 years (2.5-6.8)	36,149	③		①		③	② ③			③		①			① ② ③
				Reduced risk for cardiovascular events (due to meeting intermediate outcome targets)													
CALIBER	Longitudinal (linked EHR)	4.4 years (2.5-6.8)	36,149	① ② ④	④		② ③ ④	④	① ② ④		③ ④	②			① ② ④		① ② ④

● Poor score on quality of care, ● Moderate score quality of care

① HbA1c target not attained, ② Blood pressure target not attained, ③ Lipid target not attained

① HbA1c target attained, ② Blood pressure target attained, ③ Lipid target attained, ④ Composite (dual/triple) target attained

EHR, electronic health record; SCD, sudden cardiac death.

Table 6.4 Comparison of Study 3 with existing trials targeting glycaemic control

Trial	N patients	Median follow-up (years)	Intervention	HbA1c level (%) achieved (median)	Cardiovascular endpoint													
					Cardiovascular death	All-cause death	MACE	Stable angina	Unstable angina	Myocardial infarction	Coronary death	Sudden cardiac death	Heart failure	TIA	Ischaemic stroke	Subarachnoid haemorrhage	Intracerebral haemorrhage	PAD	AAA
UKPDS* (1998)[49,154]	3,867	10	SU/insulin *vs* diet	7.0 *vs* 7.9		▽		←△→		▽	▽	▽	▽		←←←←△→→→→				
	1,704 (overweight)	10.7	Metformin *vs* diet	7.4 *vs* 8.0		▼				▽	▽	▽	▽		←←←←▽→→→→			▽	
DIGAMI 2 (2005)[164]	1,253 (with MI)	2.1	Dual insulin *vs* add-on insulin *vs* standard	7.2 *vs* 7.2 *vs* 7.3 (mean 24h)		△ △													
PROactive (2005)[166]	5,238	34.5 months (mean)	Add-on pioglitazone *vs* placebo	7.0 *vs* 7.6		▽	▼	←←←▽→→→								←←←▽→→→			
ADVANCE (2008)[52]	11,140	5	Intensive *vs* standard	6.5 *vs* 7.5 (mean)	▽	▽	▽			←←←▽→→→			▽		←←←←△→→→→			▽	
ACCORD (2008)[165]	10,251	3.5 (mean)	Intensive *vs* standard	6.4 *vs* 7.5	▲	▲	▽			▼			△		←←←←△→→→→				
VADT (2009)[155]	1,791	5.6	Intensive *vs* standard	6.9 *vs* 8.4				←△→						△				▽	
RECORD (2009)[167]	4,447	5.5	Add-on rosiglitazone *vs* placebo	7.5 *vs* 7.9 (mean)	▽	▽	▽			△			▲		←←←←▽→→→→				
BARI 2D (2009)[163]	2,368	5.3	Insulin-sensitisation *vs* insulin-provision	7.0 *vs* 7.5 (mean)		▽	▽												
HEART2D (2009)[162]	1,115	2.7 (mean)	Prandial *vs* basal insulin	7.7 *vs* 7.8 (mean)	△	△				△	△		▽		←←←←△→→→→				
ORIGIN* (2012)[161]	12,537	6.2	Insulin glargine *vs* standard	6.2 *vs* 6.5	△		△		▽	←△→			▽		←←←←△→→→→				
SAVOR-TIMI (2013)[168]	16,492	2.1	Add-on saxagliptin *vs* placebo	7.7 *vs* 7.9 (mean)			△												
EXAMINE (2013)[169]	5,380	1.5	Add-on alogliptin *vs* placebo	7.7 *vs* 8.0 (mean)			▽												

TECOS (2015)[156]	14,671	3.0	Add-on sitagliptin *vs* placebo	7.2 *vs* 7.3 (mean)		△	▽		▽				△									
ELIXA (2015)[157]	6,068	25 months	Add-on lixisenatide *vs* placebo	7.1 *vs* 7.4 (mean)	▽	▽			△	△			▽	←←←←△→→→→								
EMPA-REG OUTCOME (2015)[160]	7,020	3.1	Add-on empaliflozin *vs* placebo	7.8 *vs* 8.2 (mean)	▼	▼	▼		▽	▽			▼	▽	←←←△→→→							
LEADER (2016)[158]	9,340	3.8	Add-on liraglutide *vs* placebo	7.8 *vs* 8.2 (mean)	▼	▼	▼		▽	▼			▽	▽	←←←▽→→→							
SUSTAIN-6 (2016)[159]	3,297	2.1	Add-on semaglutide *vs* placebo	0.5 mg: 7.6 *vs* 8.3 1.0 mg: 7.3 *vs* 8.3 (mean)	▽	△	▼		▽	▽			△	←←←←▼→→→→								
CALIBER (real-world setting using linked EHR)	36,149	4.4	N/A *HbA1c target achieved vs target not achieved*	≤7.4 *(threshold)*	▼			▽	△	▽	▽	▽	▼	▽	△	▽	△	▼	△			
			HbA1c unmeasured vs target not achieved	>7.4	△			△	▲	△	△	△	△	△	△	▽	▲	△	▽			

* Involving newly diagnosed T2D

▽ Better outcome (reduced risk or longer survival); △ Worse outcome (excess risk or shorter survival); ▼ Significant better outcome; ▲ Significant worse outcome; Symbol flanked by arrows represents composite endpoint of indicated columns.

Abbreviations: AAA, abdominal aortic aneurysm; EHR, electronic health record; MACE, major adverse cardiovascular events (CV mortality, non-fatal MI, non-fatal stroke); PAD, peripheral arterial disease; TIA transient ischaemic attack.

Table 6.5 Comparison of Study 3 with existing trials targeting blood pressure control

Trial	N patients	Median follow-up (years)	Intervention	Blood pressure level (mmHg) achieved (mean)	Cardiovascular endpoint													
					Cardiovascular death	All-cause death	MACE	Stable angina	Unstable angina	Myocardial infarction	Coronary death	Sudden cardiac death	Heart failure	TIA	Ischaemic stroke	Subarachnoid haemorrhage	Intracerebral haemorrhage	PAD	AAA
UKPDS* (1998)[87]	1,148	8.4	Captopril/atenolol *vs* diet	144/82 *vs* 154/87		▽		←△→		←▽→		△	▼		←←←←▼→→→→			▽	
HOPE (2000)[170]	3,577	4.5 (mean)	Ramipril *vs* placebo	140/77 *vs* 143/77	▼	▼	▼		▽	▼			▼	▼	←←←▼→→→				
IDNT (2001)[174]	1,715	2.6	Add-on irbesartan *vs* amlodipine *vs* placebo	140/77 *vs* 141/77 *vs* 144/80	△ ▽					▽ ▼			▽ △		←←←▽→→→ ←←←▽→→→				
RENAAL (2001)[173]	1,513	3.4 (mean)	Add-on losartan *vs* placebo	140/74 *vs* 142/74						▼			▼						
DIABHYCAR (2004)[171]	4,912	47 months (mean)	Add-on ramipril *vs* placebo	142/80 *vs* 143/80	△					▽			▽		←←←←△→→→→				
ADVANCE (2007)[91]	11,140	4.3 (mean)	Perindopril + indapamide *vs* placebo	136/73 *vs* 140/73	▼	▼	▽			←←←▽→→→			▽		←←←←▽→→→→				
DIRECT-Protect 2 (2008)[175]	1,905	4.7	Candesartan *vs* placebo	136/77 *vs* 139/78 (hypertensive), 128/74 *vs* 132/76 (normotensive)			▽												
ACCORD (2010)[89]	4,733	4.7 (mean)	Intensive *vs* standard	119/64 *vs* 134/71 (1st year)	△	△	▽			▽			▽		←←←←▼→→→→				
ALTITUDE (2012)[172]	8,561	32.9 months	Add-on aliskiren *vs* placebo	141/74 *vs* 142/74	△	△				←△→		▲	▽		←←←←△→→→→				
CALIBER (real-world setting using linked EHR)	36,149	4.4	N/A *BP target achieved vs target not achieved*	≤145/85 *(threshold)*	▼			▽	△	▼	▽	▽	▼	▽	▼	△	▽	▼	△
			BP unmeasured vs target not achieved	>145/85	△			△	△	▽	△	△	▲	△	▽	▽	△	△	▽

* Involving newly diagnosed T2D

▽ Better outcome (reduced risk or longer survival); △ Worse outcome (excess risk or shorter survival); ▼ Significant better outcome; ▲ Significant worse outcome; Symbol flanked by arrows represents composite endpoint of indicated columns.

Abbreviations: AAA, abdominal aortic aneurysm; EHR, electronic health record; MACE, major adverse cardiovascular events (CV mortality, non-fatal MI, non-fatal stroke); PAD, peripheral arterial disease; TIA transient ischaemic attack.

Table 6.6 Comparison of Study 3 with existing trials targeting lipid control

Trial	N patients	Median follow-up (years)	Intervention	Total cholesterol level (mmol/L) achieved (mean)	Cardiovascular endpoint														
					Cardiovascular death	All-cause death	MACE	Stable angina	Unstable angina	Myocardial infarction	Coronary death	Sudden cardiac death	Heart failure	TIA	Ischaemic stroke	Subarachnoid haemorrhage	Intracerebral haemorrhage	PAD	AAA
ALLHAT-LLT (2002)[181]	3,638	4.8 (mean)	Pravastatin *vs* standard	-		△				←▽→			aggregated						
HPS (2003)[177]	5,348	4.8 (mean)	Simvastatin *vs* placebo	-						←▼→					←←←← ▼ →→→→				
CARDS (2004)[176]	2,838	3.9	Atorvastatin *vs* placebo	4.03 *vs* 5.34 (2nd year)		▽			←←←←← ▼ →→→→→						←←←← ▼ →→→→				
4D (2005)[178]	1,255	4	Atorvastatin *vs* placebo	1.86 *vs* 3.10 (LDL, median 4w)		▽	▽			▽				△	←←← ▲ →→→				
FIELD (2005)[179]	9,795	5	Fenofibrate *vs* placebo	4.23 *vs* 4.56	△	△				▼	△				←←← ▽ →→→				
ASPEN (2006)[180]	2,410	4	Atorvastatin *vs* placebo	4.0 *vs* 4.9	△			←△→		←▽→					←←←← ▽ →→→→				
CALIBER (real-world setting using linked EHR)	36,149	4.4	N/A *Cholesterol target achieved vs target not achieved*	≤5 *(threshold)*	▽			▽	▽	▼	▽	▽	△	▼	△	▽	△	▽	▽
			Cholesterol unmeasured vs target not achieved	>5	▲			▽	△	△	▲	▽	▲	▽	▲	△	△	△	▽

▽ Better outcome (reduced risk or longer survival); △ Worse outcome (excess risk or shorter survival); ▼ Significant better outcome; ▲ Significant worse outcome; Symbol flanked by arrows represents composite endpoint of indicated columns.
Abbreviations: AAA, abdominal aortic aneurysm; EHR, electronic health record; MACE, major adverse cardiovascular events (CV mortality, non-fatal MI, non-fatal stroke); PAD, peripheral arterial disease; TIA transient ischaemic attack.

6.6.3 Strengths and limitations

The strengths of Study 3 lie in the cohort size and the prospective nature of the data with sufficient follow-up period which allow investigation of the initial presentations of specific CVD. Achievement of glycaemic, blood pressure and total cholesterol targets was examined either individually or in combination to facilitate comparison with existing studies which defined target achievement differently. Patients without intermediate outcome measurement who are commonly excluded or mistakenly classified into a group failing to meet the target in other studies have been recognised in this study to genuinely represent the quality of care and to enable assessment of a poorer situation than getting measured but failing to meet the target in terms of its relationship with CVD.

This study has some important limitations. The observational nature of these studies does not allow causal relationships to be inferred from my data. Moreover, despite controlling for many covariates, residual confounding by unrecorded or unidentified factors cannot be excluded. For example, this study did not control for diet and diabetes education and supports which are also central to T2D management. Physical activity, which is not less important to target attainment, was found to be non-significant in univariate analysis, perhaps due to being poorly recorded. Similarly, treatment with cardiovascular medication after diagnosis was not controlled for despite potentially having greater effects than baseline treatment on the development of CVDs. Misclassification is possible due to coding errors in clinical practice, particularly for less reliably coded CVD such as stable angina.[4,237] Finally, there were considerable missing data on baseline variables; these seemed to be missing at random and should ideally be imputed. This study used a missingness indicator as previously performed in another CALIBER study[255] and the results are, therefore, more prone to bias. In the next PhD studies (**Chapter 8 Chapter 10**), multiple imputation will be applied to overcome the bias.

6.6.4 Clinical and research implications

Study 3 provided new evidence which informs clinicians, trialists and policy makers about priorities to be set in improving healthcare and prognosis for T2D. This study has documented both the cardiovascular benefits of meeting intermediate outcome targets and the harms of having the intermediate outcomes unmeasured relative to a group of patients who failed to meet the targets. These findings imply that there are still many areas in the processes for T2D care which need further enhancement for more cardiovascular protection and lower T2D burden. The heterogeneous effects on a wide range of CVDs from early target achievement of key intermediate outcomes after diagnosis of T2D imply that a target-based approach should remain emphasised as part of comprehensive management of T2D. The most common incident cardiovascular complications in newly diagnosed T2D include stable angina, heart failure and PAD, implying that these endpoints merit consideration in trials providing different treatment strategies from conventional cardiovascular endpoints.

6.6.5 Conclusion

This study documented contemporary cardiovascular phenotypes which manifested earlier than myocardial infarction and stroke following T2D presentation. Initial achievement of intermediate outcome targets exhibited heterogeneous associations with the incident CVDs. Importantly, stronger protective associations with stable angina, myocardial infarction, heart failure, PAD and mortality were observed with the achievement of composite targets.

6.7 Chapter summary

Using a relatively large sample size and rich clinical data held in the CALIBER research framework, Study 3 has provided a new insight into how early achievement of key intermediate outcome targets in T2D management were differently associated with specific initial presentations of CVDs. My findings are associative and do not imply causality; therefore, further studies applying a different approach to measuring intermediate outcomes are warranted to support the findings.

The next chapter will specifically explore data from repeat HbA1c measurement in order to develop a metric to define glycaemic control longitudinally. The metric developed will be used to examine whether long-term glycaemic control – as opposed to snapshot control in this chapter – is also associated with the development of CVDs (**Chapter 8**) and microvascular diseases (**Chapter 10**).

Chapter 7

Exploration of repeat HbA1c measures as a longitudinal metric for glycaemic control

One is too small a number to achieve greatness.
— John Maxwell

7.1 Chapter outline

Whilst HbA1c is routinely measured to monitor glycaemic control, the extent to which its repeated measures over time in real clinical settings might add information has rarely been studied. The time spent with HbA1c recorded below target level over the disease course may offer a more informative measure for T2D management relative to the traditional, one-off time point measurement of HbA1c. This chapter contains an exploration of repeat HbA1c records in CALIBER's newly diagnosed T2D cohort without prior CVDs and the preparatory work to develop a longitudinal measure of glycaemic control.

7.2 Abstract

Background. Repeat HbA1c measures retrieved from EHRs provide timely access to patients' diabetes care, the time element of which should enable development of a long-term glycaemic control metric. Research on longitudinal patterns of HbA1c as well as predictors of HbA1c frequency is lacking. Importantly, time spent at glycaemic target has never been studied despite its potential for evaluating preventative T2D care.

Objective. (i) To identify the longitudinal patterns of HbA1c measures after initial T2D diagnosis and before the presence of a cardiovascular complication, (ii) to identify predictors for number of HbA1c measures, (iii) to develop a longitudinal metric of glycaemic control, and (iv) to identify patients' characteristics which may relate to their longitudinal glycaemic control.

Methods. A cohort of newly diagnosed T2D patients in CALIBER eligible for this study was identified and their HbA1c records over time were scrutinised. Mixed Poisson regression was used to explore factors associated with frequency of HbA1c measures. Using a cumulative interval between successive HbA1c measures, duration of glycaemic control over a patient's follow-up was developed as average annual TIme at TaRgEt (TITRE). The association between cardiovascular risk factors and TITRE-HbA1c was examined by multinomial logistic regressions.

Results. A cohort of 34,660 patients for the TITRE-HbA1c and cardiovascular outcomes study was established with a median follow-up 4.4 years (IQR 2.5-6.8). The TITRE was calculable in 30,221 patients using 264,111 HbA1c measures (214,527 intervals). The median number of HbA1c measures per person over the whole follow-up was 6 (3-11), the median annual number of HbA1c measures was 1 (IQR 0-2) and median time between successive measures up to one year apart was 5.6 months (IQR 4.5-6.7). The number of HbA1c measures decreased significantly over the years of follow-up. TITRE values showed a non-linear distribution (median 4.3%, IQR 0-26.7) with high proportions on both tails (0% and 100%). Demographic and cardiovascular risk factors were associated with lower TITRE, whereas early prescription of diabetes medication appeared to be associated with higher TITRE.

Discussion. These initial findings inform the analysis plan for subsequent studies investigating the associations of TITRE-HbA1c and T2D complications (**Chapters 8 and 10**). Baseline and follow-up factors were found to be confounders needing adjustment in the subsequent studies.

7.3 Introduction

A single 'snapshot' measurement of HbA1c is considered the gold standard assay for monitoring diabetes control and this approach has been widely adopted in both clinical practice and research.[31-33] International guidelines recommend HbA1c be measured at least 6-monthly and more frequently in diabetes patients who fail to meet their glycaemic target. In the absence of consensus for optimal frequency of HbA1c testing, studies have reported clinical variation. At a population level, overtesting of HbA1c (i.e. repeat tests within 90 days) was substantial in the US setting,[291]

while either over- or undertesting (i.e. single test in a year) was prevalent in the UK setting.[292] Such lack of conformity to the guidelines was further shown to lead to under- or over-treatment that may have caused patient harm (e.g. deteriorating glycaemic control, hypoglycaemia due to treatment intensification).[291,293]

Despite the variation, recommendation for routine monitoring implies that frequency for HbA1c tests is no less important than achieving glycaemic control. Moreover, the availability of HbA1c data routinely collected and electronically recorded has offered the potential for evaluation of guideline adherence in order to improve diabetes care and outcomes. Yet repeated measures of HbA1c in real clinical settings has rarely been studied. By incorporating the time course factor, duration under glycaemic control can be estimated and may provide additional information for T2D management compared to the conventional approach.

This chapter sought to exploit repeat HbA1c records by examining the monitoring patterns in newly diagnosed T2D patients and factors associated with the frequency of HbA1c measurements. A target-and-time-based metric to assess glycaemic control longitudinally was further developed by harnessing the repeated HbA1c measures.

7.4 Methods

7.4.1 Study population, study period and inclusion criteria

Patients newly diagnosed with T2D in CALIBER were included if they met the general inclusion criteria listed in **Section 3.9 on pages 111-113**. The observation period for each patient was calculated from the date T2D was first diagnosed ('index date') to the earliest administrative censoring date or the first occurrence of a cardiovascular endpoint. Patients who had prior CVD before the index date were excluded. A patient flow chart for this preliminary study is presented in **Figure 7.5 on page 221**.

7.4.2 Longitudinal pattern of HbA1c measures

Proportion of patients by number of HbA1c measures was calculated on an annual basis and continuity patterns of HbA1c tests were investigated. The latter aimed to explore the extent of HbA1c tests in a patient not performed within successive years. Other descriptive patterns investigated were annual mean HbA1c values, time interval between successive measures and time to initial follow-up HbA1c measure. These descriptive analyses were carried out to provide some insights into the nature of repeat HbA1c data for the development of the TITRE metric. Each analysis can therefore be thought of as a 'pre-TITRE' analytic component.

7.4.3 Predictors of frequency of HbA1c measures

Demographic variables, baseline cardiovascular risk factors (body mass index, systolic blood pressure, total cholesterol, HDL), baseline comorbidities (renal disease, chronic obstructive pulmonary disease [COPD]) and prescription of cardiovascular medications were explored for their associations with number of HbA1c tests received. T2D was shown to be more prevalent in COPD

patients,[294,295] the plausible contributing factors being chronic inflammation, oxidative stress, hypoxia, reduced physical activity, smoking habit and corticosteroids treatment.[296]

Additionally, the effect of follow-up year was of particular interest given the varying number of HbA1c measures over time. Assuming dependence of HbA1c measures within patient, Poisson regression with random effect was used to estimate the effect of each variable.[297] Missing baseline values were 5-multiply imputed using the chain equations (**Section 3.13.1 on pages 124-125**).

7.4.4 Development of longitudinal glycaemic control metric: Average annual TIme at TaRgEt (TITRE)

This study primarily sought to exploit HbA1c data recorded in CPRD. HbA1c is expected to be tested repeatedly in a T2D patient from which a longitudinal metric of glycaemic control can be developed. The concept of time at target was first introduced in a warfarin study[298] and has recently been redeveloped for blood pressure using the CALIBER platform.[299] Time at target in this study adopted the methods in the latter study defined as mean yearly days spent during which HbA1c levels were at or below the target – hereinafter termed as TIme at TaRgEt (TITRE). The target level chosen for the main analysis was ≤48 mmol/mol (6.5%) after the most recent NICE guideline.[33] For each patient, the number of days at glycaemic target was initially calculated as time interval (i.e. between two consecutive HbA1c measures) and there were additional rules set before final TITRE calculation.

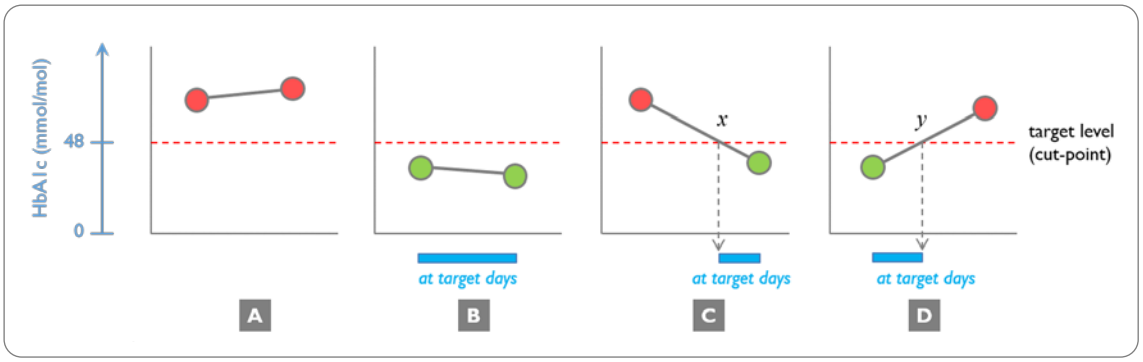
It is essential to first define the time window for TITRE-HbA1c calculation. Diabetes can be diagnosed initially on the basis of HbA1c criteria; however, this might not always be the case. In fact, other diagnostic tests such as fasting plasma glucose (FPG) and 2-hour plasma glucose (2hPG) values after a 75 g oral glucose tolerance test (OGTT) were still used frequently. Therefore, a low proportion of patients with HbA1c records within the baseline period was expected. For the TITRE analysis, baseline HbA1c value was determined from the latest measure within a year prior to or on the index date. Where baseline values were missing, no imputation was performed and the starting point for calculating initial interval was the first HbA1c measure after entry (referred to as 'index measure'). In patients with known HbA1c at baseline, the starting point was the index date, thus the initial interval was calculated as the difference between index date and index measure. The terminal point for TITRE calculation was the last HbA1c measure during a patient's observation period. Therefore, the time window for the TITRE calculation in a patient differed from, and never exceeded, the patient's follow-up period. To make it more distinctive, I used the phrases 'follow-up HbA1c period', 'follow-up HbA1c anniversary' or 'follow-up HbA1c year' interchangeably when it came to TITRE calculation, and simply 'follow-up period' to refer to a patient's whole observation period.

Detailed steps to estimate TITRE-HbA1c are explained below:

7.4.4.1 Interval between two HbA1c measures within one-year follow-up HbA1c period

Calculation of time interval between two HbA1c measures at target is straightforward (**Figure 7.1B below**). If measures at the beginning and the end were both equal to or below the HbA1c cut-point, at-target days were calculated as the difference between the dates (i.e. date of end measure minus date of beginning measure).

Figure 7.1 Time interval calculation for two successive HbA1c measures within one-year follow-up HbA1c period



If one of the two measures was above the HbA1c cut-point (**Figures 7.1C and 7.1D above**), longer steps were needed to calculate the time interval; the first step was to calculate the interval from at target (low HbA1c) to above target (high HbA1c) or vice versa. A fractional multiplier to estimate the date when HbA1c change occurred was then calculated; the calculation – assuming linear change over time – borrows the triangle proportionality theorem and is expressed in Equation (7.1) below:

$$Multiplier\ factor = \frac{HbA1c\ cut\text{-}point - Low\ HbA1c}{High\ HbA1c - Low\ HbA1c} \quad (7.1)$$

Days at glycaemic target were calculated proportionally as the product of time interval between two HbA1c measures and Equation (7.1) above:

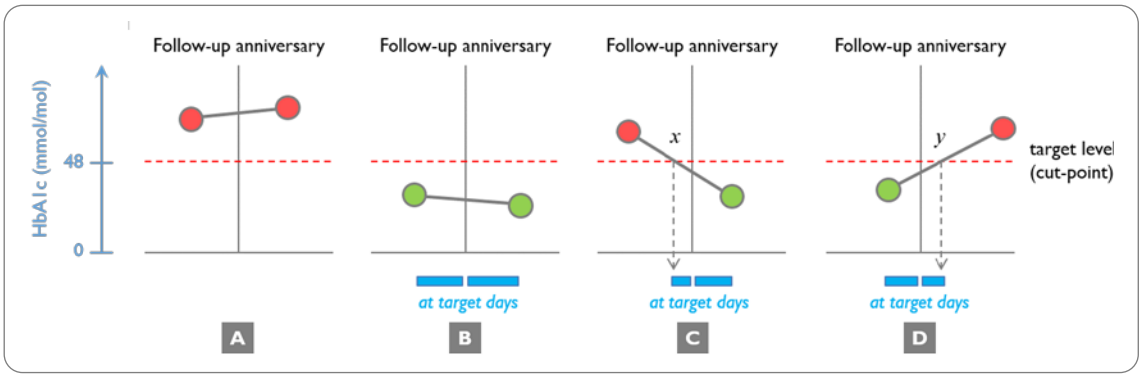
$$Days\ at\ glycaemic\ target = time\ interval * multiplier\ factor \quad (7.2)$$

The date when HbA1c change occurred (indicated by x and y in the figures) can be estimated from Equation (7.2) above by addition to or subtraction from the date of one of the successive measures, depending on the direction of the change. The estimated date helps determine the start of an at-target interval (for a change from high to low HbA1c) or the ending (from low to high HbA1c), which is useful for a mathematical proof, analysis checks or further calculation for at-target intervals involving a follow-up HbA1c anniversary (**Section 7.4.4.2 on page 215**).

7.4.4.2 Interval between two HbA1c measures which involved a follow-up HbA1c anniversary

Follow-up anniversary of HbA1c measure was determined from the index measure; whether an anniversary date fell in between the dates of two successive HbA1c measures needed to be checked at first instance to decide which interval calculation was appropriate. If an interval contained the anniversary date, at-target days were partitioned for the successive years (i.e. before and after the anniversary). If both HbA1c measures were equal to or below the cut-point, at-target days were calculated as measure date in a defined year subtracted from anniversary date, and anniversary date subtracted from measure date in the following year (**Figure 7.2 below**).

Figure 7.2 Time interval calculation for two successive HbA1c measures crossing a follow-up HbA1c anniversary



If a change from above target to at target was observed (**Figure 7.2 above**), the date of change (henceforth denoted as x) was estimated as Equation (7.2) being subtracted from the date of low HbA1c. If x fell on or after the anniversary date, at-target days in a defined year were zero, whereas at-target days in the following year were equal to Equation (7.2). If x fell before the anniversary date, at-target days in a defined year were calculated as x being subtracted from the anniversary date, whereas at-target days in the following year were equal to anniversary date being subtracted from the date of low HbA1c.

If a change from at target to above target was observed (**Figure 7.2 above**), the date of change (henceforth denoted as y) was estimated as the sum of the date of low HbA1c and Equation (7.2). If y fell on or after the anniversary date, at-target days in a defined year were calculated as the date of low HbA1c subtracted from the anniversary date, whereas at-target days in the following year were equal to anniversary date subtracted from y. If y fell before the anniversary date, at-target days in a defined year were equal to Equation (7.2), whereas at-target days in the following year were zero.

7.4.4.3 Denominators

Under an 'ideal' scenario (i.e. both HbA1c values at baseline and end of follow-up are known and intervals between measures are all less than a year), the *index date* is the starting point to calculate both initial interval and HbA1c anniversary. The denominator for the last follow-up HbA1c year is the date of last measure (or study exit) minus the date of the last HbA1c anniversary.

Under a 'non-ideal' scenario (i.e. both HbA1c values at baseline and end of follow-up are missing and at least one of the intervals exceeds one year), the *index measure* is the starting point to calculate initial interval (and HbA1c anniversary if the last measure which occurs after the first anniversary). Any intervals exceeding one year are 'excluded' before calculation (counted as zero), but the corresponding follow-up HbA1c years remain to be counted as denominators. The denominator for the last follow-up HbA1c year is the date of last measure minus the date of the last anniversary (or minus index measure if the last measure occurs before the first anniversary).

7.4.4.4 Additional rules

Lengthy intervals. Intervals derived from two successive HbA1c measures which were more than one year apart were not counted since there was too much uncertainty to assume a constant at-target state beyond one year. Moreover, the TITRE definition implies that the metric is *annual*-based. However, the follow-up year(s) within which lengthy intervals were ignored remained to be counted towards the denominator so long as other shorter intervals from the patient were observed.

Very low HbA1c value. HbA1c cannot inform short-term glucose variability; thus, a very low HbA1c level was not used to indicate a hypoglycaemia event and remained in use to estimate an at-target interval.

7.4.4.5 TITRE-HbA1c calculation

For each HbA1c anniversary year, all days at the glycaemic target calculated in a patient were summed up and subsequently calculated as percent time at target. Percent time at target was averaged over the time window for the TITRE calculation before being converted to its equivalent month to yield a final TITRE estimate. For more intuitive interpretation, TITRE was classified into six categories: missing, 0 months, <3 months, 3-<6 months, 6-<9 months and 9-12 months. A 3-month interval was arbitrarily chosen for TITRE categorisation to represent the time validity of HbA1c (given the erythrocyte's life span). TITRE was classified as missing when: a) no HbA1c records were available during follow-up, b) when a single interval could not be calculated (i.e. there was a single measure only after entry without known HbA1c at baseline), or c) HbA1c records were all beyond one year apart throughout follow-up. The concept of the TITRE metric is depicted in **Figure 7.3 below**.

Figure 7.3 Basic concept of the TITRE metric

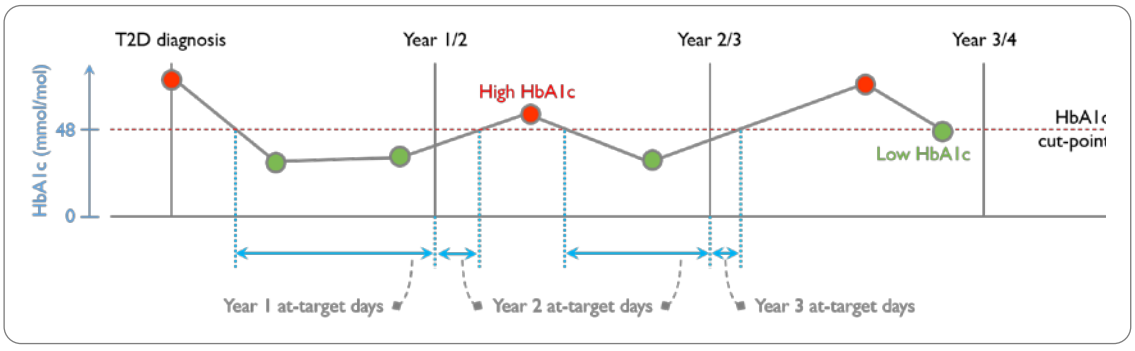
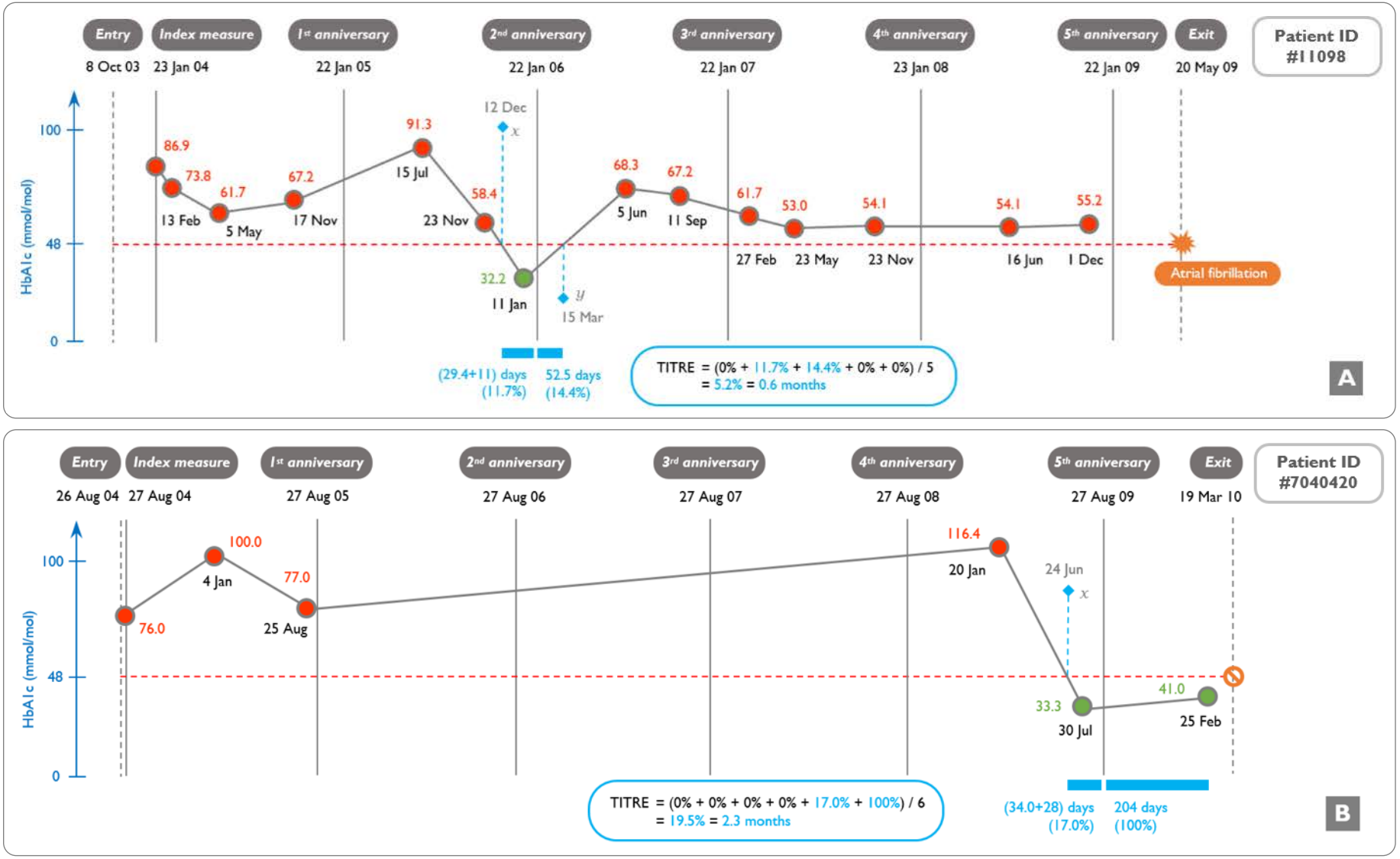
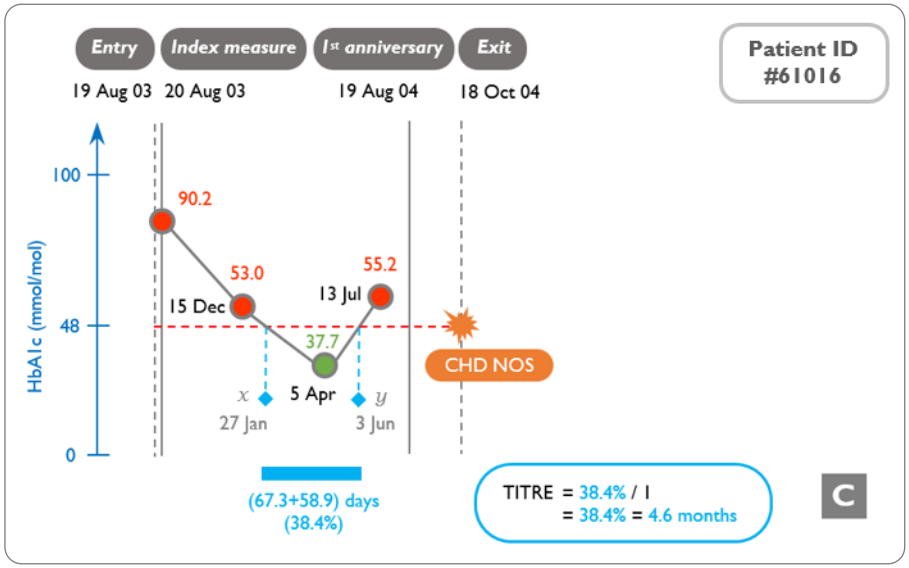
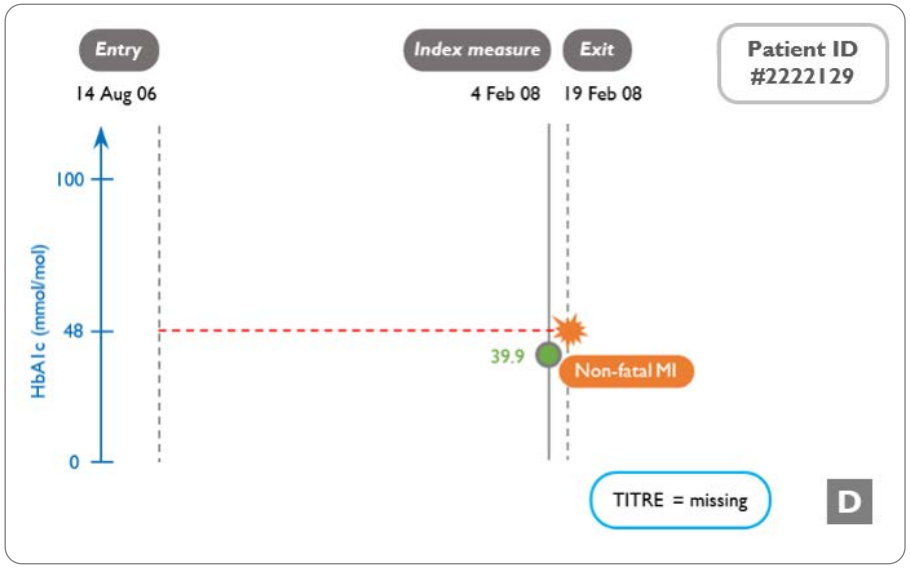
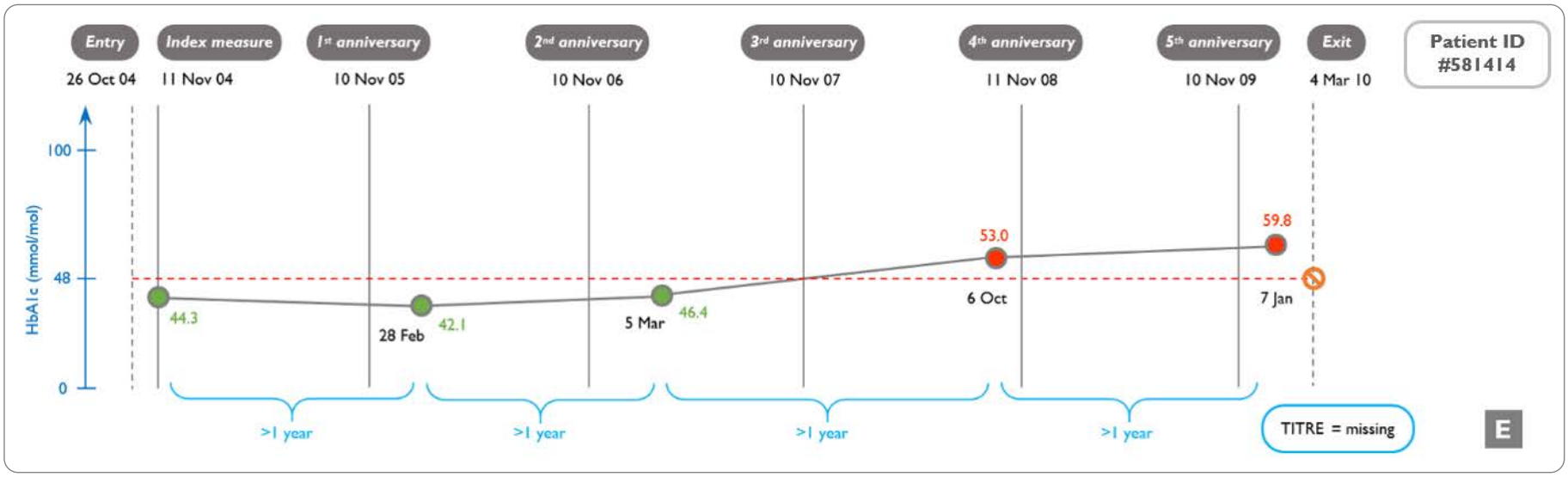


Figure 7.4 TITRE calculation illustration of five patients with differing patterns of HbA1c measurement




Entry
Index measure
1st anniversary
Exit
19 Aug 03
20 Aug 03
19 Aug 04
18 Oct 04
Patient ID #61016
HbA1c (mmol/mol)
100
48
0
90.2
53.0
15 Dec
55.2
13 Jul
37.7
5 Apr
x
27 Jan
y
3 Jun
CHD NOS
(67.3+58.9) days
(38.4%)
TITRE = 38.4% / 1
= 38.4% = 4.6 months
C


Entry
Index measure
Exit
14 Aug 06
4 Feb 08
19 Feb 08
Patient ID #2222129
HbA1c (mmol/mol)
100
48
0
39.9
Non-fatal MI
TITRE = missing
D


Entry
Index measure
1st anniversary
2nd anniversary
3rd anniversary
4th anniversary
5th anniversary
Exit
26 Oct 04
11 Nov 04
10 Nov 05
10 Nov 06
10 Nov 07
11 Nov 08
10 Nov 09
4 Mar 10
Patient ID #581414
HbA1c (mmol/mol)
100
48
0
44.3
28 Feb
42.1
5 Mar
46.4
53.0
6 Oct
59.8
7 Jan
>1 year
>1 year
>1 year
>1 year
TITRE = missing
E

7.4.4.6 Examples of TITRE-HbA1c calculation in real-setting scenarios

TITRE estimations in select patients from my study cohort are visualised in **Figures 7.4A to 7.4E on pages 217-218** to represent the complexity of longitudinal HbA1c measures in a real clinical setting. Only five real scenarios (all without known HbA1c at baseline) are presented with a detailed calculation supplied in each figure. When analysing the data, I set one year as 365.25 days and one month as 30.4375 days.

In the first scenario, HbA1c were measured frequently but only one measure was at target (**Figure 7.4A on page 217**). Two at-target intervals could be calculated from the before and after date at target since both intervals did not exceed one year. The second interval was partitioned due to crossing a follow-up HbA1c anniversary and each part contributed to partial TITRE for the respective years (i.e. before and after anniversary).

In the second scenario, HbA1c were initially measured frequently but then there was a 3-year pause before frequent measures resumed from year 5 (**Figure 7.4B on page 217**). Two last measures were at target and contributed to two at-target intervals, one of which crossed the anniversary date. All preceding follow-up HbA1c years and the years within which the lengthy intervals were observed were counted towards the denominators.

In the third scenario, the last HbA1c measure was recorded before the first HbA1c anniversary (**Figure 7.4C on page 218**); therefore, the interval between the first and last measures became the denominator.

In the fourth scenario, HbA1c were only measured once after entry and the baseline value was unknown (**Figure 7.4D on page 218**). This patient was instantly classified into the missing TITRE category because no interval was calculable.

In the fifth scenario, HbA1c levels were measured sparsely over 6 years of follow-up, and all measures – regardless of target achievement – were all beyond one year apart (**Figure 7.4E on page 218**). This patient was also classified into the missing TITRE category before any further calculations.

7.4.5 Predictors of TITRE

Distributions of TITRE by cardiovascular risk factors known to be associated with diabetes were compared. Baseline factors included age, sex, ethnicity, deprivation, smoking status, body mass index category, blood pressure, total cholesterol, HDL cholesterol, renal disease and cardiovascular medication. Time-varying factors included class of initial diabetes medication prescribed, time to initial prescription of diabetes medication and number of hypoglycaemia events. TITRE categories were considered to have a natural ordering yet the distances between TITRE categories were known (except for missing category); therefore, multinomial logistic regression was chosen over generalised ordered logistic regressions to analyse the associations between these factors and achieving greater TITRE categories versus the 3-6 month category as the reference group. The model was clustered by GP practice to account for practice heterogeneity. This analysis will help

develop an analysis plan for investigating the association between TITRE and cardiovascular outcomes in the subsequent studies.

7.5 Results

Of 52,379 newly diagnosed T2D patients in CALIBER, 17,719 were excluded for not meeting inclusion criteria (**Figure 7.5 on page 221**), generating a cohort of 34,660 patients for the TITRE study with a median follow-up of 4.4 years (IQR 2.5-6.8).

7.5.1 Characteristics of eligible patients

The characteristics of patients who were eligible and excluded for the TITRE study are compared in **Table 7.1 on page 222**. Eligible patients were younger when diagnosed (mean 59.6 *vs* 70 years), had a higher proportion of those of white ethnicity (56.5% *vs* 39.4%), were less prescribed with antihypertensives (33.7% *vs* 64.9%), lipid lowering drugs (9.1% *vs* 38.0%) and antiplatelets (4.7% and 42.4%) at baseline, but were more often prescribed with diabetes medication (78.9% *vs* 67.2%) over their follow-up period. Despite having higher values for biomarkers, completeness of baseline records was slightly higher for HbA1c but slightly lower for total cholesterol, HDL cholesterol and body mass index in eligible patients.

Figure 7.5 Patient flow chart for study on TITRE-HbA1c and cardiovascular outcomes

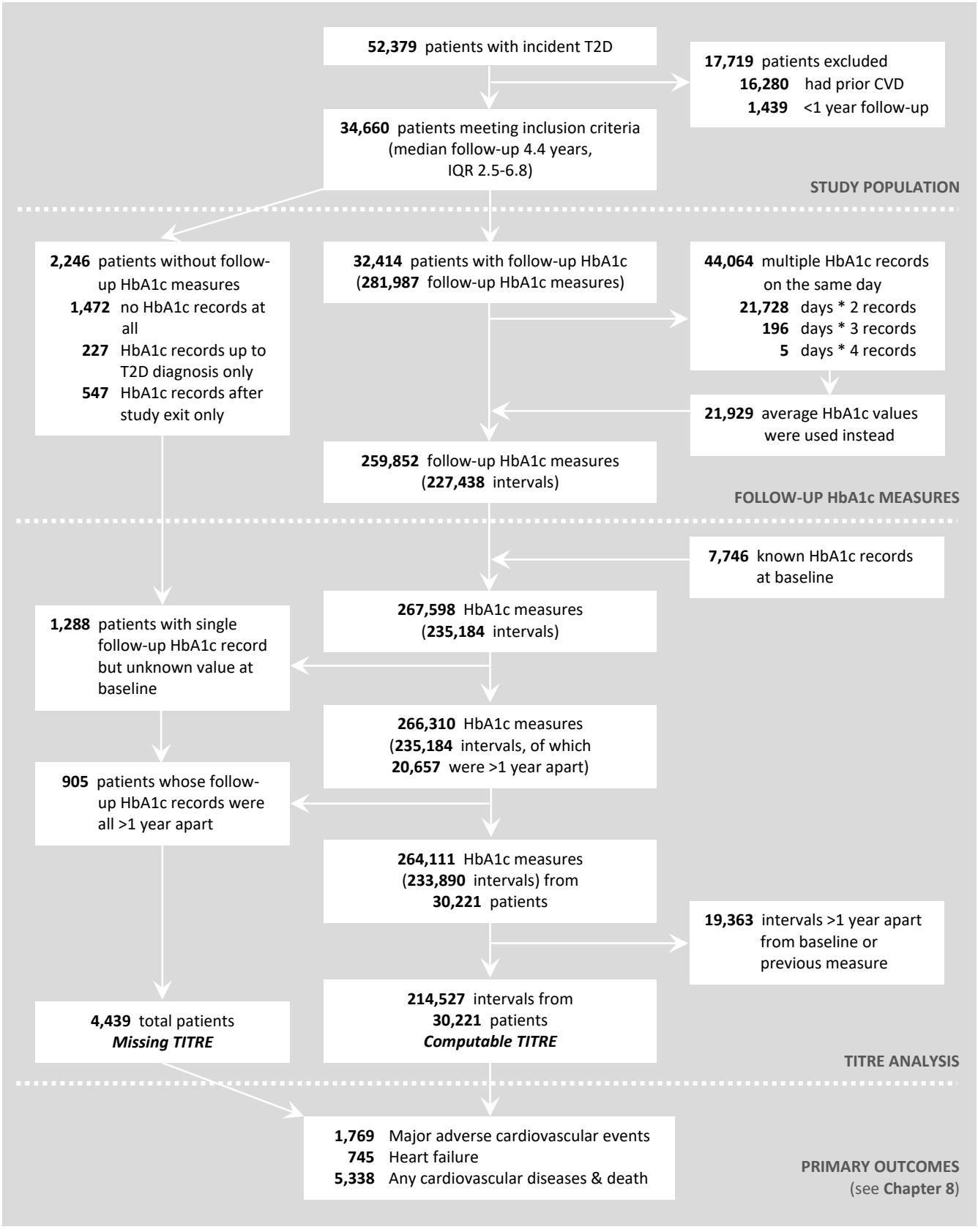


Table 7.1 Characteristics of eligible versus excluded patients for TITRE-CVD study

Characteristics	Eligible patients* (N=34,660)		Excluded patients** (N=17,719)	
Prior cardiovascular diseases, n (%)				
Coronary heart disease	-		9,869	(55.7)
Stroke	-		3,360	(19.0)
Heart failure	-		2,300	(13.0)
Peripheral arterial disease	-		1,748	(9.9)
Duration of GP registration, median (IQR) years	10.9	(6.4-15.7)	11.3	(7.4-16.4)
Year of diagnosis, n (%)				
1998-2003	15,140	(43.7)	7,701	(43.5)
2004-2006	11,401	(32.9)	5,996	(33.8)
2007-2009	8,119	(23.4)	4,022	(22.7)
Age at entry, mean (SD) years	59.6	(12.9)	70.0	(11.6)
Women, n (%)	15,935	(46.0)	7,665	(43.3)
White ethnicity, n (%)†	19,568	(56.5)	6,974	(39.4)
Most deprived quintile, n (%)†	6,754	(19.5)	3,686	(20.8)
Smoking status, n (%)				
Never	5,769	(16.6)	2,607	(14.7)
Ex-smoker	4,067	(11.7)	3,525	(19.9)
Current smoker	2,943	(8.5)	1,523	(8.6)
Baseline records, n (%)				
HbA1c	7,933	(22.9)	3,537	(20.0)
Blood pressure	34,660	(100)	17,719	(100)
Total cholesterol	17,114	(49.4)	10,041	(56.7)
HDL cholesterol	13,559	(39.1)	7,693	(43.4)
Body mass index	12,001	(34.6)	6,667	(37.6)
Baseline value				
HbA1c, mean (SD) mmol/mol	69.0	(24.8)	62.1	(22.2)
Systolic blood pressure, mean (SD) mmHg	146.2	(19.4)	143.0	(19.7)
Diastolic blood pressure, mean (SD) mmHg	85.1	(10.8)	80.4	(11.0)
Total cholesterol, mean (SD) mmol/L	5.7	(1.3)	5.0	(1.2)
HDL cholesterol, mean (SD) mmol/L	1.2	(0.4)	1.2	(0.4)
Body mass index, mean (SD) kg/m^2	32.3	(6.8)	30.9	(6.2)
Renal diseases, n (%)	432	(1.3)	749	(4.2)
Baseline cardiovascular medications, n (%)				
Blood pressure lowering medications	11,686	(33.7)	11,495	(64.9)
Lipid lowering medications	3,138	(9.1)	6,724	(38.0)
Antiplatelets	1,616	(4.7)	7,518	(42.4)
Class of first diabetes medication prescribed, n (%)				
Never prescribed	7,315	(21.1)	5,810	(32.8)
Insulin	363	(1.1)	239	(1.4)
Metformin‡	21,205	(61.2)	8,405	(47.4)
Sulphonylureas	5,381	(15.5)	3,118	(17.6)
Thiazolidinediones	290	(0.8)	109	(0.6)
Acarbose	42	(0.1)	16	(0.1)
DPP4 inhibitors	6	(0.0)	2	(0.0)
GLP1 agonists	2	(0.0)	1	(0.0)
Meglitinides	56	(0.2)	19	(0.1)
Time to initial diabetes medication prescription, median (IQR) months§	4.3	(0.3-25.2)	4.3	(0.5-23.0)

*Newly diagnosed T2D aged 30 years or older. **Excluded if had prior CVD or had less than one year follow-up.
†Missing values: deprivation 0.3% (105 eligible patients, 48 excluded patients), ethnicity 34.5% (11,960 eligible patients) and 57.9% (10,266 excluded patients), smoking status 63.1% (21,881 eligible patients) and 56.8% (10,064 patients).
‡Includes combination with thiazolidinedione or DPP4 inhibitor.
§Among patients ever prescribed: 78.9% (27,345 eligible patients) and 67.2% (11,909 excluded patients).

7.5.2 Patterns of repeat HbA1c measures

7.5.2.1 Yearly pattern of HbA1c measures

There were 707 combinations of yearly pattern for HbA1c tests in the study cohort. Most HbA1c measures in a patient were tested in consecutive years from initial T2D diagnosis and only approximately 30% were tested intermittently (**Table 7.2 below**). Over 6% of the cohort were never measured during their follow-up, approximately 8% were never measured after one year since diagnosis and a lower proportion of patients received their initial test just after the first year of follow-up (details not shown).

Table 7.2 Most common yearly pattern of HbA1c tests after initial T2D diagnosis

Yearly pattern of HbA1 tests*	N	%
. . . . .	2,246	6.5
1	2,453	7.1
1 2	4,610	13.3
1 2 3	3,711	10.7
1 2 3 4	2,940	8.5
1 2 3 4 5	2,524	7.3
1 2 3 4 5 6	2,088	6.0
1 2 3 4 5 6 7	1,597	4.6
1 2 3 4 5 6 7 8	1,146	3.3
1 2 3 4 5 6 7 8 9	678	2.0
1 2 3 4 5 6 7 8 9 10 . . .	346	1.0
1 2 3 4 5 6 7 8 9 10 11 . .	164	0.5
. 2	478	1.4
. 2 3	334	1.0
. 2 3 4	267	0.8
. 2 3 4 5	200	0.6
. 2 3 4 5 6	189	0.5
. 2 3 4 5 6 7	181	0.5
. 2 3 4 5 6 7 8	195	0.6
. 2 3 4 5 6 7 8 9	222	0.6
1 . 3	269	0.8
1 . 3 4	173	0.5
1 2 . 4	224	0.6
. . 3	212	0.6
. . 3 4	190	0.5
. . 3 4 5	163	0.5
(other patterns)	6,860	19.8
	34,660	100.0

*Receiving tests in the corresponding years (indicated by numbers).
Dot represents year in which HbA1c is not tested.
The longest duration of follow-up possible is 13 years.

7.5.2.2 Yearly frequency of HbA1c measures

The median total frequency of HbA1c tests for a patient over the follow-up years was 6 (IQR 3-11) (**Figure 7.6 on page 224**). Yearly estimates were shown in **Appendix F, Figure F7.1 on page 359**; median frequency was highest in the first year and mean frequency never reached 2 over time.

The overall mean annual frequency of HbA1c tests was 1.4 (SD 1.2). These estimates indicate an undertesting since current guidelines recommend at least two HbA1c tests a year for diabetes monitoring.

Mean HbA1c values per patient showed upward trends over time and were all above the recommended target of 48 mmol/mol (**Figure 7.7 below**). However, target was met by year 5 if less stringent cut-point (58 mmol/mol) was applied. Despite being represented by a comparable proportion of patients who were ever tested over a decade, these findings suggest that maintaining glycaemic control for a longer period poses an additional challenge for T2D care.

Figure 7.6 Total number of HbA1c tests per patient during follow-up (N=34,660)

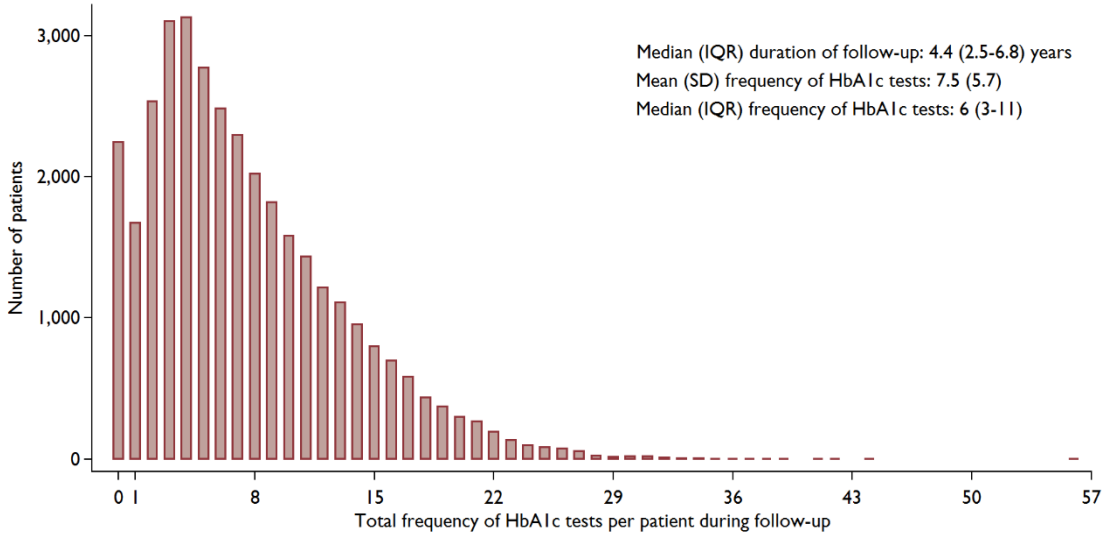
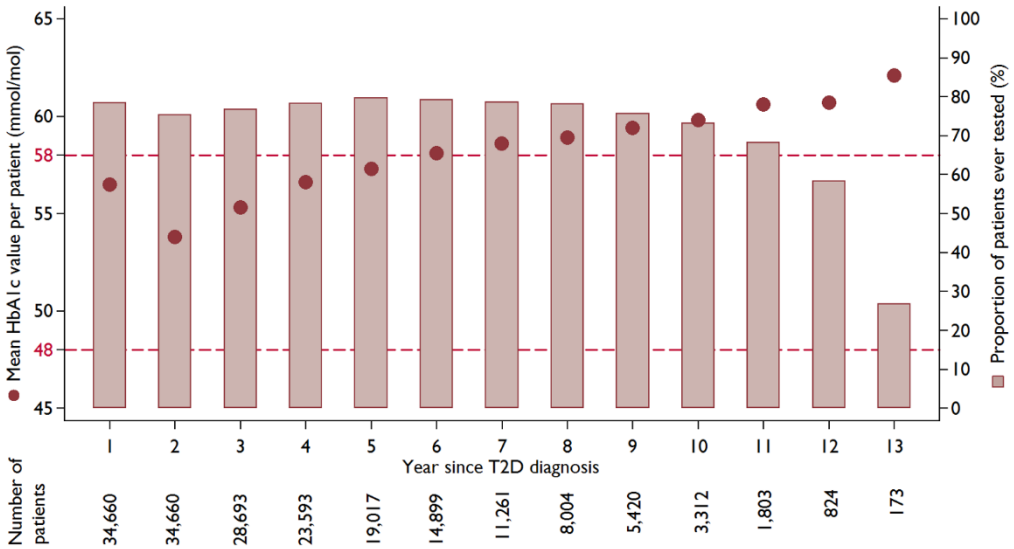


Figure 7.7 Mean follow-up HbA1c value per patient over time (N=32,414)



7.5.2.3 Time to initial follow-up HbA1c measure

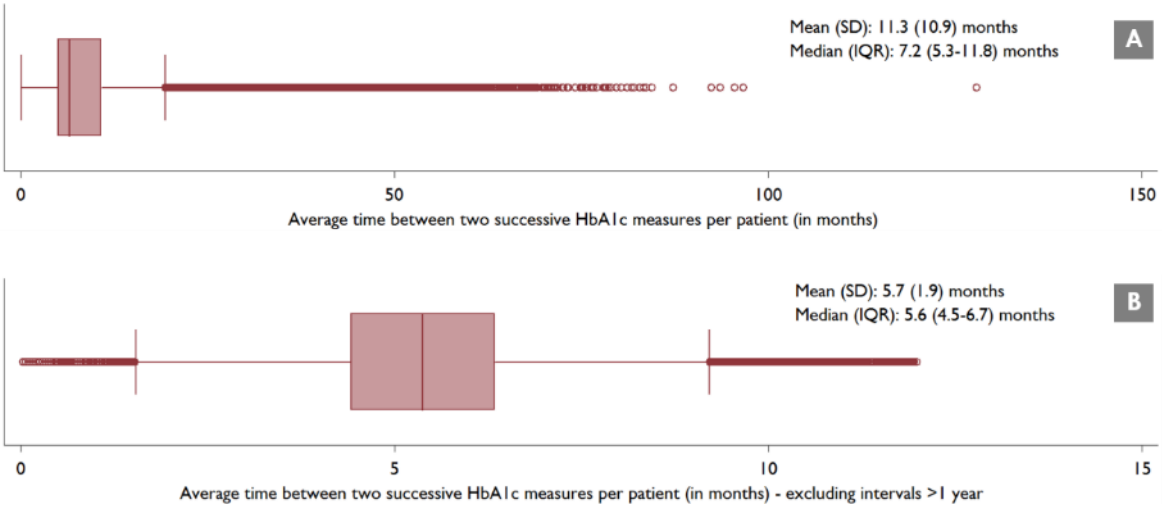
Only 7,933 (22.9%) patients in the study cohort had HbA1c records at baseline with a mean (SD) value of 69.0 (24.8) mmol/mol. Of these patients, 1,644 (20.7%) had HbA1c ≤48 mmol/mol and this estimate was lower than that for excluded patients (N=988, 27.9%).

In patients with non-missing follow-up HbA1c (N=32,414), the median time needed to get the initial follow-up HbA1c measured was 3.2 months (IQR 1.3-9.5). The estimate remained unchanged when analysed according to whether or not baseline HbA1c was missing, although a wider range was observed in those without baseline HbA1c (median (IQR) 3.3 (1.0-12.9) months versus 3.2 (2.0-5.5) months).

7.5.2.4 Time interval between successive HbA1c measures

There were 259,852 potential follow-up HbA1c measures and an additional 7,746 baseline measures in 32,414 patients, but further examination allowed only 264,111 measures – from which 214,527 eligible intervals were retrieved – from 30,221 patients for TITRE analysis (**Figure 7.5 on page 221**). Reasons for further patient exclusion were due to having a single measure only after entry without a known HbA1c at baseline (1,288 patients, 4%) and having follow-up HbA1c measures which were all more than one year apart throughout the observation period (905 patients, 2.8%); these patients were classified into missing TITRE along with another 2,246 patients who had no follow-up HbA1c measures over their follow-up period. The reason for further 'measure exclusion' in patients with computable TITRE was due to lengthy intervals from the baseline or previous measure (N=19,363). The latter exclusion referred to an omission of intervals beyond one year from the TITRE calculation while keeping both connecting HbA1c measures, because each measure might still be used to estimate other intervals flanking the lengthy one.

Figure 7.8 Distribution of time between successive HbA1c measures



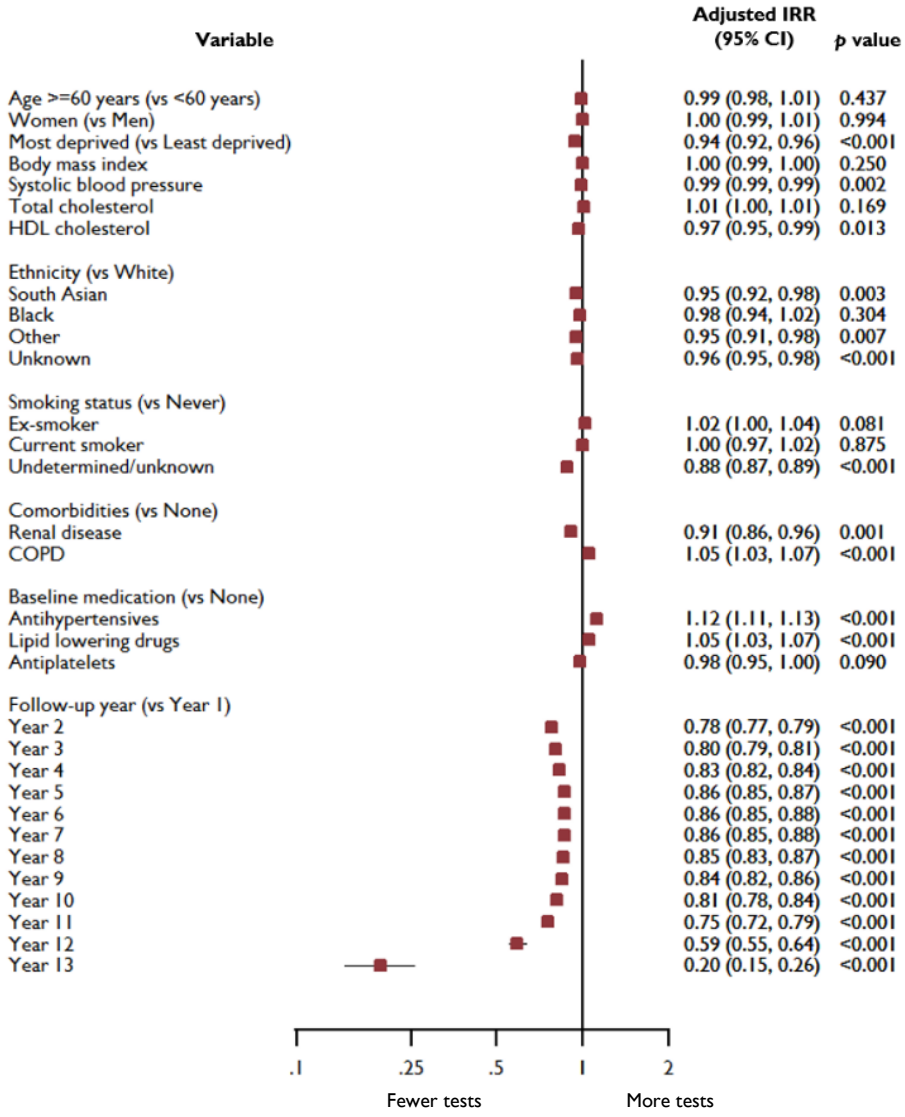
The distribution of average time between measures per patient was highly skewed when lengthy intervals were included with a median (IQR) of 7.2 (5.3-11.8) months (**Figure 7.8A above**),

but roughly normally distributed after their omission with a median (IQR) of 5.6 (4.5-6.7) months (**Figure 7.8B on page 225**), thereby justifying the reason for not counting such intervals towards the TITRE calculation.

7.5.3 Predictors of frequency of HbA1c measures

Results from the mixed Poisson regression is summarised in **Figure 7.9 below**. South Asian ethnicity, most deprived patients and having renal disease were more likely to receive 5-9% fewer HbA1c measures over the follow-up period. Systolic blood pressure and HDL cholesterol values at baseline were also associated with fewer HbA1c measures. In contrast, receiving antihypertensives and lipid lowering drugs prior to T2D diagnosis were associated with 12% and 5% increases in HbA1c test frequency, respectively.

Figure 7.9 Predictors of total number of HbA1c measures



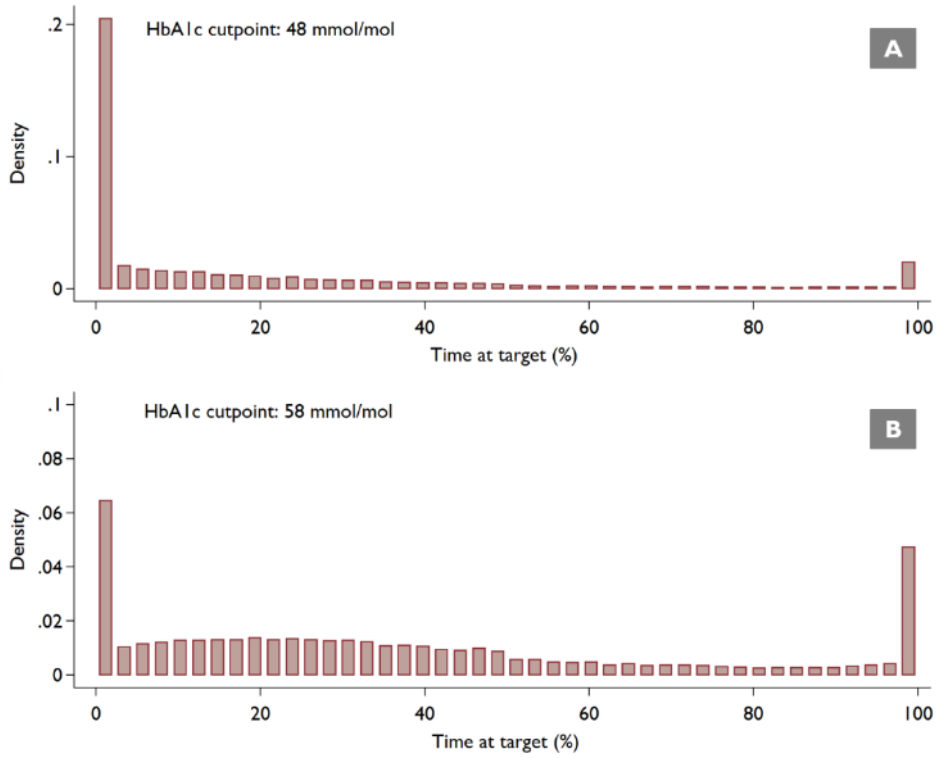
Importantly, the estimates suggest that the follow-up year was significantly associated with a continuing decrease in receiving HbA1c measures. Relative to the first year, the decrease

ranged from 15% to 20% within a decade after having T2D. With a standard deviation between-patient of 0.33, the median incidence-rate ratio can be calculated as $[\exp\sqrt{2^{*}\,0.33^{-3/4}}] = 1.38$ which means that half the time, the ratio of the expected number of HbA1c measures will lie in a range from 0.73 (=1/1.38) to 1.38, and the other half of the time, the ratio will lie outside that range.

7.5.4 TITRE-HbA1c

TITRE-HbA1c were calculated in 30,221 patients and defined as missing in 4,439 patients. The median (IQR) time window for TITRE calculation was 3.4 (1.7-5.6) years. **Figure 7.10A below** shows that non-missing TITRE distribution – applying HbA1c <48 mmol/mol as the cut-point – was predominated by 0% value (N=12,190, 40.3%) and roughly U-shaped with a median TITRE of 4.3% (IQR 0-26.7). A similar distribution was retained when setting a higher cut-point at 58 mmol/mol (**Figure 7.10B below**). While this might suggest the difficulty of achieving glycaemic control over time in most patients in the cohort, it is noteworthy that the proportion of patients with 100% TITRE was also relatively high.

Figure 7.10 TITRE-HA1c distribution

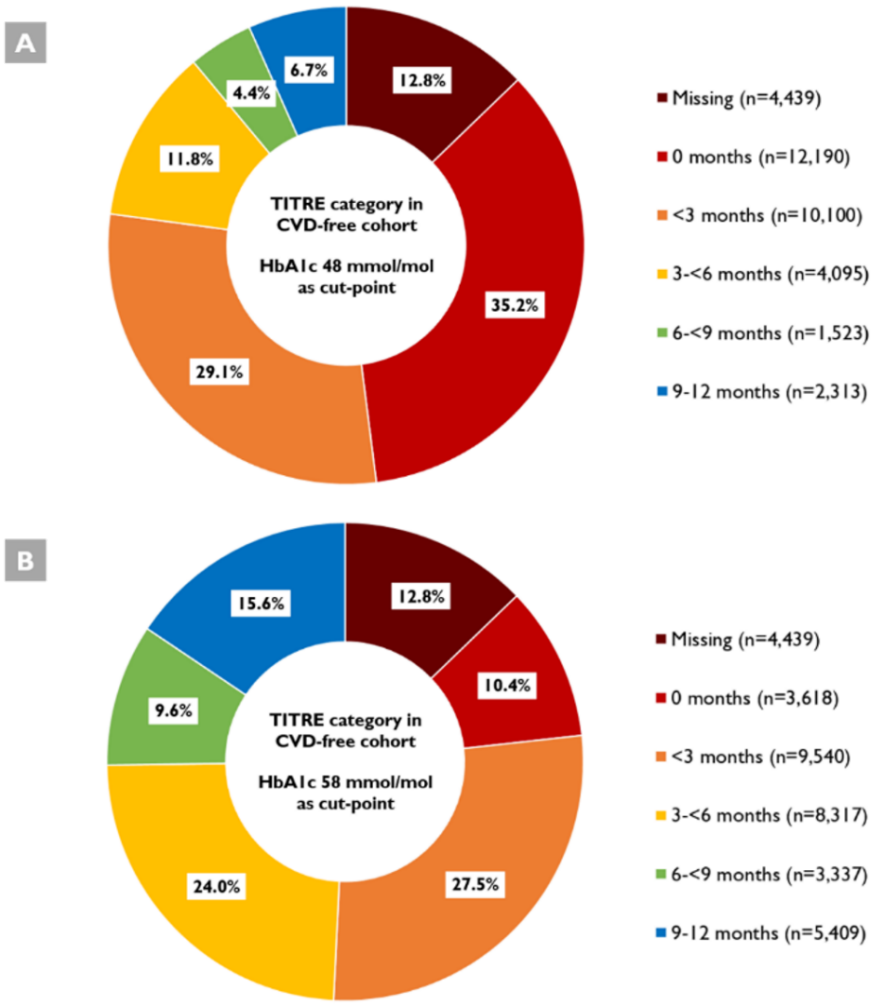


Using an HbA1c cut-point of 48 mmol/mol, I did some checks on patients with 100% TITRE (N=1,319) in terms of whether their HbA1c values were consistently low from the beginning. Analysis on this sub-cohort showed that all 635 (48.1%) patients with known baseline HbA1c had low values at entry; this number only constituted 38.6% of all patients whose HbA1c levels were low at baseline (N=1,644), thus although misclassification for the T2D cohort was possible, most patients with low HbA1c levels at baseline had at least one above-target value during the

follow-up so that their TITRE value could not amount to 100%. All the remaining 684 patients with missing baseline HbA1c also had low values at the index measure without prior records of diabetes medication from initial diagnosis. The selected characteristics of this sub-cohort are summarised in **Appendix F, Table F7.1 on page 358** and compared against patients with a TITRE value between 0% and 100% (N=16,712, median (IQR) TITRE 18.5% (7.1%-37.5%)). Comparisons on the follow-up period and time window for TITRE calculation suggested that immortal time bias was possible; had patients with 100% TITRE been observed for longer, there might have been above-target HbA1c values recorded over time if this sub-cohort were indeed not from a low-risk group nor misclassified as having T2D.

Further checks on sub-cohort with 0% TITRE showed that the median follow-up was 4.4 years (IQR 2.6-7.0) and the median time window for TITRE calculation was 3.0 years (IQR 1.5-5.2), whereas patients with missing TITRE had a median follow-up of 2.8 years (IQR 1.7-4.7). Although immortal time bias was also likely to be operating in the latter sub-cohort, these patients will be retained in the main analysis in the following chapter to represent the 'failure-of-care' group. Sensitivity analysis to confirm survivor bias will be performed by excluding patients with 100% TITRE.

Figure 7.11 Distribution of CVD-free patients by TITRE-HbA1c category (N=34,660)



Patient distribution according to the pre-planned TITRE categories is presented in **Figure 7.11A on page 228**. The lowest proportions were the 6-<9 months category followed by the 9-12 months category. Of those in the 9-12 months category, only 994 (43.0%) had lower than 100% TITRE values. The composition changed considerably when a less stringent cut-point was applied, the 6-<9 months and 0 months categories being the lowest proportions (**Figure 7.11B on page 228**) and 2,385 (44.1%) patients in the 9-12 months category had lower than 100% TITRE values.

7.5.5 Associations of patient characteristics and TITRE categories

Patient characteristics by TITRE categories are compared in **Table 7.3 on pages 230-231**. The duration of the follow-up, and TITRE calculation time window accordingly, were shortest in the 9-12 months category with a median (IQR) of 2.4 (1.5-4.2) years. Again, this might indicate a survivor bias provided that they entered the cohort at an older age. The second shortest value for follow-up years was in the missing category; over a quarter of patients in the category were first identified as having T2D through secondary care, while in all other categories the estimates were only approximately 3%.

Compared to higher TITRE categories, proportions of those of white ethnicity were lower in the missing (51.3%) and 0 months (54.4%) categories. In contrast, the proportion of current smokers was highest in the 0 months category (9.9%). Higher comorbidities and prescriptions of cardiovascular medication were observed in patients in higher TITRE categories; however, they were also older when diagnosed with T2D. Other biomarkers appeared to be broadly similar across TITRE categories.

HbA1c at baseline and during the first follow-up year were better recorded for higher TITRE categories (63.6% and 92.0%, respectively in the 9-12 months category). These might partially explain why HbA1c values at both time-points were lowest in the highest category (mean (SD) 54.1 (19.9) mmol/mol at baseline and 45.6 (13.4) mmol/mol at initial follow-up). Interestingly, the proportion of patients who never received diabetes medication was also highest in the 9-12 months category (52.3%) despite the shortest time to initial prescription in patients ever prescribed (median (IQR) 0.4 (0-5.3) months).

Regression analysis further showed that patients of black ethnicity, who currently smoked and received OHAs after diagnosis were less likely to achieve the 9-12 months TITRE category compared to the 3-<6 months (**Figure 7.12 on page 232**). However, it was timing for treatment rather than the type of diabetes medication which was shown to contribute more to achieving longer duration at glycaemic control. Results for other TITRE categories are presented in **Figure F7.2 on pages 360-362**.

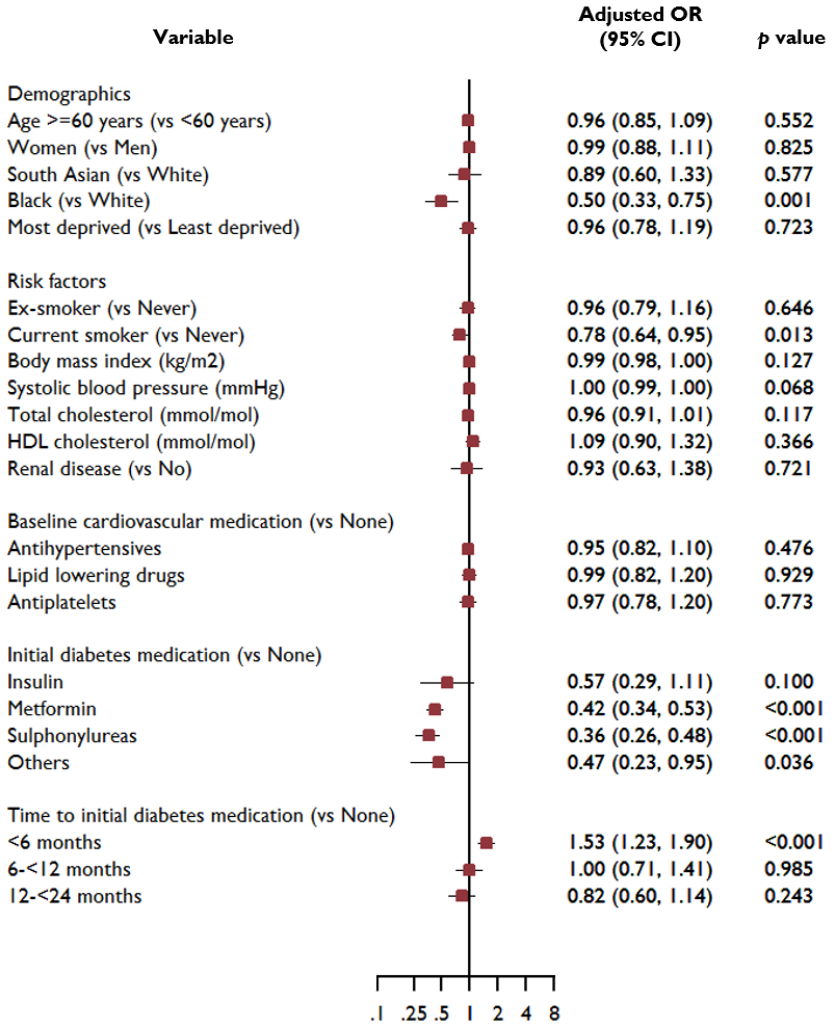
Table 7.3 Patient characteristics by TITRE categories (N=34,660)*

Characteristic	Missing N=4,439		0 months N=12,190		<3 months N=10,100		3-<6 months N=4,095		6-<9 months N=1,523		9-12 months N=2,313	
Duration of GP registration before entry (years)	7.4	(2.8-12.4)	10.6	(5.9-15.4)	11.6	(8.5-16.9)	11.4	(7.8-16.8)	11.4	(8.3-16.6)	11.1	(7.2-16.3)
Duration of follow-up (years)	2.8	(1.7-4.7)	4.4	(2.6-7.0)	5.8	(3.8-7.9)	4.3	(2.8-6.2)	3.6	(2.2-5.6)	2.4	(1.5-4.2)
TITRE calculation time window (years)	N/A		3.0	(1.5-5.2)	4.7	(2.9-6.6)	3.2	(1.9-5.1)	2.7	(1.6-4.6)	1.1	(0.7-2.8)
Demographic												
Age at entry†	61.0	(15.3)	57.4	(12.6)	59.4	(12.1)	61.8	(12.2)	62.4	(12.0)	63.4	(12.8)
Women	2,104	(47.4)	5,371	(44.1)	4,662	(46.2)	1,974	(48.2)	719	(47.2)	1,105	(47.8)
White ethnicity	2,275	(51.3)	6,627	(54.4)	5,961	(59.0)	2,420	(59.1)	915	(60.1)	1,370	(59.2)
Most deprived	1,006	(22.7)	2,452	(20.1)	1,865	(18.5)	834	(20.4)	306	(20.1)	428	(18.5)
Cardiovascular risk factors at baseline												
Ex-smoker	320	(7.2)	1,285	(10.5)	1,112	(11.0)	598	(14.6)	283	(18.6)	456	(19.7)
Current smoker	334	(7.5)	1,202	(9.9)	747	(7.4)	340	(8.3)	124	(8.1)	204	(8.8)
Body mass index†	31.6	(7.8)	32.5	(6.8)	32.6	(6.5)	32.3	(6.6)	32.4	(6.8)	31.7	(6.7)
Systolic blood pressure†	145.1	(20.0)	146.0	(19.9)	147.4	(19.5)	146.4	(18.7)	146.1	(18.3)	143.9	(17.7)
Total cholesterol†	5.6	(1.2)	5.8	(1.4)	5.8	(1.3)	5.6	(1.2)	5.6	(1.3)	5.5	(1.3)
HDL cholesterol†	1.3	(0.4)	1.2	(0.3)	1.2	(0.4)	1.2	(0.4)	1.2	(0.4)	1.3	(0.4)
Comorbidities												
Renal disease	63	(1.4)	115	(0.9)	87	(0.9)	65	(1.6)	42	(2.8)	60	(2.6)
Chronic obstructive pulmonary disease	250	(5.6)	730	(6.0)	643	(6.4)	281	(6.9)	122	(8.0)	183	(7.9)
Cardiovascular medications at baseline												
Antihypertensives	1,007	(22.7)	3,364	(27.6)	3,702	(36.7)	1,772	(43.3)	737	(48.4)	1,104	(47.7)
Lipid lowering drugs	219	(4.9)	916	(7.5)	859	(8.5)	508	(12.4)	233	(15.3)	403	(17.4)
Antiplatelets	169	(3.8)	414	(3.4)	451	(4.5)	268	(6.5)	122	(8.0)	192	(8.3)
HbA1c measurements												
Yearly frequency of tests†	0.2‡	(0.3)	1.5	(0.7)	1.6	(0.6)	1.6	(0.6)	1.7	(0.6)	1.3	(0.6)
Non-missing baseline HbA1c	350	(7.9)	2,651	(21.7)	1,722	(17.0)	988	(24.1)	752	(49.4)	1,470	(63.6)
Baseline HbA1c†	61.1	(23.0)	79.2	(23.8)	70.0	(24.1)	67.3	(23.9)	65.7	(23.5)	54.1	(19.9)
Initial follow-up HbA1c†	55.8‡	(20.7)	71.1	(21.1)	59.7	(21.1)	51.7	(18.1)	52.3	(17.9)	45.6	(13.4)
Time to initial follow-up HbA1c (months)	11.4‡	(3.0-28.5)	3.3	(1.1-12.1)	2.8	(0.8-7.6)	2.7	(0.9-5.6)	2.4	(0.8-4.4)	2.9	(1.2-5.2)
Non-missing follow-up HbA1c within first year	1,089‡	(24.5)	9,084	(74.5)	8,209	(81.3)	3,503	(85.5)	1,414	(92.8)	2,127	(92.0)
Snapshot control within first year	523‡	(11.8)	245	(2.0)	5,149	(51.0)	2,914	(71.2)	1,193	(78.3)	2,079	(89.9)

Initial diabetes medications during follow-up												
Never prescribed	2,208	(49.7)	732	(6.0)	1,292	(12.8)	1,342	(32.8)	531	(34.9)	1,210	(52.3)
Insulin	60	(1.4)	168	(1.4)	82	(0.8)	30	(0.7)	8	(0.5)	15	(0.7)
Metformin[§]	1,460	(32.9)	8,834	(72.5)	6,892	(68.2)	2,226	(54.4)	863	(56.7)	930	(40.2)
Sulphonylureas	673	(15.2)	2,269	(18.6)	1,728	(17.1)	455	(11.1)	111	(7.3)	145	(6.3)
Thiazolidinediones	26	(0.6)	143	(1.2)	81	(0.8)	25	(0.6)	9	(0.6)	6	(0.3)
Acarbose	5	(0.1)	15	(0.1)	9	(0.1)	7	(0.2)	1	(0.1)	5	(0.2)
DPP4 inhibitors	1	(0.0)	4	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
GLP1 agonists	1	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)	0	(0.0)	0	(0.0)
Meglitinides	5	(0.1)	25	(0.2)	15	(0.2)	9	(0.2)	0	(0.0)	2	(0.1)
Time to initial prescription (months)[¶]	10.6	(0.4-40.9)	4.5	(0.4-21.4)	5.9	(0.5-28.9)	3.2	(0.1-26.3)	1.0	(0-13.1)	0.4	(0-5.3)
Data source for initial T2D diagnosis												
CPRD	3,253	(73.3)	11,769	(96.6)	9,786	(96.9)	3,974	(97.0)	1,486	(97.6)	2,253	(97.4)
HES	1,186	(26.7)	421	(3.4)	314	(3.1)	121	(3.0)	37	(2.4)	60	(2.6)

*Estimates are number (%) for categorical variables and median (IQR) for continuous variables unless marked with † which are mean (SD).
[‡]Not missing due to incorporation of patients with all lengthy intervals throughout follow-up period into this category.
[§]Includes combination with thiazolidinedione or DPP4 inhibitor.
[¶]Among patients ever prescribed.

Figure 7.12 Associations of patient characteristics with the 9-12 months TITRE category*



*3-<6 months TITRE category as the reference group.

7.6 Chapter summary

A CALIBER cohort of 34,660 patients newly diagnosed with T2D with a median follow-up of 4.6 years was eligible for preliminary analysis exploring repeat HbA1c records and duration of glycaemic control. Median HbA1c tests received over the follow-up period was 7 with median time between tests 5.5 months when measures beyond one year apart were omitted. Temporal trends for HbA1c measures suggest that T2D care fell short of the current recommendation for biannual (i.e. 6-monthly) testing. Patients on blood pressure and lipid lowering medications, however, were more likely to be measured more frequently.

A time-based metric for glycaemic control was developed as average annual TIme at TaRgEt (TITRE) using a total of 214,527 repeat HbA1c data from 30,221 patients. Median time window for TITRE calculation was 3.4 years and median TITRE value was 4.3%. TITRE distribution was non-linear, predominated by 0% and 100% values. There might be potential survivor bias in study

cohort, yet paucity of baseline HbA1c records and sparse interval between measures presented further challenges to the metric development.

Patients in higher TITRE categories were older, had more comorbidities and received more cardiovascular medication, but results from multivariate analysis (using the middle TITRE category as a reference) did not significantly support their associations. Rather, those who were older, with non-white ethnicities, deprivation, total cholesterol and current smoking showed significant associations with lower TITRE. Type of initial diabetes medication was associated with lower TITRE but timing to the prescription appeared to be more important for achieving higher TITRE. These findings suggested that the both baseline and time-varying factors were important confounders and it is important to adjust for them in the multivariable models investigating TITRE and T2D complications.

The established cohort will be used to investigate the associations between TITRE and cardiovascular outcomes in **Chapter 8**. The TITRE metric developed in this chapter will be re-tested in another cohort to investigate its associations with microvascular complications (**Chapter 10**). A sensitivity analysis excluding patients with 100% TITRE will be performed in the subsequent chapters as it was shown to potentially lead to survivor bias.

Chapter 8

Study 4 – Repeated measures of HbA1c, duration at glycaemic control and cardiovascular outcomes

> Quality is not an act, it is a habit.
> — Aristotle

8.1 Chapter outline

This chapter presents Study 4 which examines the associations between duration at glycaemic control and cardiovascular outcomes in CALIBER's cohort, building primarily on the TITRE metric based on repeat HbA1c measures as described in **Chapter 7**. Comparisons for cardiovascular outcomes using other glycaemic control metrics are also presented.

8.2 Abstract

Background. Clinical studies on T2D have traditionally used short-term glycaemic control metrics measured on limited occasions to assess treatment effectiveness or patient outcomes. Duration at glycaemic control calculated from repeat HbA1c measures is a novel, longitudinal metric, but whether it can be further used to estimate risk of cardiovascular outcomes needs investigating.

Objectives. To investigate the association between duration at glycaemic control and cardiovascular outcomes.

Methods. A cohort of newly diagnosed T2D, aged 30 years or older, with at least one year follow-up and free from cardiovascular events was established using CALIBER. Patients were followed up until censoring administrative date or occurrence of a cardiovascular endpoint, the primary endpoints being major adverse cardiovascular events (MACEs), heart failure, and any CVD and cardiovascular death, while the secondary endpoints were coronary artery disease (CAD), PAD, cardiovascular death and all-cause death. Longitudinal glycaemic control was estimated using a TITRE metric with HbA1c 48 mmol/mol as the cut-point. Logistic regressions with a random effect were used to estimate risk of cardiovascular outcomes, adjusted for baseline and follow-up covariates and weighted by duration of follow-up.

Results. The study cohort comprised 34,660 patients and the median (IQR) follow-up was 4.4 (2.5-6.8) years. There were 1,769 presentations with MACE, 745 with heart failure and 5,338 with any CVDs and cardiovascular death. TITRE-HbA1c value (in %) was significantly associated with lower risk of MACE, all CVDs and death, CAD and cardiovascular death. Compared with patients in the 3-<6 months TITRE category, those in the 0 months category had higher risk of MACE (OR 1.27, 95% CI 1.04-1.53) and cardiovascular death (OR 1.43, 95% CI 1.07-1.92). Patients with missing TITRE had double the risk of all study endpoints but PAD. The higher TITRE category was not associated with a lower risk of cardiovascular outcomes unless a higher HbA1c cut-point was set at 58 mmol/mol.

Conclusions. Categorical TITRE-HbA1c were marginally associated with risk of cardiovascular outcomes in newly diagnosed T2D. Compared with the middle TITRE category, risk excess was only observed in the missing category for all endpoints and in the 0 months category for MACE and cardiovascular death.

8.3 Introduction

Controlling glycaemia plays a crucial role in the prevention of cardiovascular events in T2D, yet many studies suggest that well-controlled HbA1c values are only found in 50-65% across different healthcare settings.[1,68] As diabetes progresses, complications will gradually manifest themselves particularly when HbA1c levels are poorly controlled.[4,5] It can be argued that the complications would develop sooner in patients with less time spent under glycaemic control. The 2015 ADA/EASD consensus recommends that an HbA1c target of <7% (53 mmol/mol) be achieved within 3

months of initial treatment,[31] while the most recent NICE guideline advocates a tighter target of <6.5% (48 mmol/mol) which should be achieved within a 3-6 months period.[33]

Little is known about the extent of sustaining glycaemic control in the longer run and what the implications are for the onset of T2D complications. Both observational studies and trials have typically used patients' baseline data to assess cardiovascular risks. Recent studies using CPRD data reported associations between average HbA1c levels over follow-up period and myocardial infarction and heart failure.[48,138] There appears to have been no attempt thus far to specifically quantify time spent at glycaemic control from repeat HbA1c measures over the course of T2D and, more importantly, to further explore its relationship with diabetes complications. These are important issues to address since glycaemic control tends to fluctuate with time and interval between HbA1c measures can vary between and within individuals as a result of practice heterogeneity or patient compliance with scheduled tests. While the TITRE-HbA1c metric has been developed for estimating duration at glycaemic control (**Chapter 7**), this chapter examined its performance in predicting the risk of cardiovascular outcomes.

8.4 Methods

8.4.1 Study population and inclusion criteria

The study cohort was drawn from CALIBER and previously described in **Chapter 7**. Briefly, newly diagnosed T2D patients aged 30 years or older were included. Patients with less than a year follow-up who had CVD prior to the date of initial T2D diagnosis were excluded. Patients without HbA1c records during follow-up were retained to represent a group with poor quality of care. The flow chart of eligible patients is presented in **Figure 8.1 on page 240**.

8.4.2 Follow-up and endpoints

Eligible patients were followed up while registered at a practice until their first occurrence of a CVD, death or transfer out of the practice. CVDs were identified from any of the constituent data sources (**Section 3.3 on pages 98-105**) and referred to angina (unstable and stable), fatal and non-fatal myocardial infarction, sudden cardiac death or arrhythmia, atrial fibrillation, heart failure, TIA, stroke (ischaemic and haemorrhagic), PAD and AAA.

The primary endpoints were major adverse cardiovascular events (shortened as MACE, a composite of myocardial infarction, stroke and cardiovascular death), heart failure and a composite of any CVDs and cardiovascular death. The secondary endpoints were CAD (a composite of angina, myocardial infarction and coronary death), PAD, cardiovascular death and all-cause death.

8.4.3 Exposures

8.4.3.1 HbA1c levels

Accumulating evidence demonstrated that higher HbA1c values were associated with increased risk of CVDs,[3,4,48,138] therefore a similar trend was expected from my study cohort. I selected a range

of existing glycaemic control metrics which utilise either single or repeat HbA1c records. Snapshot glycaemic control metrics included baseline HbA1c (defined as the most recent HbA1c value within a year prior to T2D diagnosis), early snapshot glycaemic control (a categorical metric similar to Study 3, defined as whether or not glycaemic target was met within the first year from diagnosis) and the latest HbA1c (the last HbA1c record before follow-up ended). 'Semi-longitudinal' glycaemic control metrics included extended baseline (average of HbA1c values recorded 3 years prior to and after T2D diagnosis),[4] mean HbA1c (defined as the average of all HbA1c values measured during follow-up) and updated mean HbA1c (mean HbA1c was re-estimated each time a new record became available).[48,138] For snapshot glycaemic control, patients were classified as at target (as reference group), above target and missing. For other metrics, patients were classified into five groups: <48 mmol/mol, 48-<58 mmol/mol (reference group), 58-<68 mmol/mol, ≥68 mmol/mol and missing.

8.4.3.2 Glycaemic variability

In addition to the above glycaemic control metrics, emerging metrics which account for intrapersonal HbA1c variation from one visit to the next were also analysed in this study. A substantial body of evidence showed that greater glycaemic variability was associated with cardiovascular outcomes.[70,189,192] For this analysis, I only included patients with at least two HbA1c measurements after T2D diagnosis. Glycaemic variability metrics considered in this study were adjusted SD, CV, VIM, ARV, SV and mean absolute residual of serially measured HbA1c. Definition of these metrics was previously discussed in **Section 1.1.3.2 on pages 30-35** and their calculations are summarised in **Appendix B on page 325**. Distribution of HbA1c variation values measured using each metric were inspected and transformation was performed where necessary. Patients were classified according to quartiles of the metrics, 1st quartile (i.e. least variability) being the reference group.

8.4.3.3 Duration at glycaemic target

The main exposure in Study 4 was duration of glycaemic control, estimated as TITRE from repeated HbA1c records in CPRD (**Chapter 7**). Unlike extended baseline, mean or updated mean HbA1c, which essentially only concatenate repeated measurements, TITRE-HbA1c also incorporated time element between measurements and can, therefore, be considered a 'full' longitudinal metric for glycaemic control.

Methods to estimate TITRE have been described in **Section 7.4.4 on pages 213-219**. In short, date of first and last HbA1c records during the follow-up period became the starting and terminal points, respectively for TITRE calculation. Day-interval between two consecutive HbA1c measures was then individually calculated. Only intervals which contained at least one measure at target were further considered. Any at-target intervals spanning beyond one year were calculated as zero and intervals crossing the HbA1c anniversaries were calculated separately on a yearly basis. Duration at target was then averaged annually and expressed as a percentage, before being summed up and re-averaged over the TITRE calculation time window. The TITRE estimate was finally converted into its equivalent month and classified into six categories: missing, 0 months,

<3 months, 3-<6 months, 6-<9 months and 9-12 months. The missing TITRE category was defined as having no HbA1c records during the follow-up period, having a single follow-up HbA1c record only without a known baseline value or having intervals which were all above one year throughout the follow-up period. A TITRE of 3-<6 months was chosen as the reference category to illustrate the results from lower and higher TITRE categories. Examples of TITRE estimations were visualised in **Figures 7.4A to 7.4E on pages 217-218**.

In order to verify the reliability of the TITRE metric for risk assessment of cardiovascular outcomes, indirect comparison was made by visual inspection against predictive performance of other glycaemic control or variability metrics (**Section 8.4.3.2 on page 237**), based on the assumption that estimates of lower TITRE categories should be commensurable with those of higher HbA1c levels or greater variability.

8.4.4 Covariates

Baseline covariates included demographic variables (age at T2D diagnosis, gender, ethnicity and deprivation), cardiovascular risk factors (body mass index, smoking status, blood pressure, total and HDL cholesterols), renal disease and prescriptions of cardiovascular medication. Covariates during the follow-up period were class of initial diabetes medication and time to first prescription of diabetes medication. Other variables considered in the multivariate analysis were total number of HbA1c measures, snapshot glycaemic control, adjusted SD of HbA1c, mean HbA1c, and annual frequency of hypoglycaemic events (time-varying). All covariates were extracted from CPRD.

8.4.5 Statistical analysis

Patient characteristics were tabulated and statistically compared, as appropriate, by one-way analysis of variance or Kruskal-Wallis non-parametric tests for continuous variables, and chi-square tests for categorical variables. Cumulative incidence curves of cardiovascular endpoint by TITRE category were generated under a competing risks framework.

I used logistic regressions with random effect to evaluate the associations between TITRE (either as a continuous and categorical variable) and risk of cardiovascular endpoints. The cluster variable was GP practice; despite the longitudinal nature of HbA1c data (i.e. data are dependent observation within a patient), clustering by patient was not performed in the multilevel analysis for two reasons: a) all repeat HbA1c data of a patient have been converted into a single value in TITRE, and b) two-level analysis (i.e. within patient and practice) is a computationally intensive and time consuming process. Estimates were adjusted for covariates and weighted by duration of follow-up. Missing baseline covariates were 5-multiply imputed using chained equations (**Section 3.13.1 on pages 124-125**). Associations of HbA1c levels using other glycaemic control and variability metrics and study endpoints were similarly estimated. All analyses were performed using Stata 13.0.

8.4.6 Sensitivity analysis

Sensitivity analyses were performed using a less stringent HbA1c target (≤58 mmol/mol or ≤7.5%) to define TITRE, by excluding patients with a 100% TITRE value in order to confirm whether immortal time bias operated and by excluding patients whose T2D diagnosis was first identified from HES. Sensitivity analyses were also carried out by additional adjustment for snapshot glycaemic control, mean HbA1c and adjusted SD of HbA1c, and by changing the reference group to 0 months TITRE category.

8.5 Results

The study cohort comprised 34,660 patients with a median follow-up of 4.4 years (IQR 2.5-6.8). Of these patients, 4,439 (12.8%) were classified into the missing TITRE category (**Figure 8.1 on page 240**). The median TITRE value in patients with non-missing TITRE was 4.3% (IQR 0%-26.7%). Patient characteristics according to TITRE categories were previously presented in Chapter 7 (**Table 7.3 on pages 230-231**).

8.5.1 Incidence of cardiovascular outcomes

There were 1,769 (5.1%) patients who developed MACE, 745 (2.1%) who developed heart failure and 5,338 (15.4%) who developed any CVD and death. Cumulative incidence curves for study endpoints by TITRE category were plotted in **Figure 8.2 on page 241**. The incidence was constantly higher in the missing TITRE category but the estimates for non-missing categories showed a mixed order.

The median time to cardiovascular event by TITRE category is compared in **Appendix F, Table F8.1 on page 362**. Overall, the longest time to event was consistently observed in the <3 months category. The missing and highest TITRE categories appeared to broadly share shortest time to event.

The proportion of TITRE categories for all study endpoints was fairly comparable (**Figure F8.1 on page 362**). The proportions of missing TITRE were higher for composite than specific endpoints. The estimate was higher for MACE than composite for all cardiovascular endpoints.

Figure 8.1 Patient flow chart for Study 4

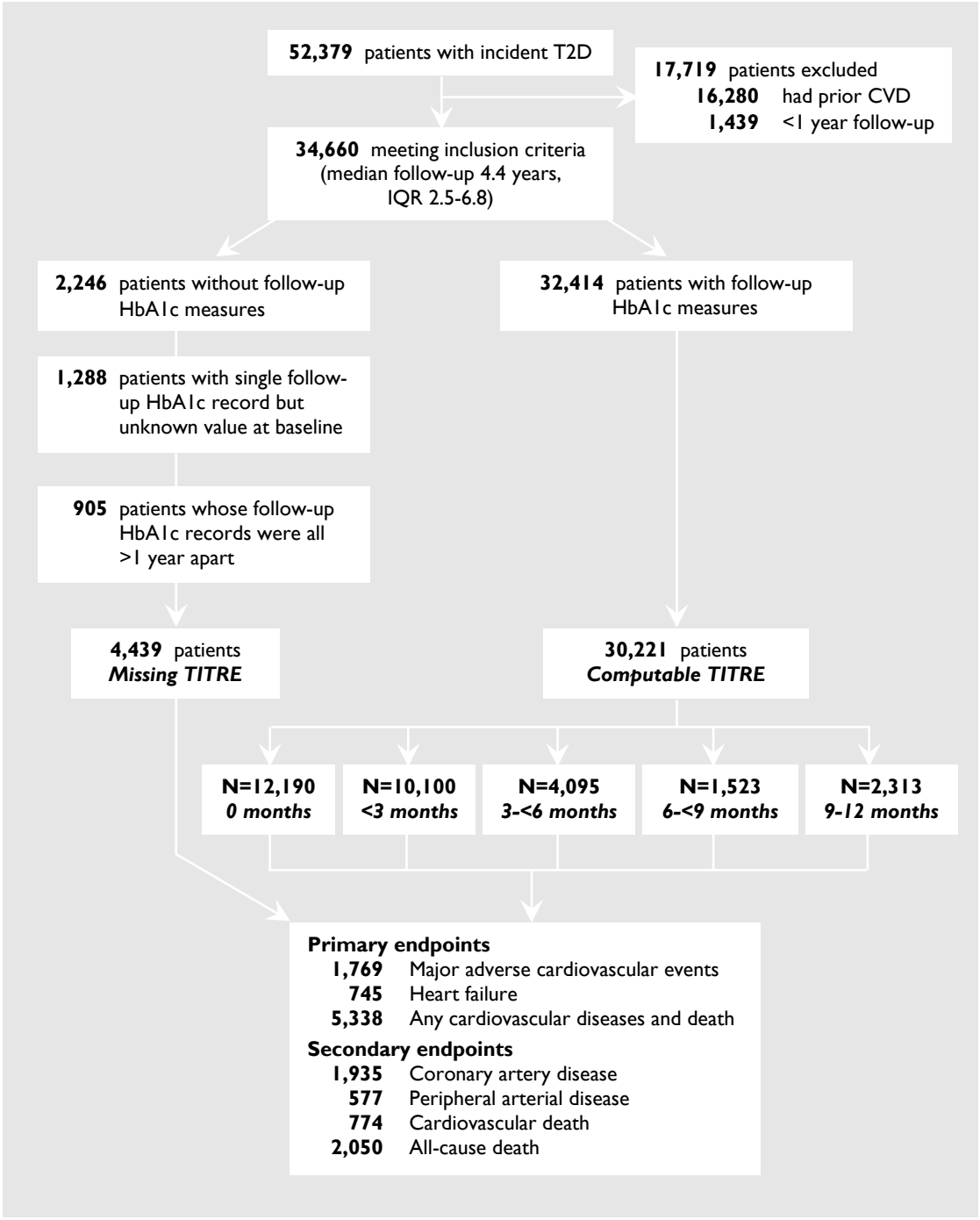
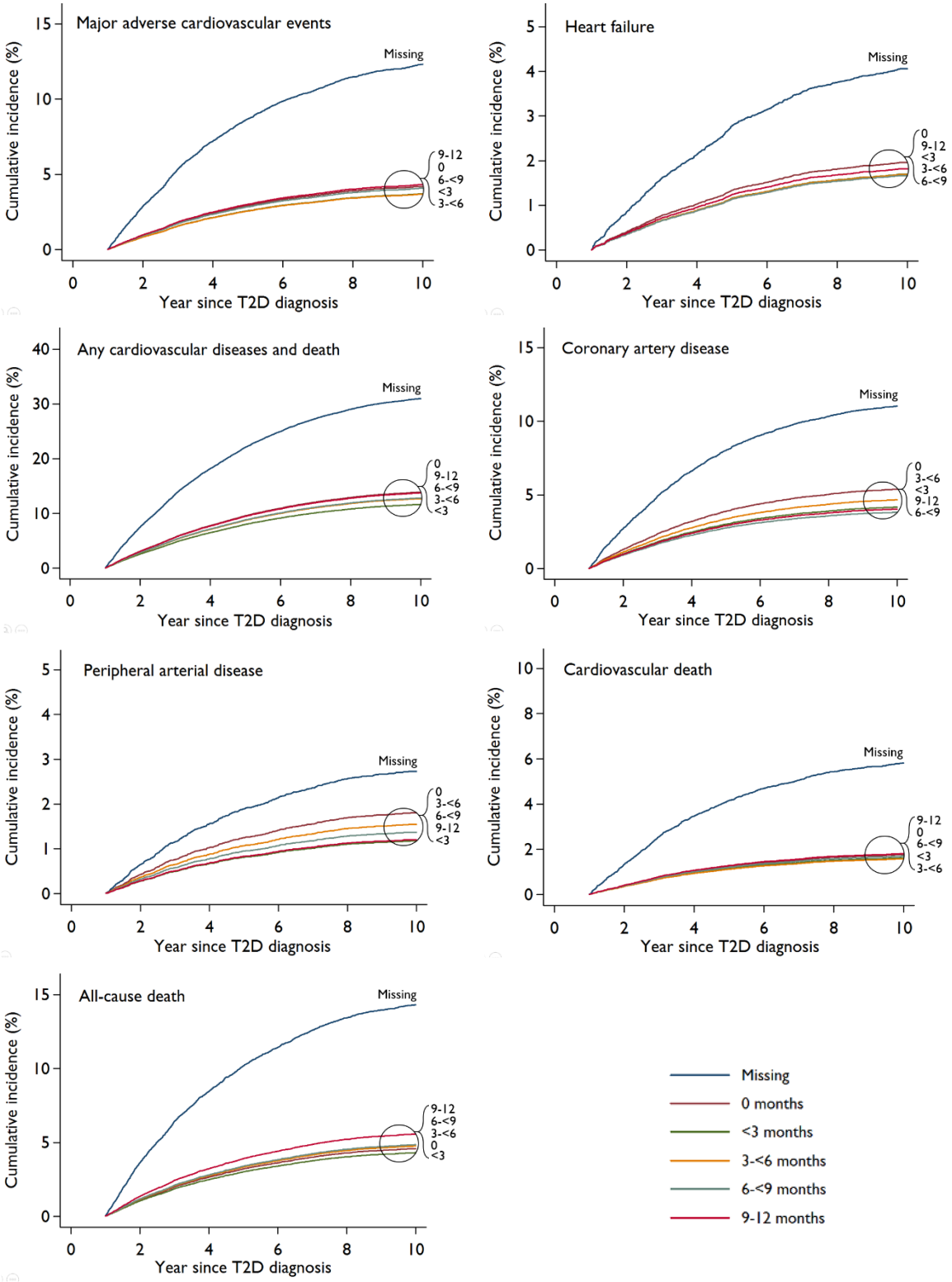


Figure 8.2 Cumulative incidence curves for cardiovascular outcomes by TITRE category



8.5.2 HbA1c levels and cardiovascular outcomes

HbA1c values measured using different glycaemic control metrics were normally distributed with all means above 55 mmol/mol (**Figure F8.2 on page 363**). Stepwise HbA1c levels across glycaemic control metrics generally showed J-shaped association with risk of cardiovascular outcomes; the risk was consistently greatest and at least doubled with missing HbA1c records (**Figure 8.3 on page 243 and Figure F8.3 on pages 364-366**). A more consistent pattern to assess the cardiovascular risk was observed when using an extended HbA1c baseline, mean and updated mean HbA1c. Snapshot glycaemic control within the first year showed a similar predictive pattern. Baseline and latest HbA1c categories were the least stable metrics to assess the cardiovascular risk as reflected by absurd patterns, although latest HbA1c showed better performance than baseline value for assessing death-related risks.

8.5.3 Glycaemic variability and cardiovascular outcomes

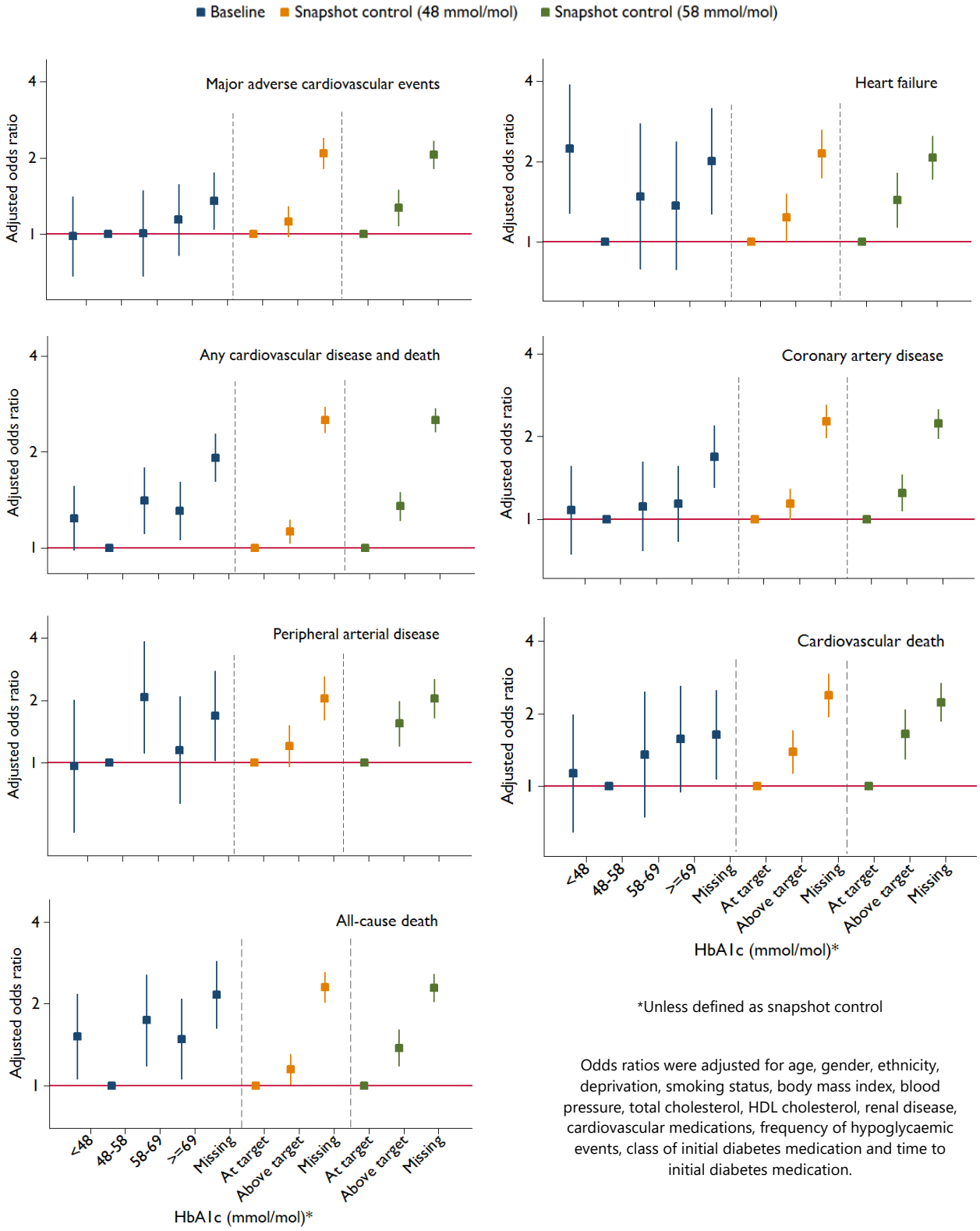
Glycaemic variability was measured in 31,126 patients who had at least two HbA1c records during follow-up. HbA1c values measured using different variability metrics were all highly skewed with medians ranging from 6.2 to 13.4 mmol/mol (**Figure F8.4 on page 366**). The values were approximately normally distributed by square root transformation with medians ranging from 2.5 to 3.7 mmol/mol. Analyses of the association with cardiovascular outcomes showed no differences between quartiles of original and transformed HbA1c variation values (data not shown). **Figure 8.4 on pages 244-245** summarises the association between quartiles of the original glycaemic variability measured using different metrics with cardiovascular outcomes. For most outcome risks, observed patterns of the association were paradoxical with highest quartile often showing the greatest risk reduction, except for cardiovascular death and all-cause death, and to a smaller extent for MACE, which exhibited a graded, linear relationship across the metrics.

8.5.4 Duration at glycaemic target and cardiovascular outcomes

The TITRE values measured using both cut-points (48 and 58 mmol/mol) were associated with MACE, any CVDs and death, CAD and cardiovascular death; every extra unit (1%) of TITRE value was associated with tiny but significant risk reductions; the risk estimates for every 10% or 25% increase of TITRE value gave more intuitive interpretation (**Figure 8.5 on page 246**).

The results from the main analysis were plotted in **Figure 8.6 on page 247**. Compared with the 3-<6 months TITRE category, the missing category was consistently associated with significantly higher risks for all study endpoints – ranging from 1.77 (heart failure) to 2.49 (MACE), with an exception for PAD (OR 1.13, 95% CI 0.81-1.56). The risk excesses were retained in the 0 months category for MACE (OR 1.27, 95% CI 1.04-1.53) and cardiovascular death (OR 1.43, 95% CI 1.07-1.92), and no risk reductions for all endpoints were documented in higher TITRE categories.

Figure 8.3 Association of three different measures of glycaemic control with cardiovascular outcomes in CALIBER's T2D cohort without prior CVD

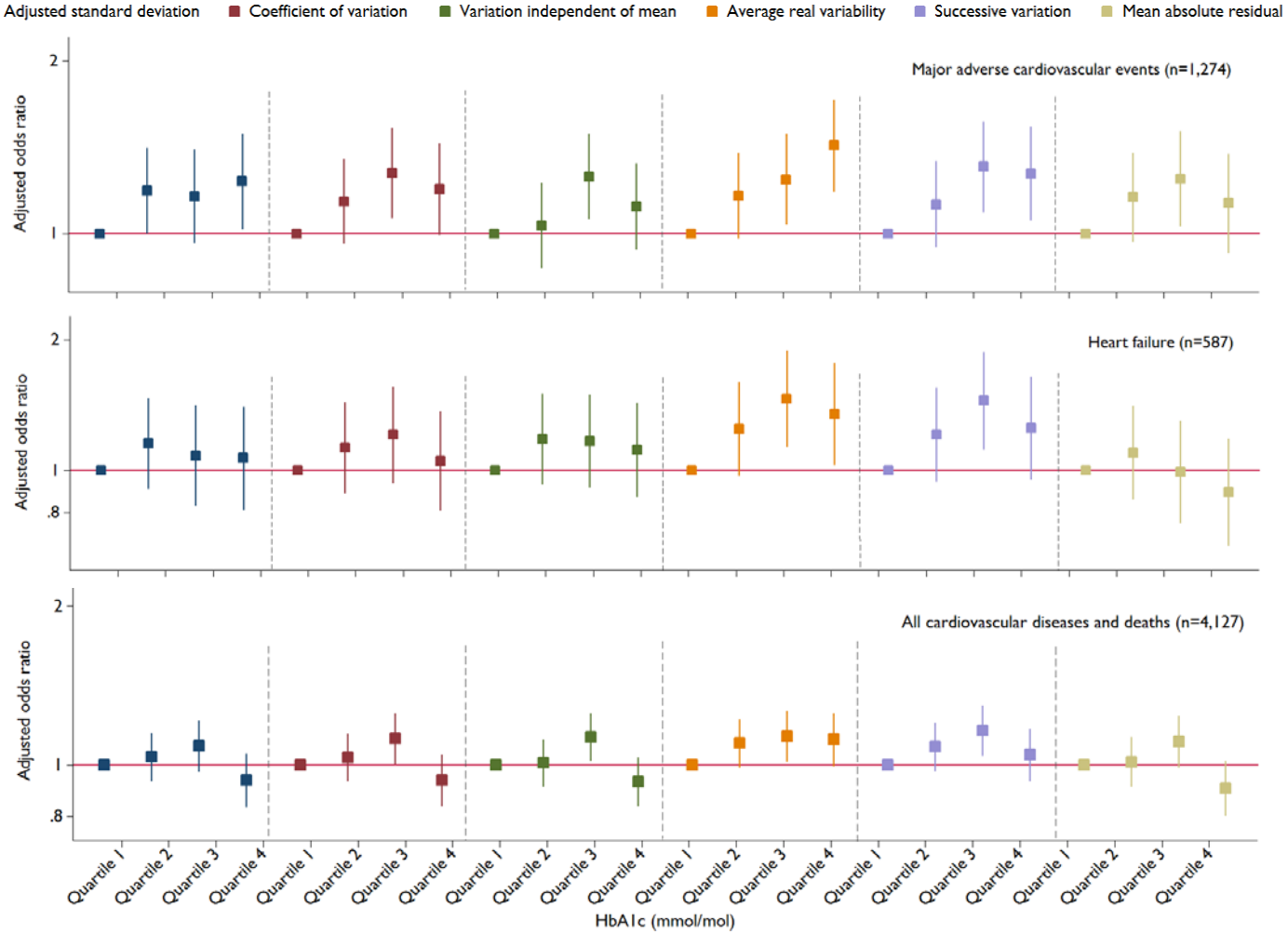


*Unless defined as snapshot control

Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure 8.4 Association of six different measures of glycaemic variability with cardiovascular outcomes in CALIBER's T2D cohort without prior CVD

Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.



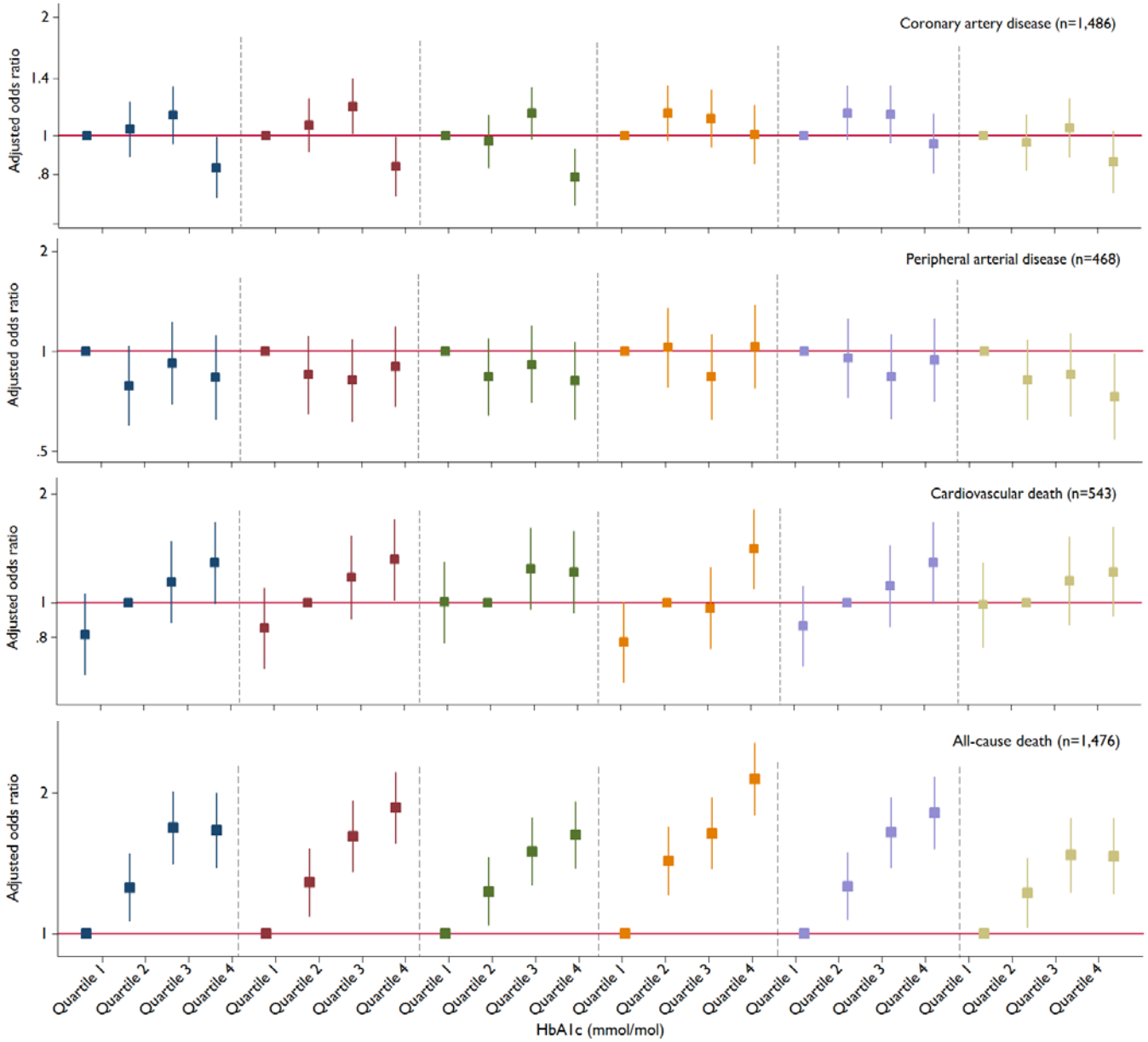
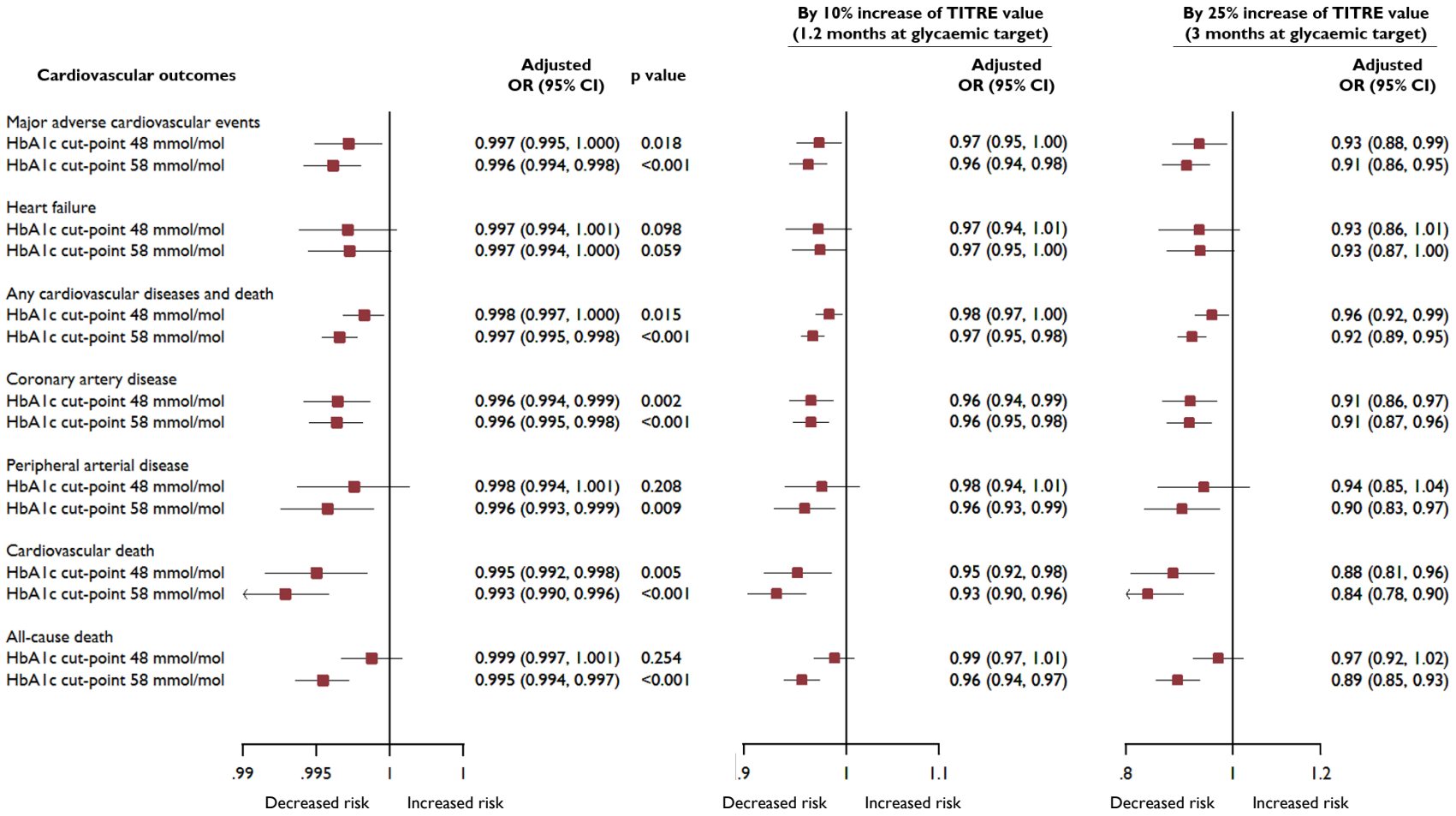
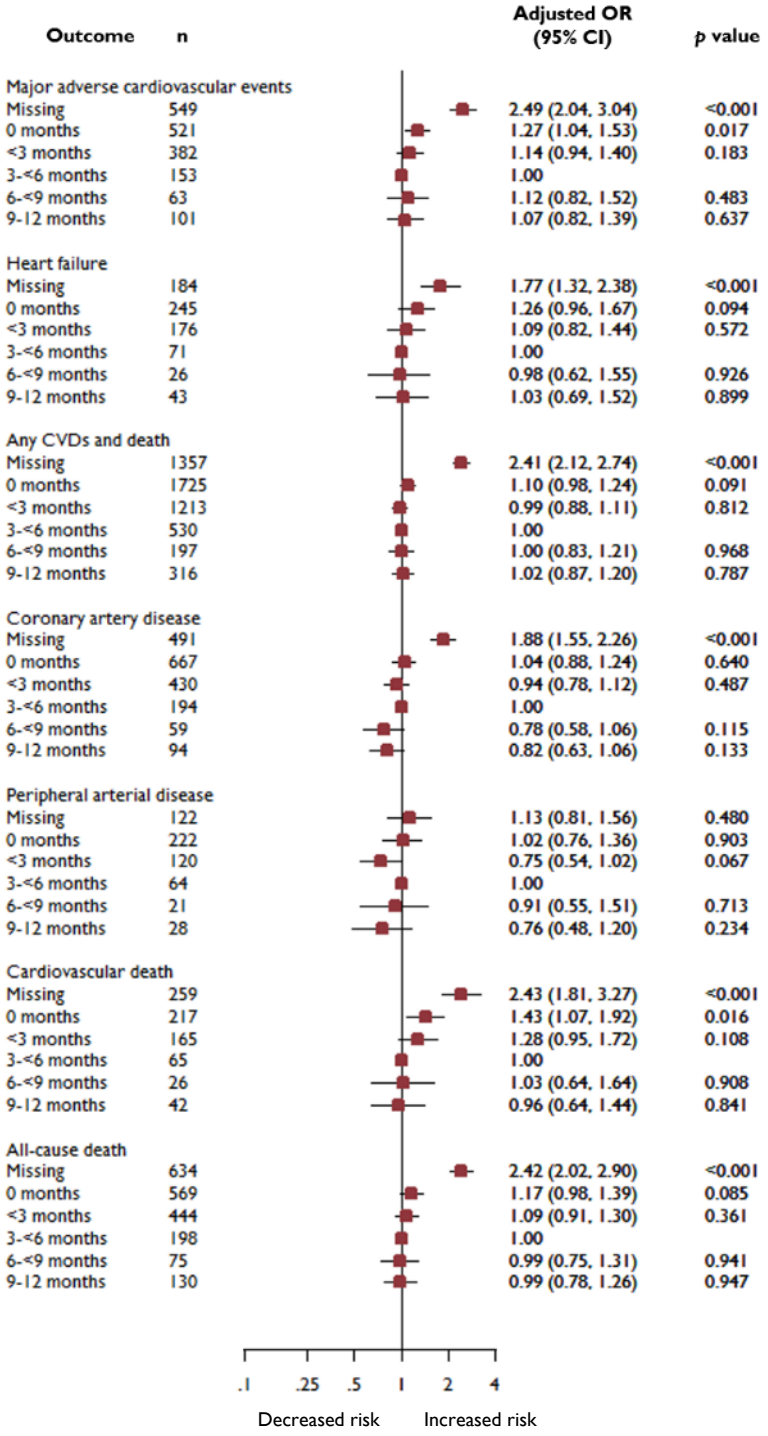

Coronary artery disease (n=1,486)
Peripheral arterial disease (n=468)
Cardiovascular death (n=543)
All-cause death (n=1,476)
Adjusted odds ratio
HbA1c (mmol/mol)
Quartile 1
Quartile 2
Quartile 3
Quartile 4

Figure 8.5 Association between non-missing TITRE values (%) and cardiovascular outcomes using two different HbA1c cut-points (N=32,414)



Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure 8.6 Adjusted odds ratios for association between TITRE category and cardiovascular outcomes (N=34,660)



Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

8.5.5 Sensitivity analysis

It was previously alluded to in **Chapter 7** that immortal time bias was possible due to a number of patients having 100% TITRE values. Nevertheless, sensitivity analysis excluding this sub-cohort showed conflicting results (**Figure F8.5 on page 368**). Greater risks for MACE and cardiovascular death were more clearly seen in higher TITRE categories although they failed to reach statistical significance, altering the pattern from nearly linear to J-shaped association. Conversely, an attenuated risk – also non-significant – was seen for heart failure.

Sensitivity analysis in patients whose T2D was first diagnosed in primary care only demonstrated few changes. At least 25% of patients in the missing TITRE category were initially identified as having T2D from secondary care, but risks for primary endpoints became only slightly higher in this category (**Figure F8.6 on page 369**).

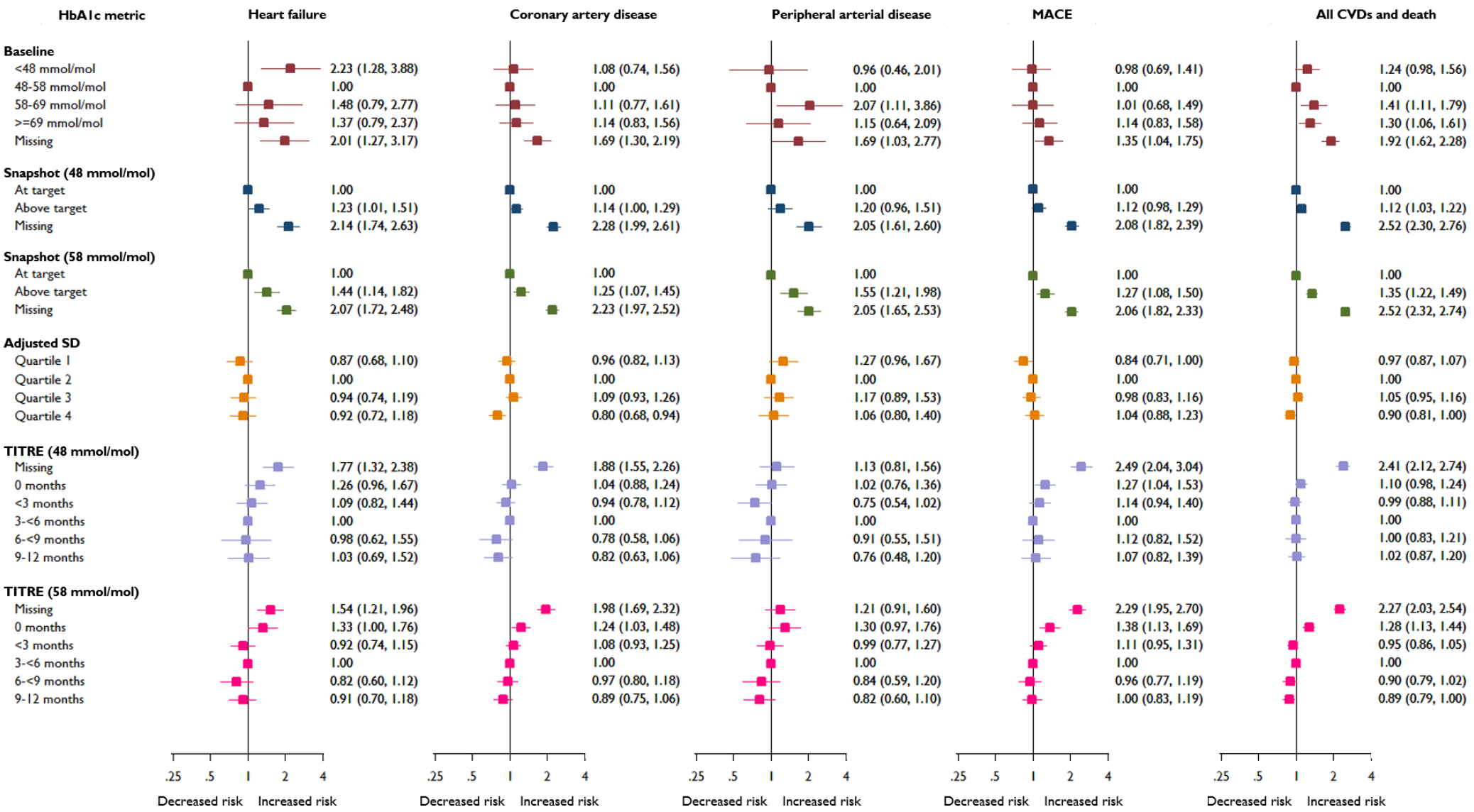
When TITRE was defined using a higher HbA1c cut-point (58 mmol/mol), the risk for PAD remained unchanged but risk excess in the 0 months category was seen for all other endpoints and risk excess in the 3 months category was observed for cardiovascular death (**Figure F8.7 on page 370**). Risk reduction was also observed for any CVD and death in the 9-12 months category although marginally significant (OR 0.89, 95% CI 0.79-0.99, p value 0.041).

Addition of snapshot glycaemic control category, mean HbA1c or adjusted SD of HbA1c into the multivariate model only made few changes to the risk estimates of TITRE category for most study endpoints (**Figures F8.8 to F8.10 on pages 371-373**). However, changing the reference group to the 0 months TITRE category provided more illuminating results with significant associations of longer duration at glycaemic target, to a variable degree, being observed for MACE, CAD, PAD and cardiovascular death (**Figure F8.11 on page 374**).

8.5.6 Comparison across main glycaemic control/variability metrics

Figure 8.7 on page 249 outlines the associations between select metrics of glycaemic control or variability and select cardiovascular endpoints. Baseline HbA1c showed linear associations with MACE and CAD only, while snapshot glycaemic control showed linear associations with all study endpoints. Adjusted SD of HbA1c did not illuminate clear association. TITRE-HbA1c appeared to show high concordance with snapshot control in the sense of linear association observed across all endpoints although the overall estimates in non-missing TITRE categories were very marginal.

Figure 8.7 Summary plot for the associations of different measures of glycaemic control/variability with cardiovascular outcomes (N=34,660)



8.6 Discussion

8.6.1 Key findings

With a median follow-up of over 4 years, only about a quarter of my study cohort achieved adequate duration at glycaemic target (i.e. above 3 months). The estimate remained below 50% when the less stringent cut-point (58 mmol/mol) was applied (**Figure 7.11B on page 228**). For indirect comparison, the proportion of patients meeting the snapshot HbA1c target (57.4 mmol/mol) during the second year (Study 2) and first year (Study 3) after diagnosis was 59.0% and 57.7% respectively. Despite the different inclusion criteria (hence cohort size) and definition of glycaemic control among the three studies, these findings suggest that maintaining glycaemic control for a longer period is even more challenging than just meeting glycaemic target on a single occasion. Study 4 reinforces the previous findings in this thesis that missed opportunities exist in T2D management.

Furthermore, this study found an association with lower risk of cardiovascular outcomes for every unit increase of duration at glycaemic target (i.e. TITRE) measured using either cut-point. Although no association with cardiovascular outcomes was documented with higher TITRE categories (6 months or over) relative to 3-<6 months TITRE, this study found that patients whose TITRE was incomputable had approximately double the risk for most cardiovascular outcomes. Similar risk excess was observed in the 0 months TITRE category for MACE and cardiovascular death.

Despite the marginal associations, application of the TITRE metric to measure long-term glycaemic control has shown a similar pattern of association with MACE and cardiovascular death to using some conventional metrics measuring short-term (i.e. snapshot control) or semi-longitudinal (i.e. mean or updated mean HbA1c) glycaemic control. The TITRE-HbA1c metric also showed good conformance to glycaemic variability (particularly ARV) in this regard; although not comparable head-to-head, TITRE-HbA1c has an advantage over glycaemic variability (which also showed marginal associations) in containing a time element. The conformational pattern with glycaemic control and variability metrics altogether should render fair validation to the TITRE metric.

8.6.2 Comparison with existing research

Strong association between HbA1c levels and cardiovascular outcomes has been previously reported,[4,48,138,186] and my replication using a similar approach showed consistent findings for composite outcomes. Stepwise associations were not observed for heart failure in my study, probably due to the smaller sample size when compared to previous research.

The evidence of the association of long-term glycaemic control which is measured in a way where time element is incorporated is lacking. To my knowledge, this study was the first to harness repeat HbA1c records to quantify time spent at glycaemic target and to investigate its relationship with cardiovascular outcomes. Other recent studies addressing longitudinal glycaemic control have focused on assessing the effect of intraindividual glycaemic variation on cardiovascular outcomes through measurement of SD, CV, SV, VIM or mean absolute residual [70,191,193]

from follow-up HbA1c. I also analysed my data using these emerging metrics but the results did not show a conforming pattern of association with either glycaemic control or TITRE metric for most cardiovascular outcomes, suggesting that TITRE-HbA1c might be a more promising metric for measuring glycaemic control longitudinally.

8.6.3 Strengths

The general strengths of the CALIBER data have been rehearsed elsewhere in this thesis which include the large cohort size to allow identification of specific CVDs, and the linkage with other health databases for diagnosis ascertainment. With specific reference to Study 4, the key strength is the ability to measure HbA1c continuously provided the prospective nature of the data, which enables development of a metric to assess glycaemic control longitudinally and allows examination of its association with cardiovascular outcomes.

8.6.4 Limitations

The construction of TITRE-HbA1c metric drawn from a population-based cohort has been previously shown to pose several challenges and, consequently, drawbacks. Firstly, the decision to confine the study population to newly diagnosed T2D only provided estimates with length time bias being minimised at the expense of a high proportion of missing HbA1c records at baseline. If a prevalent T2D cohort were chosen, fewer patients with missing baseline HbA1c might have been documented but TITRE estimates for study outcomes may represent an unbalanced effect of glycaemic control between new and old cases despite adjustment for duration of T2D; potential longitudinal glycaemic control (i.e. TITRE estimate) before study entry will be ignored ('left-truncated') among old T2D cases. Another drawback of a high proportion of missing baseline HbA1c is the presence of a time gap between initial T2D diagnosis and index measure for TITRE calculation – the index measure should ideally be the same as the index date. However, the gap would be expected in most real clinical settings where other diagnostic tests could have been preferred over HbA1c. In fact, when I performed pre-analysis using the index diagnosis to commence the TITRE calculation, no clear direction of association was found between TITRE and cardiovascular outcomes (data not shown).

Secondly, being a slightly invasive and cost-incurring test, HbA1c tends to be less measured, if not averted, compared to blood pressure. It is documented in the previous chapter that over 10% of all intervals between two successive measures exceeded one year (**Figure 7.5 on page 221**). Presence of a lengthy interval somewhere within the TITRE calculation time window has made the calculation somewhat intricate; such an interval was ignored but the respective year was still counted as a denominator, resulting in lower TITRE values and consequently a lower proportion of patients in higher TITRE categories (over 6 months).

Thirdly, the denominator for the last year of follow-up HbA1c was not calculated as a whole year but precisely calculated from the last HbA1c anniversary to the date of last HbA1c record, rendering low sensitivity. Thus, a partial TITRE value of 100% during the last follow-up

HbA1c year cannot be distinguished in terms of whether it was achieved within a shorter or longer period.

Fourthly, given a small proportion of patients having an equivalent TITRE of at least 3 months, the use of HbA1c cut-point at 48 mmol/mol appeared to be too restrictive; no evidence of significant association with cardiovascular outcomes was found for TITRE categories beyond 6 months. Sensitivity analysis using a less stringent HbA1c cut-point for TITRE altered the composition of the TITRE category to a large degree and revealed significant risk reduction for cardiovascular outcomes.

Fifthly, HbA1c is considered accurate for reflecting average blood glucose levels over 3 months. Therefore, calculation of TITRE-HbA1c which tolerated up to a one year interval between two measures might invite criticism; nonetheless it was intended to ease the computation which is on yearly basis as per TITRE definition and to accommodate patients receiving at least two tests a year, following the current recommendation, who would otherwise never be regarded as having non-missing TITRE.

Sixthly, intensification of diabetes treatment is potentially an important confounder that may mediate TITRE and cardiovascular outcomes but was not adjusted for in my analysis. Treatment intensification alone is an area of research which requires considerable effort for its identification and measurement. I included timing and initial class of diabetes drug prescribed instead in the multivariate analysis.

Seventhly, validation for TITRE-HbA1c was only performed by visual comparison with other glycaemic control metrics. The novel metric is ideally tested in other populations with a larger size than my cohort for formal validation. Given the nature of TITRE to measure long-term glycaemic control, the failure to detect the significance of non-missing TITRE estimates for assessing cardiovascular outcomes was possibly, in part, due to inadequate study size with less varying intervals between HbA1c measures.

Finally, future clinical application of the TITRE-HbA1c metric for measuring glycaemic control longitudinally will require agreement about which HbA1c cut-point should be used from the beginning, particularly for cases needing individually tailored management; altering the cut-point in the middle of the disease course would make computation even more complex.

8.6.5 Clinical and research implications

Clinical implications. This chapter consistently found a strong association between missing duration at glycaemic control and higher risk of cardiovascular outcomes which implies the importance of routine glycaemic monitoring. T2D care with aggressive medical treatment to achieve tighter glycaemic targets may be worth suspending given the potential harms of co-medications; routine testing and, where possible, maintaining long-term glycaemic control should be emphasised instead.

Research implications. The findings of this study have demonstrated that duration at glycaemic target behaved reasonably well in the risk prediction for initial CVDs, particularly events

with high occurrence. However, limitations of TITRE-HbA1c suggest that the metric still needs to be formally validated. Similar studies may be worth replicating in other settings with a large population or, at best, in a clinical trial from which more frequent HbA1c measurements for close monitoring (thus more stable intervals) can be expected. A post-trial analysis probably offers the most efficient method of cross-validation.

Despite providing dual information (glycaemic control and its duration), complexity of TITRE-HbA1c calculation and its marginal performance in assessing risk of CVDs indicate that it may not be clinically practical. In order to facilitate its clinical utility in the future – particularly once meeting formal validation – further development of 'e-TITRE' (e.g. by machine learning) and its embedment into existing EHRs in primary care needs to be considered.

8.6.6 Conclusion

The time element from glycaemic control can be harnessed to assess risks of cardiovascular outcomes. Shorter duration at glycaemic target showed marginal risk excess for MACEs and cardiovascular death. More evident association was seen in the absence of duration data on glycaemic control. Longer duration of glycaemic control was only associated with lower risk of cardiovascular events when the HbA1c target was loosened.

8.7 Chapter summary

This chapter presented application of the TITRE-HbA1c metric to test its potential in assessing the risk of macrovascular events. Duration at glycaemic target measured using TITRE based on repeat HbA1c measures showed marginal association with composite cardiovascular outcomes. The next chapter will explore longitudinal records on relevant biomarkers for phenotyping microvascular diseases; the performance of TITRE-HBA1c for risk prediction for microvascular disease will be further investigated in **Chapter 10**.

Chapter 9

Microvascular diseases in CALIBER: phenotyping and validation

> Watch the little things; a small leak will sink a great ship.
> — Benjamin Franklin

9.1 Chapter outline

This chapter elaborates the exploration and validation of: a) repeat estimated glomerular filtration rate (eGFR) measures to obtain measures for chronic kidney disease (CKD) progression, b) repeat ankle vibration sense (AVS) tests to help identify diabetic neuropathy, and c) relevant diagnosis and examination codes to establish diabetic eye diseases (DEDs) in CALIBER's incident T2D cohort, the results of which will be used to determine the initial presentation of microvascular diseases to be applied for exclusion criteria and study endpoints for Study 5 (**Chapter 10**).

9.2 Abstract

Background. Existing microvascular disease phenotypes in CALIBER have been based on diagnosis codes only and presented as patient summaries for the initial presentation. CALIBER holds longitudinal data on clinical examinations and biomarkers to help refine microvascular diseases phenotyping.

Methods. Diabetic nephropathy was defined as CKD progression based on repeated measures of eGFR. DEDs were identified from diagnosis codes, whereas diabetic neuropathy was identified from either diagnosis codes alone or with additional data from AVS tests. Validation of the microvascular disease phenotypes was performed by exploring their associations with cardiovascular death.

Results. Among 52,379 patients newly diagnosed with T2D, diabetic nephropathy occurred in 7.4% patients (1.2% occurred before or at T2D diagnosis), diabetic retinopathy in 15.4% (1.1% before or at T2D diagnosis), glaucoma in 5.8% (3.4% before or at T2D diagnosis) and diabetic neuropathy in 3.1% (<1% before or at T2D diagnosis). Capture of cataract, unspecified DEDs and blindness were small. Presence of CKD progression demonstrated positive but non-significant association with cardiovascular death (age-sex adjusted OR 1.22, 95% CI 0.95-1.55), but stages of CKD progression (compared to stable CKD) showed stepwise linear associations. Presence of diabetic retinopathy and glaucoma also showed positive but non-significant associations with cardiovascular death. Use of data on AVS tests substantially improved the capture of diabetic neuropathy but sensitivity and positive predictive value (PPV) against diagnosis codes were low at 46.1% and 7.8%, respectively and showed no association with cardiovascular death.

Conclusions. Repeat eGFR records could be validly used to identify diabetic nephropathy as indicated by significant association between eGFR-based CKD progression and cardiovascular death. Diabetic retinopathy, glaucoma and neuropathy were phenotyped from diagnosis codes, but only the latter showed strong validation against cardiovascular death.

9.3 Introduction

In **Chapter 3**, I briefly described the CALIBER phenotypes available for microvascular diseases which have been developed using diagnosis codes only. In fact, the dataset contains the patient summary for initial microvascular presentation (single information per patient) rather than longitudinal records on multi-microvascular diseases. Moreover, detailed documentation on the microvascular phenotyping algorithms is not available. CALIBER holds a large number of longitudinal data beyond diagnoses that can be utilised to expand capture of microvascular diseases. Dissimilar approaches to establish a diagnosis of microvascular disease – either for clinical or research purposes – add justification for refinement of the current CALIBER microvascular phenotypes.

In this chapter, I attempted to refine and validate microvascular disease phenotyping in CALIBER by exploring the relevant biomarkers and clinical tests. My approach incorporated longi-

tudinal records on eGFR, visual acuity and AVS tests for microvascular phenotyping (**Table 9.1 below**). The refined microvascular phenotypes will be investigated in the next chapter for their association with duration at glycaemic control.

Table 9.1 Approach used for refining microvascular disease phenotyping in CALIBER

Microvascular disease	Data explored for phenotyping refinement
Diabetic nephropathy	eGFR records† to define CKD progression
DEDs	
Retinopathy/maculopathy	Diagnosis codes*
Glaucoma	Diagnosis codes*
Cataract and unspecified DED	Diagnosis codes*
Blindness	Visual acuity test†
Diabetic neuropathy	Diagnosis codes* and AVS test†

AVS, ankle vibration test; CKD, chronic kidney disease; DED, diabetic eye disease.
*Approach used for the existing phenotyping in CALIBER; dataset contains summary data for initial presentation.
†Longitudinal data.

9.4 Methods and results

9.4.1 General methods for microvascular disease phenotyping

9.4.1.1 Study population, inclusion criteria and study period

Patients with incident T2D in CALIBER meeting general inclusion criteria listed in **Section 3.9 on pages 111-113** were included. Patient follow-up period was determined from the date of initial presentation with microvascular disease or the date of index biomarker or clinical test, whichever was recorded first after GP registration, until death or practice deregistration. The follow-up period implies that the index T2D diagnosis was ignored at this stage due to the availability of another dataset summarising the initial presentation of microvascular diseases, the date of which may not necessarily overlap the date of diagnosis codes indicative of T2D (which may include relevant complications). Definition and identification of microvascular diseases are explained in **Sections 9.4.2 to 9.4.4 on pages 257-279**.

9.4.1.2 Validation of microvascular disease phenotypes

Recent evidence showed that microvascular diseases are predictive of cardiovascular death.[266] Microvascular disease phenotypes were therefore validated through comparison of cumulative incidence curves for cardiovascular death by presence of prior microvascular diseases at T2D diagnosis; the curves were generated using the Nelson-Aalen estimator. Multivariate logistic regression with random effect (GP practice as the cluster variable) was also used to examine the association of microvascular diseases with cardiovascular death, adjusted for age and sex and weighted by duration of follow-up.

9.4.2 Diabetic nephropathy

9.4.2.1 CKD stage *versus* CKD progression

Diabetic nephropathy refers to a long-term diabetes complication affecting kidney structure or function. Current clinical guidelines have defined diabetic nephropathy slightly differently. The use of surrogate biomarkers is recommended to help determine diabetic nephropathy by CKD staging. **Table 9.2 below** summarises the current CKD classification from several guidelines using either albuminuria levels or GFR levels estimated from serum creatinine.[31,34,300,301] Depending on the clinical context, one can be more important than the other but both eGFR and albuminuria measures are pivotal for the diagnosis, assessment and overall prognosis of CKD.

Table 9.2 Classification of CKD stage by eGFR and albuminuria levels

Biomarker and criteria	CKD stage	
eGFR (ml/min/1.73 m^2)		
≥90	G1	Normal or high
60-89	G2	Mildly decreased
45-59	G3a	Mildly/moderately decreased
30-44	G3b	Moderately/severely decreased
15-29	G4	Severely decreased
<15	G5	Kidney failure
Albuminuria		
AER <30 mg/day or ACR <30 mg/g	A1	Normal/mildly increased
AER 30-300 mg/day or ACR 30-300 mg/g	A2	Moderately increased (microalbuminuria*)
AER >300 mg/day or ACR >300 mg/g	A3	Severely increased (macroalbuminuria*)

ACR, albumin creatinine ratio; AER, albumin excretion rate; eGFR, glomerular filtration rate.
*Classification used by the Kidney Disease Outcomes Quality Initiative and American Diabetes Association.[301]

With more detailed classification than albuminuria, eGFR can better discriminate patients' kidney function state and as such is generally accepted as the best index for diagnosis and assessment purposes. In fact, eGFR measures kidney function, whilst albuminuria is a marker of kidney damage. In clinical practice, assessment by combined measures as albumin-to-creatinine ratio (ACR) from spot urine may be preferred. ACR is easier to measure than albumin excretion rate (AER) as the latter needs to be measured from a timed urine collection.[302] With regard to prognostic function, a collaborative meta-analysis of 13 studies totalling 21,688 individuals with CKD reported the independent associations of a 15-unit lower in eGFR with end stage renal disease (ESRD, pooled HR 6.24) and mortality (pooled HR 1.47) after controlling for confounders and albuminuria; the risk of ESRD was halved with an eightfold increase in ACR (pooled HR 3.04, adjusted for confounders and eGFR).[303] With consistent associations observed for eGFR, the study concluded that ACR-based albuminuria provides additional prognostic information.

As previously alluded to in **Section 1.2.4 on pages 40-41**, diabetic nephropathy in T2D typically takes longer than cardiovascular complications to clinically manifest although it may be present at the time of diagnosis. Whilst kidney failure is a distinct, final stage nephropathy, diabetes clinical trials have, therefore, commonly added subclinical endpoints such as micro- and macroalbuminuria. Nevertheless, eGFR-based CKD stages were rarely used in most trials whilst clinical guidelines have recognised the potential and impact of rapid development of CKD in

diabetic individuals. A post-trial analysis from the ACCORD trial used a generic eGFR decline from baseline to define one of its diabetic nephropathy endpoints (**Table 9.3 below**). Differing definition and identification of nephropathy as study endpoints in diabetes outcome trials are summarised in **Appendix E on pages 340-345**.

Table 9.3 Definition of CKD progression for diabetes based on eGFR values

Reference	Definition of CKD progression
ACCORD (2008)[53]	A decrease of >20 ml/min per 1.73 m^2 in eGFR from baseline
NICE (2014)[304]	• A sustained decrease in eGFR of ≥25% and a change in eGFR category within 12 months, or • A sustained decrease in eGFR of ≥15 ml/min/1.73 m^2 per year
NKF-FDA (2014)[305]	A decline in eGFR of 30% or 40% over 2-3 years
SPRINT (2015)[306]	• With CKD at baseline: a reduction in eGFR of ≥50% • Without CKD at baseline: ≥30% reduction in eGFR to <60 ml/min/1.73 m^2 • eGFR reduction is confirmed by subsequent laboratory test at least 90 days later

ACCORD, Action to Control Cardiovascular Risk in Diabetes trial; NICE, National Institute for Health and Care Excellence; NKF-FDA, National Kidney Foundation and US Food and Drug Administration; SPRINT, Systolic Blood Pressure Intervention trial.

9.4.2.2 Identification and validation of CKD progression

Diabetic nephropathy tends to be irreversible but its deterioration can be delayed with early recognition of CKD progression and prompt intervention. CALIBER holds several data on kidney diseases and related biomarkers. In particular, serum creatinine or eGFR records from routine T2D monitoring should enable identification of CKD progression because CKD stage cannot be specifically identified from CALIBER's constituent data sources using diagnosis codes alone. Thus, for Study 5, I used repeated eGFR measures extracted from CPRD to define diabetic nephropathy with particular emphasis on the subsequent CKD progression. Due to the different classification system, I did not link eGFR data to albuminuria data for CKD phenotyping although they could be complementary for CKD ascertainment.

Identification. I applied the NICE criteria[304] to CALIBER's incident T2D cohort (N=52,379) to define CKD progression. Patients were followed-up from index eGFR measure from registration until death or practice deregistration, irrespective of their index T2D diagnosis. eGFR values have been calculated from serum creatinine using the CKD-EPI formula as expressed in Equation (9.1).[307]

$$eGFR = 141 * \min(SCr / K, 1)^{\alpha} * \max(SCr / K, 1)^{-1.209} * 0.993^{Age} * 1.018\ [\text{if female}] * 1.159\ [\text{if black}] \quad (9.1)$$

where SCr = standardised serum creatinine (mg/dL) = creatinine * 0.010746
K = 0.7 (females) or 0.9 (males)
α = -0.329 (females) or -0.411 (males)

Compared to the CKD Modification of Diet in Renal Disease (MDRD) Study equation,[308] CKD-EPI is more accurate in higher eGFR ranges (>60 ml/min/1.73 m^2) and numeric values can be reported throughout the entire range.[302]

I first checked the eGFR records; if any duplicates on the same day existed for a patient, de-duplication was performed by generating an average value. Index eGFR was defined as the first eGFR measure irrespective of time of first established diagnosis of T2D. CKD progression was determined from initial eGFR decline meeting NICE criteria and confirmed by a subsequent eGFR decline which was at least 90 days later to exclude causes of acute eGFR deterioration. For each patient, both NICE criteria were applied to determine the earliest date on which an eGFR decline occurred. I ignored any CKD progressions and/or reversions thereafter.

Patients who had no eGFR record or only a single eGFR record during follow-up were classified into an undetermined category. Patients with multiple eGFR records who did not show progression to a more severe CKD stage were classified into a stable category. Patients who were initially identified as being at a higher CKD stage who then maintained a less severe stage thereafter were also classified into a stable rather than an undetermined category; such cases are somewhat tricky but unless the initial stage is an acute state, permanent reversion of the CKD stage is less likely. Patients with an initial CKD stage G1 who progressed to stage G2 were also classified into a stable category. Clinical-wise, CKD stages G1 and G2 are still regarded as normal in the absence of additional evidence of kidney damage (e.g. urinalysis, histological and imaging results, kidney transplantation); therefore, I only considered initial progression to stage G3a or higher. CKD progression might not necessarily occur in a stepwise manner. For example, a patient with an index eGFR of 75 ml/min/1.73 m^2 (CKD stage G2) could silently have experienced an initial decline to eGFR of 28 ml/min/1.73 m^2 which fell into a CKD stage G4 category although his/her subsequent records might indicate a reversion to a less severe CKD stage. In such a case, the patient was classified into progression to G4 category.

Overall, CKD progression was categorised into six categories: progression to stages G3a, G3b, G4 and G5, stable and undetermined. Patients who experienced CKD progression before their T2D diagnosis were classified as having prior nephropathy and were excluded from the cohort for study on duration at glycaemic target and microvascular outcomes (**Chapter 10**).

Phenotype validation. To validate the CKD progression phenotype, cumulative incidence curves for cardiovascular death were compared between patients with and without prior nephropathy at T2D diagnosis. The incidence curves for cardiovascular death by CKD progression category were also inspected in patients free from prior nephropathy. I used multivariate logistic regression with random effect (GP practice being the cluster variable) to examine the association of CKD progression and cardiovascular death. Estimates were adjusted for age and sex and weighted by duration of follow-up.

9.4.2.3 Descriptives of repeat eGFR measures

Yearly pattern of eGFR measures. Most eGFR measures in a patient were tested in consecutive years (either from index eGFR or initial T2D diagnosis) and only approximately 25% were tested intermittently (**Table 9.4 on page 261**). About a quarter of the cohort were never measured.

Number of eGFR measures. The median total frequency of eGFR measures for a patient over the follow-up years after index eGFR was 7 (IQR 0-13) (**Figure 9.1A on page 261**); the estimate was lower (median 5, IQR 0-10) when measured after diagnosis of T2D (**Figure 9.1B on page 261**). Duration of follow-up was shorter when the frequency was measured after index eGFR, suggesting that index eGFR was more likely measured after T2D diagnosis, not before.

Mean eGFR values. In patients whose eGFR was ever tested, the mean eGFR values over the years of follow-up ranged from 70-75 ml/min per 1.73 m^2 (**Figures 9.2A and 9.2B on page 262**).

Time between successive eGFR measures. The distribution of time on average between eGFR measures per patient after index eGFR was highly skewed with a median (IQR) of 6.5 (4.9-8.5) months (**Figure 9.3A on page 262**), but roughly normally distributed after omitting the lengthy intervals (data not shown). The estimate after diagnosis of T2D was slightly lower (median 6.2 months, IQR 4.6-8.2) (**Figure 9.3B on page 262**).

Table 9.4 Most common yearly pattern of eGFR measures

Yearly pattern of eGFR measures after index eGFR*	N	%
. . . . .	13,537	25.8
1	1,890	3.6
1 2	2,829	5.4
1 2 3	2,737	5.2
1 2 3 4	2,485	4.7
1 2 3 4 5	2,514	4.8
1 2 3 4 5 6	2,993	5.7
1 2 3 4 5 6 7	2,649	5.1
1 2 3 4 5 6 7 8	2,132	4.1
1 2 3 4 5 6 7 8 9	1,626	3.1
1 2 3 4 5 6 7 8 9 10 . . .	918	1.8
1 2 3 4 5 6 7 8 9 10 11 . .	474	0.9
1 . 3	396	0.8
1 . 3 4	378	0.7
1 . 3 4 5	454	0.9
1 . 3 4 5 6	480	0.9
1 . 3 4 5 6 7	481	0.9
1 . 3 4 5 6 7 8	451	0.9
1 . 3 4 5 6 7 8 9	455	0.9
1 . 3 4 5 6 7 8 9 10 . . .	311	0.6
1 2 . 4	271	0.5
1 2 . 4 5	269	0.5
1 2 . 4 5 6	314	0.6
1 2 . 4 5 6 7	286	0.5
1 2 . 4 5 6 7 8	239	0.5
1 2 . 4 5 6 7 9 10	229	0.4
(other patterns)	10,581	20.2
	52,379	100.0

*Receiving measures in the corresponding years after index eGFR (indicated by numbers).
Dot represents year after index eGFR in which eGFR is not measured.
The longest duration of follow-up possible is 13 years.

Yearly pattern of eGFR measures after T2D diagnosis†	N	%
. . . . .	13,624	26.0
1	2,378	4.5
1 2	4,764	9.1
1 2 3	4,014	7.7
1 2 3 4	3,304	6.3
1 2 3 4 5	2,919	5.6
1 2 3 4 5 6	2,457	4.7
1 2 3 4 5 6 7	1,914	3.7
1 2 3 4 5 6 7 8	1,292	2.5
1 2 3 4 5 6 7 8 9	858	1.6
1 2 3 4 5 6 7 8 9 10 . . .	429	0.8
1 2 3 4 5 6 7 8 9 10 11 . .	217	0.4
. 2	705	1.3
. 2 3	526	1.0
. 2 3 4	441	0.8
. 2 3 4 5	365	0.7
. 2 3 4 5 6	302	0.6
. 2 3 4 5 6 7	309	0.6
. 2 3 4 5 6 7 8	299	0.6
. 2 3 4 5 6 7 8 9	214	0.4
1 . 3	322	0.6
1 . 3 4	245	0.5
1 . 3 4 5	198	0.4
1 2 . 4	242	0.5
. . 3	213	0.4
. . 3 4	215	0.4
(other patterns)	9,613	18.4
	52,379	100.0

†Receiving measures in the corresponding years after T2D diagnosis (indicated by numbers).
Dot represents year after T2D diagnosis in which eGFR is not measured.
The longest duration of follow-up possible is 13 years.

Figure 9.1 Total number of eGFR measures per patient during follow-up

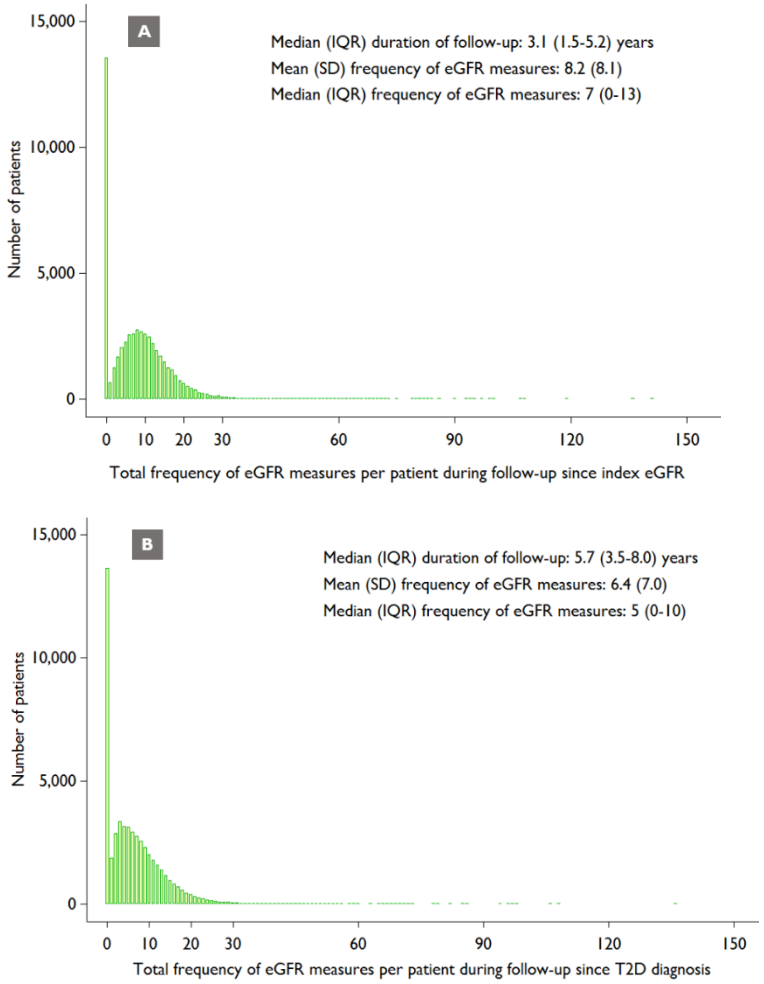
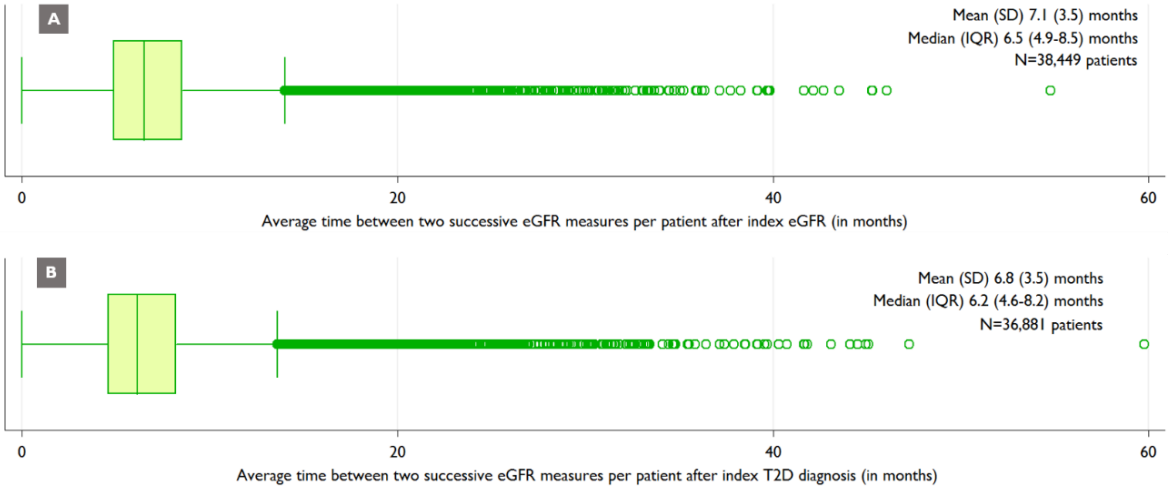


Figure 9.2 Mean follow-up eGFR value per patient over years of follow-up

Figure 9.3 Distribution of time between successive eGFR measures

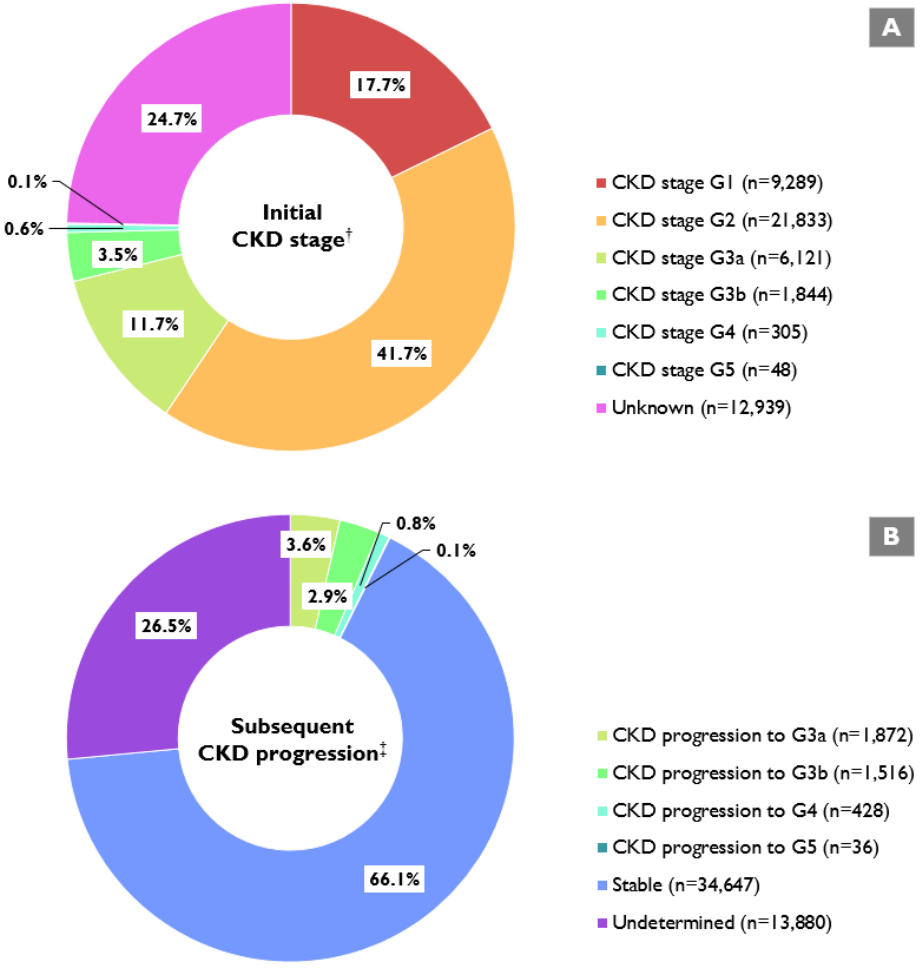


9.4.2.4 Initial CKD stage and subsequent CKD progression in incident T2D

Patient distribution by initial CKD stage is presented in **Figure 9.4A below**. The proportion was highest in T2D patients with CKD stage G2 (41.7%) followed by stage G1 (17.7%). The proportion of patients with severe nephropathy (stages G4 and G5) was less than 1%. About a quarter of the incident T2D cohort never had their eGFR measured so their index nephropathy was unknown.

Figure 9.4B below depicts patient distribution by subsequent CKD progression regardless of date of index T2D diagnosis. About two-thirds of the cohort whose index nephropathy was known never progressed to more severe stages. CKD progression status could not be determined in about a quarter of patients due to there being no eGFR records or only a single eGFR record available. In total, only 3,852 patients (7.4%) developed CKD progression; patients who progressed to higher stages were inversely proportional, with only 3.6% progressing to stage G3a and less than 0.1% to stage G5.

Figure 9.4 Distribution of initial CKD stages and subsequent CKD progressions in CALIBER's incident T2D cohort (N=52,379)



†After index eGFR (ignoring initial T2D diagnosis).
‡During follow-up (from index eGFR until death or deregistration).

Table 9.5 Matrix showing subsequent CKD progression from initial CKD stage*

Initial CKD stage	Subsequent CKD progression						
	G2	G3a	G3b	G4	G5	Stable	Undetermined
Unknown	-	-	-	-	-	-	12,939
G1	641	114	14	1	1	8,281	237
G2	-	1,758	585	30	2	19,040	418
G3a	-	-	917	93	5	4,934	172
G3b	-	-	-	304	4	1,448	88
G4	-	-	-	-	24	265	16
G5	-	-	-	-	-	38	10

*Data are number of patients.

Table 9.5 above displays the connection matrix between initial CKD stage and subsequent CKD progression. To give a more thorough picture, distribution of index CKD stages, subsequent CKD progression and flow of progression were visualised altogether in chord diagrams.

Figure 9.5 Distribution and direction of subsequent CKD progressions*

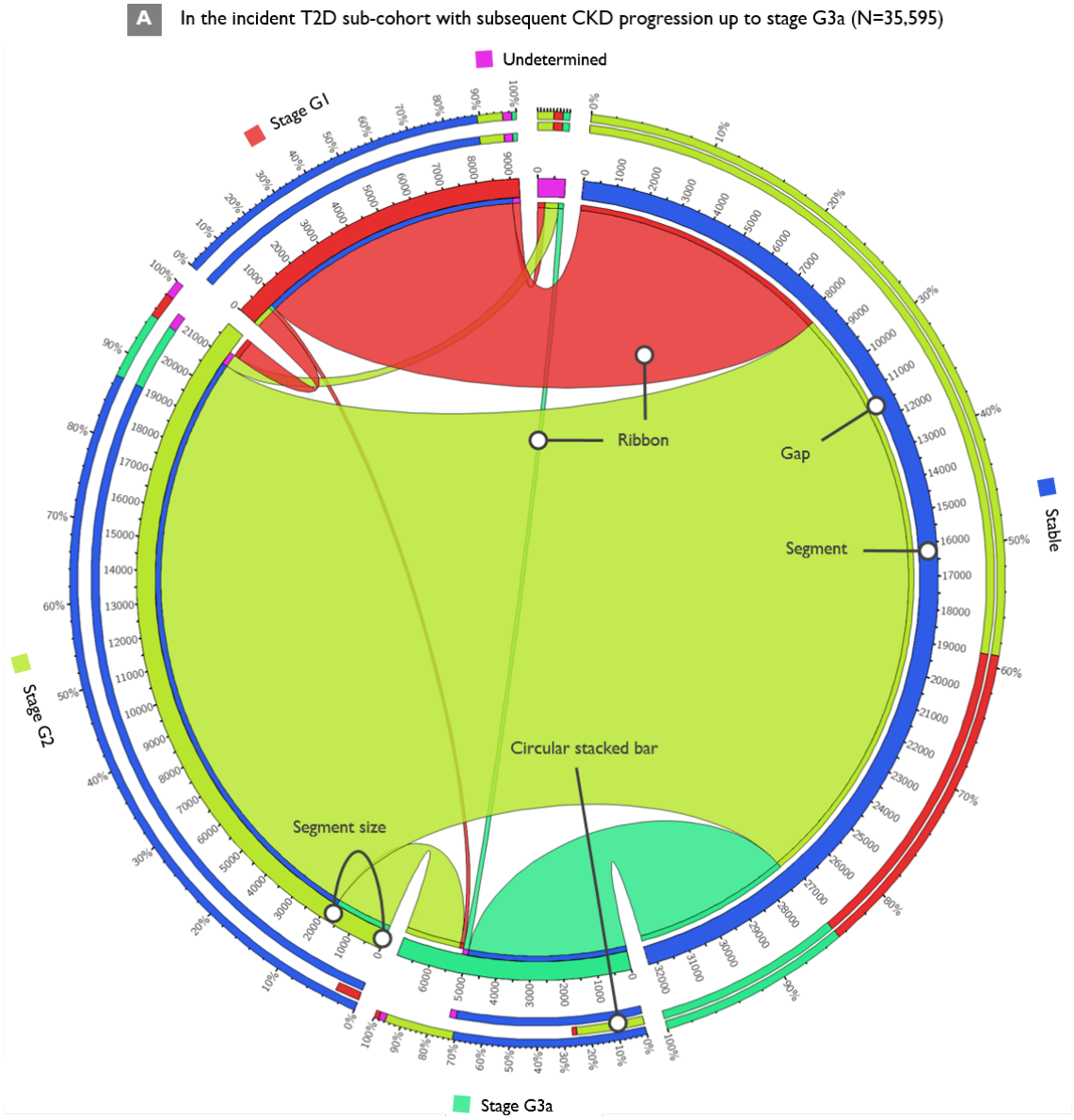
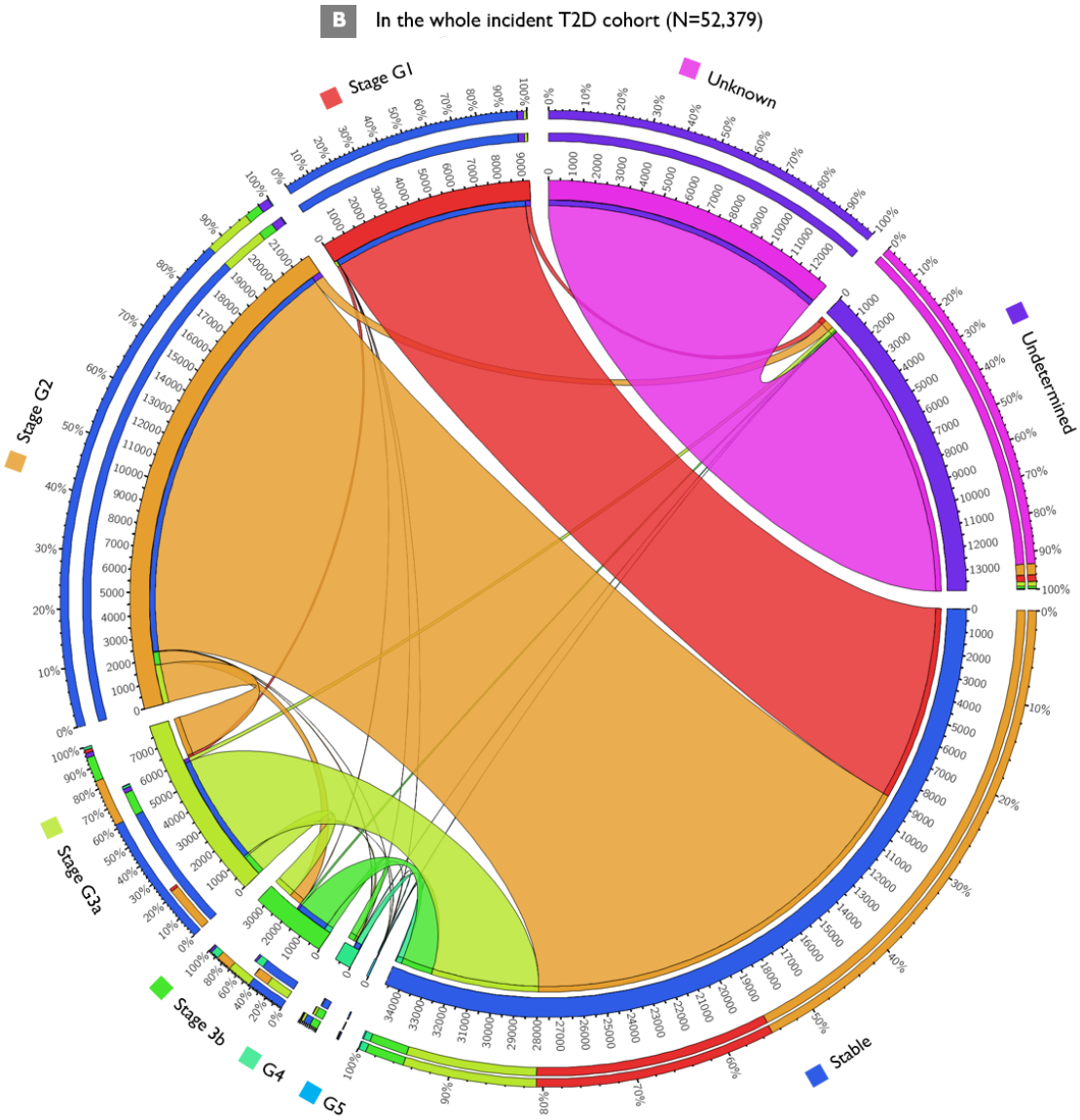


Figure 9.5A on page 264 shows the flow in a sub-cohort who might progress up to CKD stage G3a (N=35,595). Of the 9,273 patients whose initial CKD stage was G1 (coded in red), 641 (6.9%) patients progressed to stage G2 (lime), 114 (1.2%) progressed to stage G3a (tosca), 8,281 (89.3%) never progressed or stable (blue) and the remaining could not be determined (magenta). Of the 21,216 patients whose initial CKD stage was G2, 1,758 (8.3%) progressed to stage G3a, 19,040 (89.7%) never progressed and 418 (10.0%) was undetermined. Of the 5,106 patients whose initial CKD stage was G3a, 4,934 (96.6%) never progressed and 172 (3.4%) was undetermined. Initial CKD stage (origin) and subsequent CKD progression (terminal) are represented by circular segments. Origin is colour-coded and indicated by ribbon which touches the segment, while terminal has the same colour as their origin and is indicated by gap between the ribbon and the segment. Segment width indicates stage or progression size with estimated number of patients shown in the inner circle. Relative contribution of each CKD stage or progression to the total patients in each category is encoded by circularly re-arranged stacked bars (in descending order) with estimated



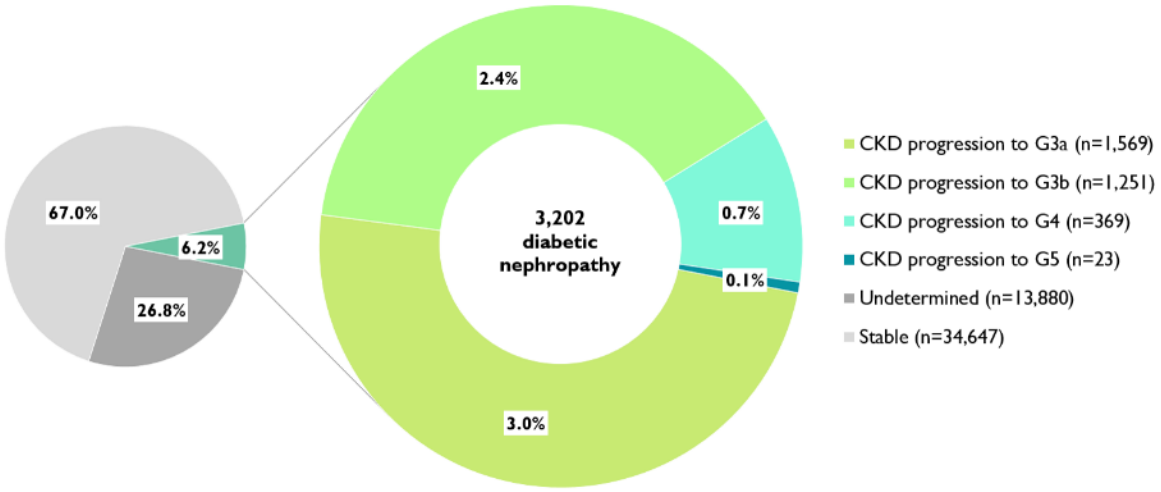
*In Panel B, stable category from CKD stage G1 (N=8,922) includes 641 cases which originally progressed to stage G2.

proportion in the outer circles. The outermost layer of the outer circles displays cumulative proportion from origin and terminal, the middle layer displays proportion from terminal only and the innermost layer displays proportion from origin only.

Figure 9.5B on page 265 illustrates the full flow to subsequent CKD progressions in the whole cohort (N=52,379). Although proportions differed slightly from the previous figure due to changes in the number of patients, the diagram clearly shows the substantial proportion of patients who never progressed to higher CKD stages, 55.0% of which was contributed by patients with initial CKD stage G2. Thus, despite being common in newly diagnosed T2D, initial CKD stage G2 was relatively stable. In fact, the occurrence of CKD progression prior to or at T2D diagnosis was only found in 650 patients (1.2% of total cohort).

Distribution of subsequent CKD progression after T2D diagnosis is plotted in **Figure 9.6 below**. The proportion of patients with CKD progression was inversely proportional to the level of progression (i.e. lowest proportion in CKD progression to stage G5).

Figure 9.6 Distribution of subsequent CKD progression in CALIBER's T2D cohort without prior nephropathy (N=51,729)



Of 3,852 total patients with nephropathy, 650 (16.9%) had CKD progression before or at T2D diagnosis. These patients were older and the proportion of women was higher than those without nephropathy at T2D diagnosis (**Table 9.6 on page 267**). Given the longer GP registration in patients with prior nephropathy but a higher proportion of patients diagnosed with T2D in more recent years (2007-2009), one of the possibilities is that chronicity of kidney damage has led to secondary diabetes. Uremic toxins, vitamin D deficiency, metabolic acidosis, inflammation, anemia and cachexia are thought to be responsible for insulin resistance and impaired glucose homeostasis in non-diabetic CKD patients.[309]

Table 9.6 Demographic characteristics of patients with and without prior nephropathy at T2D diagnosis

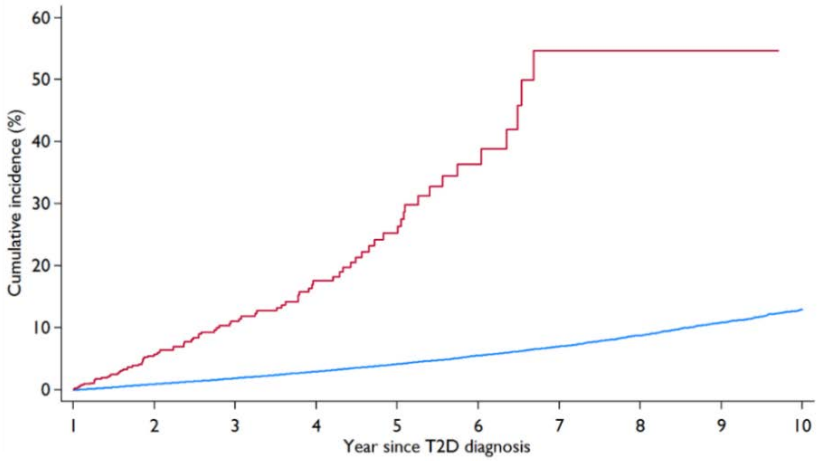
Characteristics	With prior nephropathy (N=650)		Without prior nephropathy (N=51,729)	
Duration of GP registration before entry, median (IQR) years	13.3	(10.3-18.8)	11.1	(6.7-15.9)
Year of T2D diagnosis, n (%)				
1998-2003	78	(12.0)	22,763	(44.0)
2004-2006	242	(37.2)	17,155	(33.2)
2007-2009	330	(50.8)	11,811	(22.8)
Age at entry, mean (SD) years	76.3	(9.3)	63.0	(13.4)
Women, n (%)	390	(60.0)	23,210	(44.9)
White ethnicity, n (%)*	337	(51.9)	26,205	(50.7)
Most deprived quintile, n (%)*	100	(15.4)	10,340	(20.0)

*Proportion of non-missing data: 57.6% for ethnicity and 99.7% for deprivation.

9.4.2.5 CKD progression and risk of cardiovascular death

Figure 9.7 below shows that the incidence of cardiovascular death was higher among patients with prior nephropathy. As would be expected, the incidence among patients without prior nephropathy was proportional to the severity of CKD progression (**Figure 9.8 on page 268**). Further analysis showed that cardiovascular death was significantly associated with severity of CKD progression but not with prior nephropathy at T2D diagnosis (**Figure 9.9 on page 268**) and this should suffice to validate CKD progression phenotype despite a seemingly paradoxical estimate for the undetermined category. However, the lower risk of cardiovascular death in the undetermined category can be explained by the contribution of possibly healthier patients in whom no eGFR was ever measured or of patients with a less severe stage and single eGFR record only.

Figure 9.7 Cumulative incidence curve for cardiovascular death by presence of nephropathy at T2D diagnosis (N=52,379)

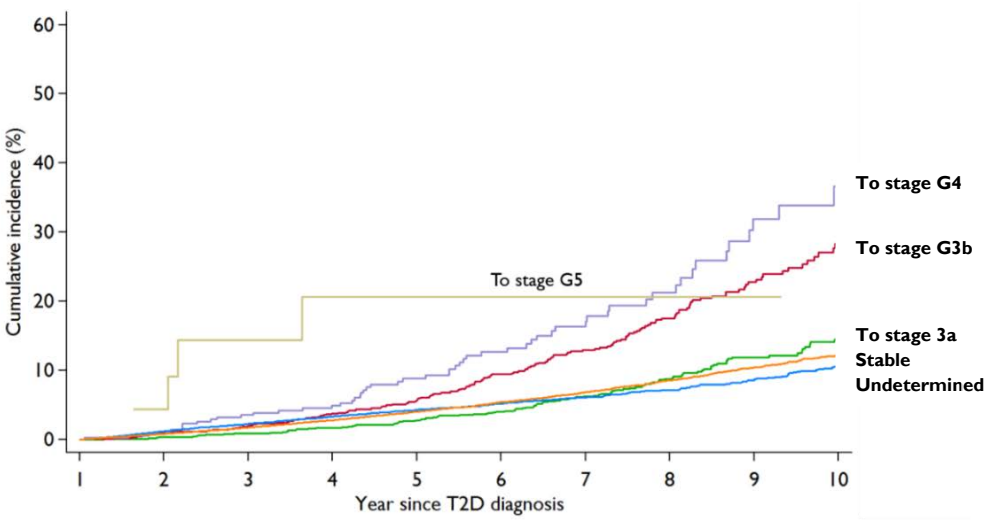


Prior nephropathy											Total events*
No	440	382	369	331	295	234	202	159	91	52	2,593
	51,729	43,975	37,069	30,563	24,474	18,792	3,686	9,456	5,934	3,371	
Yes	30	18	13	9	8	5	0	0	0	0	83
	650	417	262	160	90	41	17	9	2	0	

*Included events until year 13

For each group in the risk tables, numbers in the first row denote number of events, while numbers in the second row denote number of patients at risk.

Figure 9.8 Cumulative incidence curve for cardiovascular death by CKD progression category in incident T2D cohort without prior nephropathy (N=51,729)

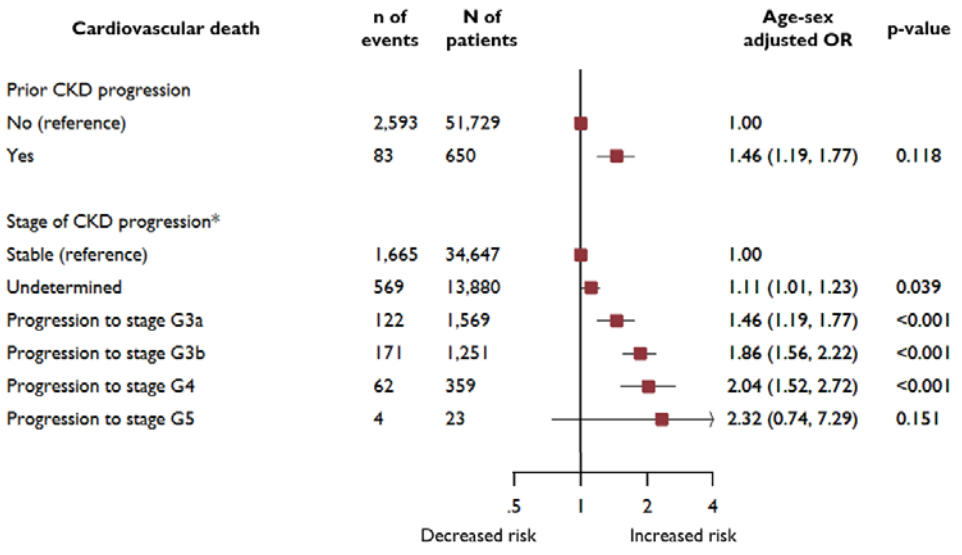


CKD progression											Total events*
Undetermined	150	111	87	63	45	33	28	26	17	7	569
	13,880	11,287	9,202	7,365	5,760	4,344	3,109	2,108	1,315	708	
Stable	268	242	246	227	198	153	128	91	53	37	1,665
	34,647	29,599	24,967	20,563	16,428	12,544	9,078	6,215	3,889	2,219	
To stage G3a	5	8	12	13	14	20	18	16	8	2	122
	1,569	1,525	1,453	1,335	1,174	1,003	803	622	400	262	
To stage G3b	12	11	19	18	30	22	22	18	11	4	171
	1,251	1,197	1,117	1,011	873	710	554	411	270	148	
To stage G4	4	8	4	10	8	6	6	8	2	2	62
	359	346	313	275	227	180	137	97	59	34	
To stage G5	1	2	1	0	0	0	0	0	0	0	4
	23	21	17	14	12	11	5	3	1	0	

*Included events until year 13

For each group in the risk tables, numbers in the first row denote number of events, while numbers in the second row denote number of patients at risk.

Figure 9.9 Age and sex adjusted odds ratios for the association between nephropathy and cardiovascular death



*Among patients without prior nephropathy (CKD progression) at T2D diagnosis (N=51,729).

9.4.3 Diabetic eye diseases

9.4.3.1 Diabetic retinopathy and other DEDs in incident T2D

Identification of diabetic retinopathy. For the purpose of Study 5, I defined diabetic retinopathy as a composite of diabetes-related retinopathy and maculopathy. Retinopathy and maculopathy were identified from CPRD or HES by diagnosis codes indicative of the diseases, the earliest record of which determined initial diabetic retinopathy. At least five categories of diabetes-related retinopathy alone could be recognised from the Read and ICD-10 codes: background, pre-proliferative, active proliferative, treated/stable proliferative and unspecified diabetic retinopathies. Maculopathy was identified from any diagnosis related to diabetes-related macular oedema by ruling out prior age-related macular degeneration or other macular degenerative diseases. **Figure 9.10A on page 270** shows identification of overall diabetic retinopathy from both data sources. Among 52,379 patients with incident T2D, there were 8,044 cases of diabetic retinopathy, 1.1% of which occurred prior to or at T2D diagnosis. Linkage with HES data appeared to improve the capture of diabetic retinopathy.

Identification of other DEDs. This referred to non-retinal eye complications which included glaucoma, cataract, unspecified DEDs and blindness. Glaucoma, cataract and unspecified DEDs affecting at least one eye were identified by diagnosis codes from CPRD and HES and the earliest date of each diagnosis from either data source was used to determine the respective DED. Blindness referred to severe sight impairment in at least one eye and it was inferred from eye test result, extracted from CPRD, showing visual acuity of less than 3/60.[237] The earliest date when the poor result was recorded was used to determine initial blindness. In the absence of clinical data on visual field (perimetry) tests, I did not deduce blindness from visual acuity between 3/60 and 6/60 or over despite the presence of glaucoma in the same eye; diagnosis of glaucoma can be established without evidence of reduced field of vision. **Figures 9.10B to 9.10D on page 270** shows identification of other DEDs in the newly diagnosed T2D cohort according to data source. There were 3,054 cases of glaucoma, 59.1% of which occurred before or at T2D diagnosis. Cataract and unspecified DED were merged due to the small number of individual events and there were 218 cases altogether, 3.2% of which occurred before or at T2D diagnosis. Blindness was identified in 186 patients, 15.1% of which occurred before or at T2D diagnosis.

Initial presentation of diabetic retinopathy. Patient distribution by initial diabetic retinopathy occurring after T2D diagnosis (N=52,289) is presented in **Figure 9.11A on page 271**. To ensure an adequate number of patients falling into a more specific category, I reclassified diabetic retinopathy into four categories: NPDR (including background and pre-proliferative retinopathies), PDR (including active and treated/stable retinopathies), maculopathy and unspecified diabetic retinopathy. There were 15.2% incident diabetic retinopathy, the highest proportion was NPDR (8.7%) and the lowest was PDR (0.2%).

Figure 9.10 Identification of diabetic retinopathy and other DEDs in CALIBER's incident T2D cohort (N=52,379)

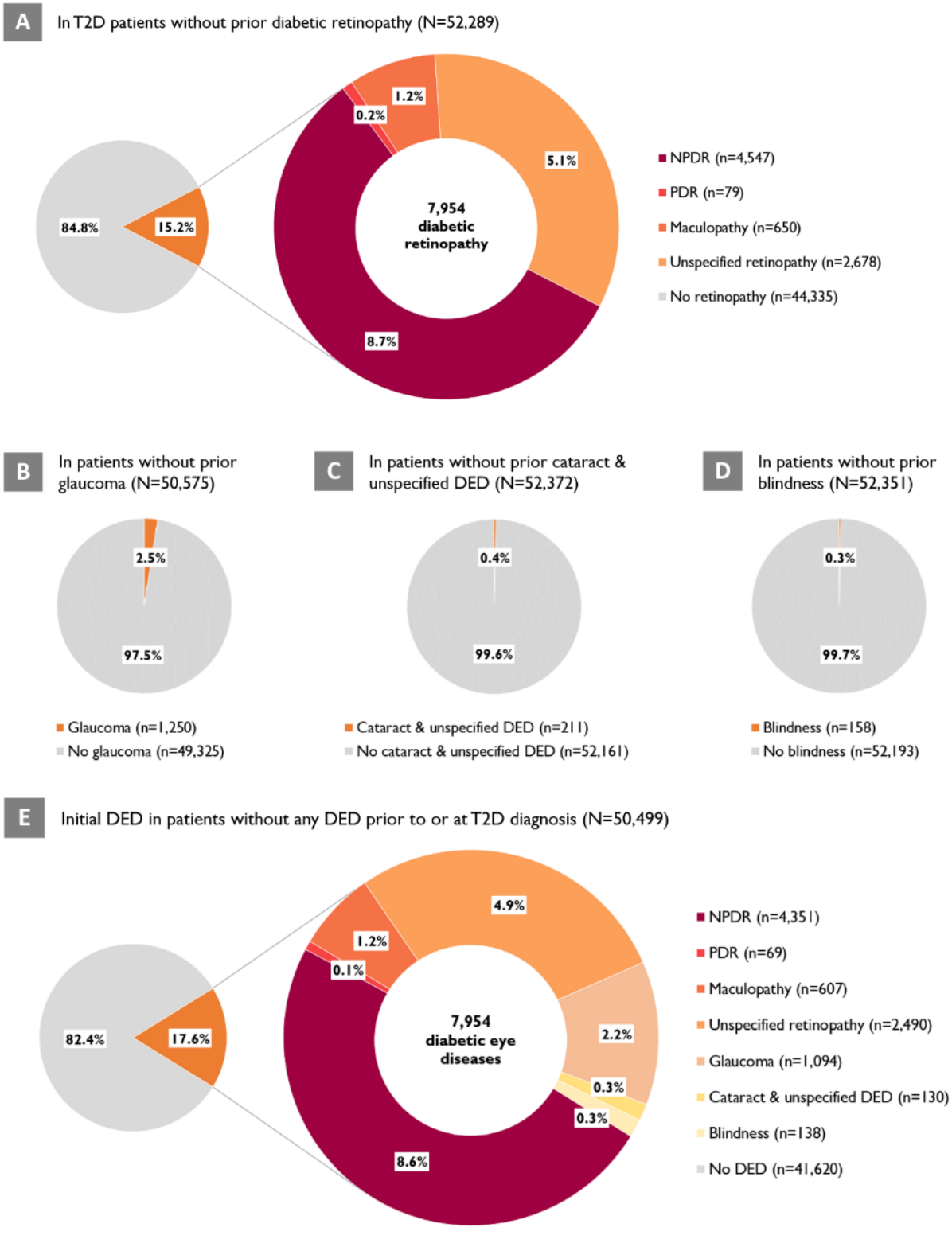
†Initial cases after index eGFR (ignoring initial T2D diagnosis).
‡Baseline refers to one year period before initial T2D diagnosis.

Initial presentation of other DEDs. Patient distribution according to other DEDs is individually presented in **Figures 9.11B to 9.11D on page 271**. There were 2.5% incident cases of glaucoma, 0.4% incident cases of cataract and unspecified DED and 0.3% incident cases of blindness in different cohorts free from the respective diseases at baseline.

Initial presentation of all DEDs. Overall, there were 1,880 (3.6%) patients who had any DED at baseline. Accounting for competing DEDs, the distribution of initial presentation with any DED after T2D diagnosis is presented in **Figure 9.11E on page 271**. Among 50,499 patients free from any DED at baseline, the highest proportion of initial DED was NPDR (8.6%) followed by

unspecified retinopathy (4.9%) and glaucoma (2.2%) – these were raw estimates before validation of the DEDs. Validation results for DED phenotypes are presented in **Section 9.4.3.2 on page 272.**

Figure 9.11 Distribution of initial diabetic retinopathy and other DEDs after T2D diagnosis in CALIBER's incident T2D cohort



9.4.3.2 DEDs and risk of cardiovascular death

Figure 9.12A on page 273 shows that incidence of cardiovascular death was higher among patients with prior diabetic retinopathy at T2D diagnosis. A similar finding was seen for glaucoma (**Figure 9.12B on page 273**), but not for other DEDs (data not shown) which was likely due to the small number of the latter events resulting from poor recording, lack of linkable data for diagnosis ascertainment or simply rare occurrence. Further analysis on the associations of cataract, unspecified DED and blindness with cardiovascular death failed to yield discernible estimates (data not shown). On the basis of these, cataract, unspecified DED and blindness phenotyping failed validation and were, therefore, no longer considered as potential microvascular endpoints (and consequently as exclusion criteria) in Study 5. As for diabetic retinopathy and glaucoma, each showed positive but non-significant association with cardiovascular death (**Figure 9.13 on page 274**). Further analysis according to retinopathy category showed mixed results, with negative associations observed for NPDR and maculopathy; these are not consistent with an existing study reporting the opposite.[311] To follow the argument on unspecified stroke that is most likely ischaemic stroke, or unspecified CHD that is most likely unstable angina, it is also likely that unspecified retinopathy is mostly cases of NPDR; if this holds true, then the negative association could be shifted to the right (or at least neutralised if not supportive of a positive association). Apart from this possibility, I considered the validation of diabetic retinopathy phenotype as a composite entity adequate on the basis of its positive association – although non-significant – with cardiovascular death.

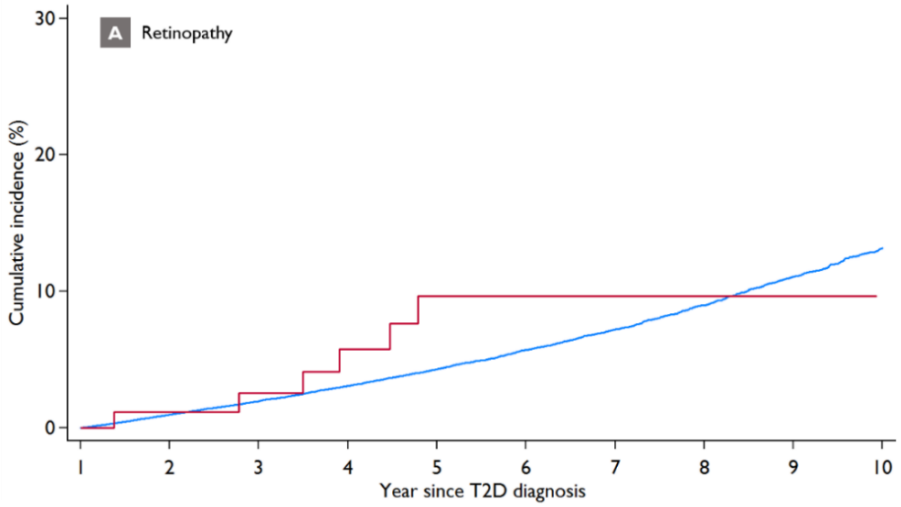
9.4.3.3 Initial presentation of DED in incident T2D

Figure 9.14 on page 274 summarises the final initial DEDs in patients without prior retinopathy and glaucoma at T2D diagnosis after accounting for competing events. Omission of cataract, unspecified DED and blindness enabled more capture of diabetic retinopathy and glaucoma as initial DED. Of the 52,379 patients with incident T2D, 50,488 (96.4%) had no prior DEDs at T2D diagnosis, 8,723 (17.3%) of whom developed incident DED. NPDR was the most common initial DED (8.7%), followed by unspecified retinopathy (5.0%) and glaucoma (2.2%).

Similar to diabetic nephropathy with inverse proportion for a higher stage of CKD progression, the proportion of more severe diabetes retinopathies (PDR and maculopathy) were also much smaller than NPDR. This would be expected though in incident T2D where late stages of complication should rarely be found.

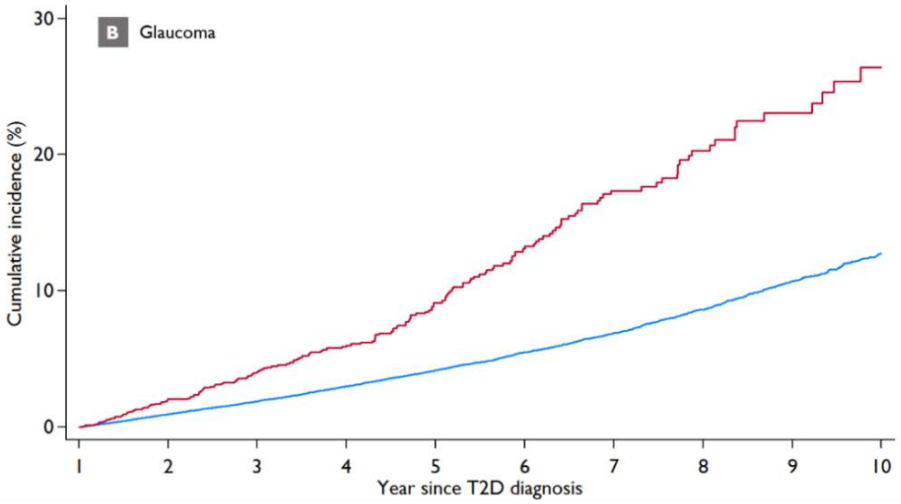
It is also interesting to note the discernible proportion of glaucoma because it is traditionally not considered a T2D complication, let alone as an initial presentation. Nonetheless, evidence showed that glaucoma is increasingly linked to diabetes.[312,313] Microvascular damage can impair blood flow to the anterior optic nerve, resulting in optic nerve damage and eventually primary open-angle glaucoma. Neovascular glaucoma – a secondary type – was also shown to consistently relate to PDR. PDR may cause hypoxia in the retina and other ocular tissue, causing an increased expression of VEGF which stimulates neovascularisation of the iris or the anterior chamber angle, eventually blocking the ocular drainage.[313]

Figure 9.12 Cumulative incidence curve for cardiovascular death by presence of prior DED at T2D diagnosis (N=52,379)



Prior retinopathy											Total events*
No	469	399	380	338	303	239	202	159	91	52	2,670
	52,289	44,315	37,264	30,664	24,517	18,789	13,668	9,439	5,917	3,361	
Yes	1	1	2	2	0	0	0	0	0	0	6
	90	77	67	59	47	44	35	26	19	10	

*Included events until year 13

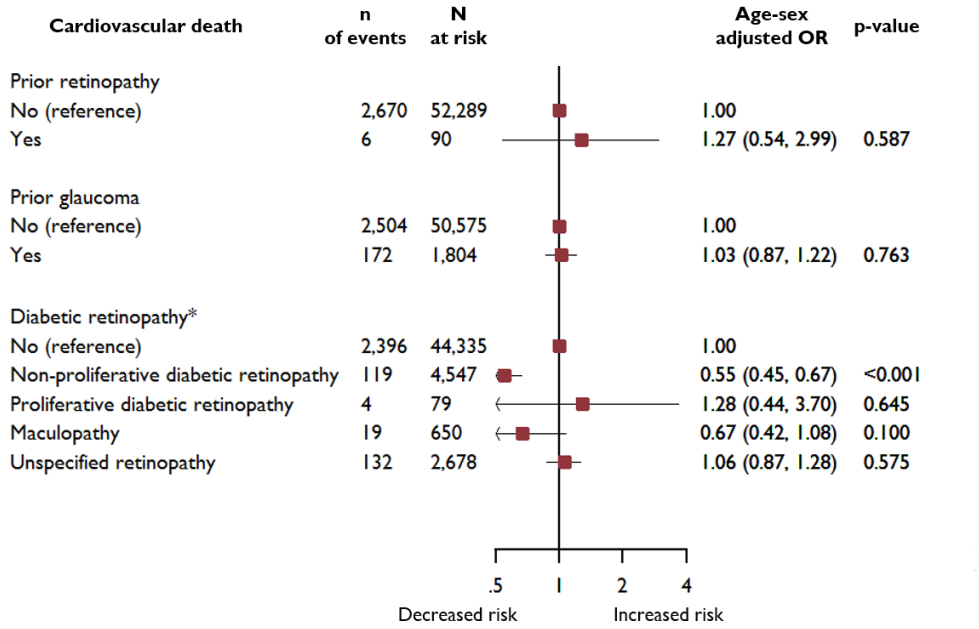


Prior glaucoma											Total events*
No	437	374	360	314	277	220	193	153	87	52	2,504
	50,575	42,918	36,119	29,769	23,830	18,290	13,312	9,202	5,777	3,283	
Yes	33	26	22	26	26	19	9	6	4	0	172
	1,804	1,474	1,212	954	734	543	391	263	159	88	

*Included events until year 13

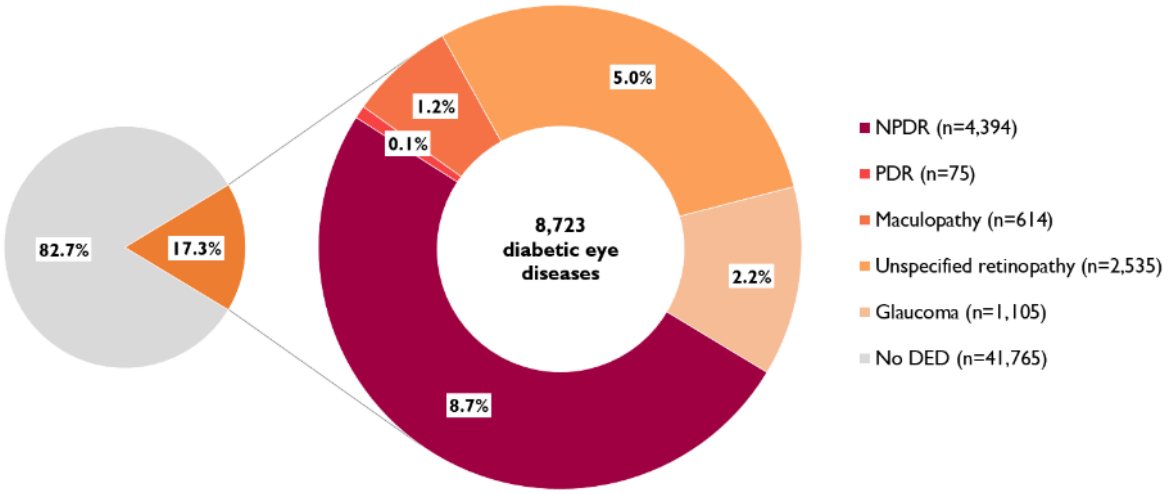
For each group in the risk tables, numbers in the first row denote number of events, while numbers in the second row denote number of patients at risk.

Figure 9.13 Age and sex adjusted odds ratios for the association between presence of prior DED at T2D diagnosis and cardiovascular death (N=52,379)



*Among patients without prior retinopathy at T2D diagnosis (N=52,289).

Figure 9.14 Final initial DED in patients without prior DED at T2D diagnosis (N=50,488)



Basic characteristics of patients with and without prior DEDs at baseline are compared in **Table 9.7 on page 275**. Patients with prior DED were older, more likely to be women and of white ethnicity.

Table 9.7 Demographic characteristics of patients with and without prior DED at T2D diagnosis

Characteristics	With prior DED (N=1,891)		Without prior DED (N=50,488)	
Duration of GP registration before entry, median (IQR) years	11.4	(7.6-16.7)	11.1	(6.8-15.9)
Year of diagnosis, n (%)				
1998-2003	799	(42.3)	22,042	(43.7)
2004-2006	629	(33.3)	16,768	(33.2)
2007-2009	463	(24.5)	11,678	(23.1)
Age at entry, mean (SD) years	72.6	(11.3)	62.8	(13.4)
Women, n (%)	960	(50.8)	22,640	(44.8)
White ethnicity, n (%)*	968	(51.2)	25,574	(50.7)
Most deprived quintile, n (%)*	377	(19.9)	10,063	(19.9)

*Proportion of non-missing data: 57.6% for ethnicity and 99.7% for deprivation.

9.4.4 Diabetic neuropathy

9.4.4.1 Diabetic neuropathy in incident T2D

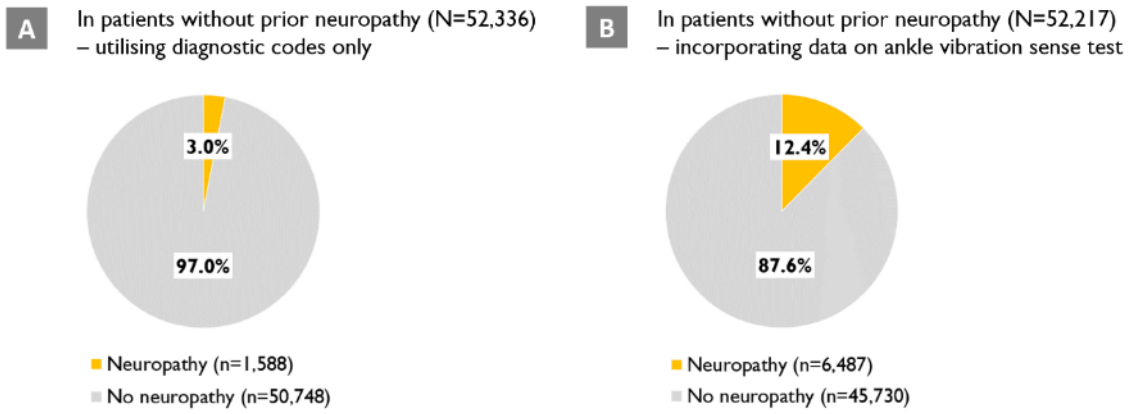
Identification of diabetic neuropathy from diagnosis codes. Diabetic neuropathy was defined as a composite of nerve disorders complicating diabetes which includes neuritis, peripheral neuropathy, autonomic neuropathy, neuropathic arthropathy, amyotrophy and unspecified diabetes-related neuropathy. Diabetic neuropathy was identified by diagnosis codes from either CPRD or HES, and the earliest record of the diagnosis determined the initial diabetic neuropathy. **Figure 9.15A on page 276** shows identification of diabetic neuropathy using both data sources; neuropathy was identified in only 1,631 (3.1%) patients, a small proportion of which occurred prior to or at T2D diagnosis.

Identification of diabetic neuropathy using AVS test. Compared with other microvascular complications, diabetic neuropathy is relatively underdiagnosed given the variable symptoms, thus may be less well-recorded. To improve capture of this complication, I sought to incorporate records on AVS test extracted from CPRD. Diabetic neuropathy was determined from the test results if there was absence of sense at least in one ankle or diminished sense in both ankles. **Figure 9.15B on page 276** shows that among the 31,775 T2D patients who were ever tested for their AVS, 5,597 (17.6%) showed abnormal results on dates separate to their T2D and neuropathy diagnosis. The intersection between identification by AVS test and by diagnosis code is displayed in **Figure 9.15C on page 276**.

Initial presentation of diabetic neuropathy. Initial diabetic neuropathy after T2D diagnosis occurred in 3.0% of patients when diagnosis codes were the only data used for identification (**Figure 9.16A on page 276**). The incidence of neuropathy increased considerably to 12.4% when AVS test results were utilised (**Figure 9.16B on page 276**). Of note, the number of patients in the two cohorts differed only slightly due to more patients being excluded by abnormal tests. These findings imply that harnessing the test to rule out prior neuropathy had little effect, but if used to capture incident neuropathy after T2D diagnosis it may lead to overestimation which will likely impact more on the configuration of initial microvascular complications (with competing diabetic nephropathy and retinopathy) rather than on the size of the population cohort for Study 5.

Figure 9.15 Identification of diabetic neuropathy in CALIBER's incident T2D cohort (N=52,379)

Figure 9.16 Initial diabetic neuropathy in patients without prior neuropathy at T2D diagnosis



Diagnostic validity of AVS test. To evaluate the diagnostic validity of the AVS test, sensitivity and PPV were estimated among patients who had ever received the test before being diagnosed later with neuropathy (N=31,483) by contrasting positive test results against neuropathy diagnosis. **Table 9.8 below** demonstrates that both sensitivity and PPV were low at 46.1% and 7.8%, respectively, suggesting that the AVS test is not good enough for identifying diabetic neuropathy. High specificity and negative predictive value (NPV) were irrelevant here since neuropathy is not diabetes-specific (i.e. it can be caused by other diseases) and I did not aim to rule out diabetic neuropathy using the test (i.e. normal result cannot guarantee the absence of *non*-peripheral neuropathy). In **Section 9.4.4.2 below,** the association with cardiovascular death between neuropathy captured using both methods was compared to confirm that the AVS test should not be utilised for neuropathy phenotyping.

Table 9.8 Diagnostic validity of AVS test for identification of diabetic neuropathy (N=31,483)

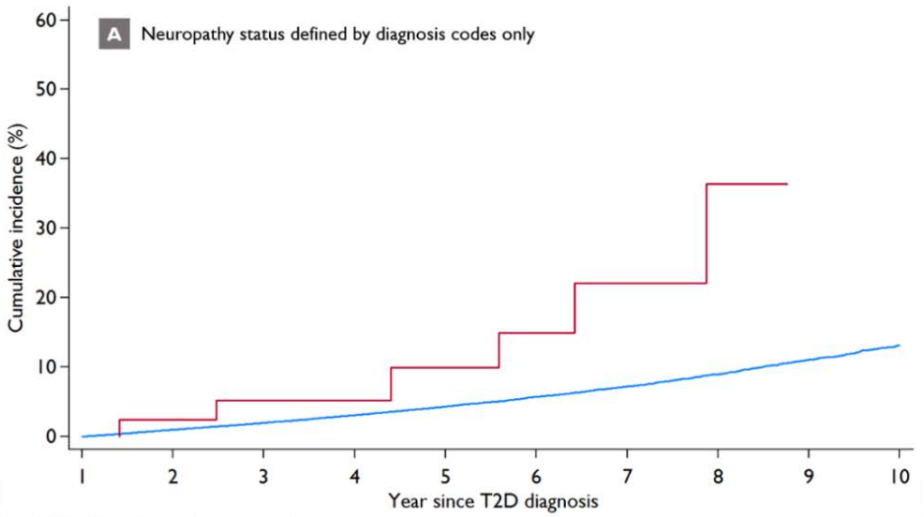
		Abnormal AVS test		
		Positive	Negative	
Diabetic neuropathy diagnosis	Yes	427	499	Sensitivity = **46.1%**
	No	5,018	25,539	Specificity = **83.6%**
		PPV = **7.8%**	NPV = **98.1%**	

AVS, ankle vibration test; NPV, negative predictive value; PPV, positive predictive value.

9.4.4.2 Diabetic neuropathy and risk of cardiovascular death

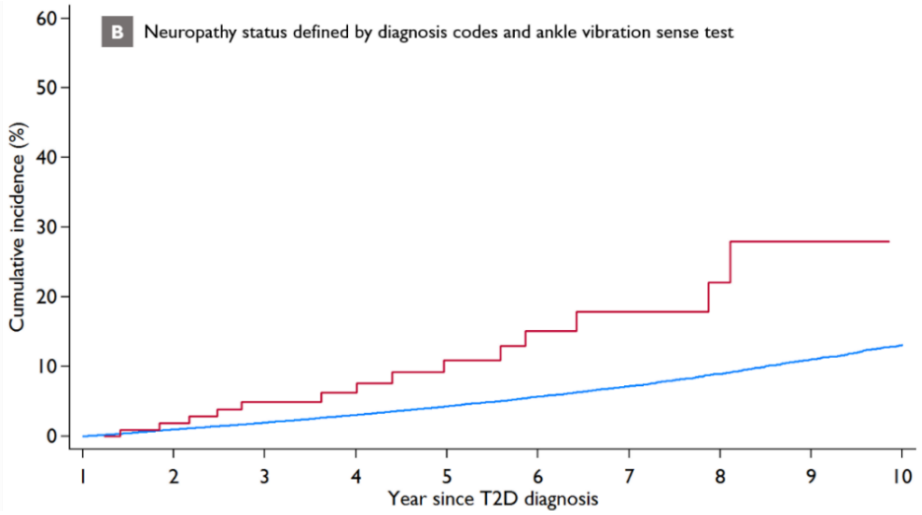
Incidence of cardiovascular death was higher among patients with prior diabetic neuropathy at T2D diagnosis (**Figures 9.17A and 9.17B on page 278**). Regression analysis showed that prior neuropathy was associated with a higher risk of cardiovascular death by nearly threefold (OR 2.87, 95% CI 1.16-7.09, p=0.023) when neuropathy was identified using diagnosis codes only. The increased risk was attenuated and lost statistical significance when the AVS test was also used for neuropathy phenotyping (OR 1.64, 95% CI 0.91-2.97, p=0.099) (**Figure 9.18 on page 279**). On the basis of this analysis and the sensitivity and PPV estimates, I decided to define neuropathy using diagnosis codes only.

Figure 9.17 Cumulative incidence curve for cardiovascular death by presence of prior neuropathy at T2D diagnosis (N=52,379)



Neuropathy status defined by diagnosis codes only											Total events*
No	469	399	382	339	302	238	201	159	91	52	2,670
	52,336	44,353	37,297	30,699	24,544	18,816	13,695	9,459	5,933	3,368	
Yes	1	1	0	1	1	1	1	0	0	0	6
	43	39	34	24	20	17	8	6	3	3	

*Included events until year 13

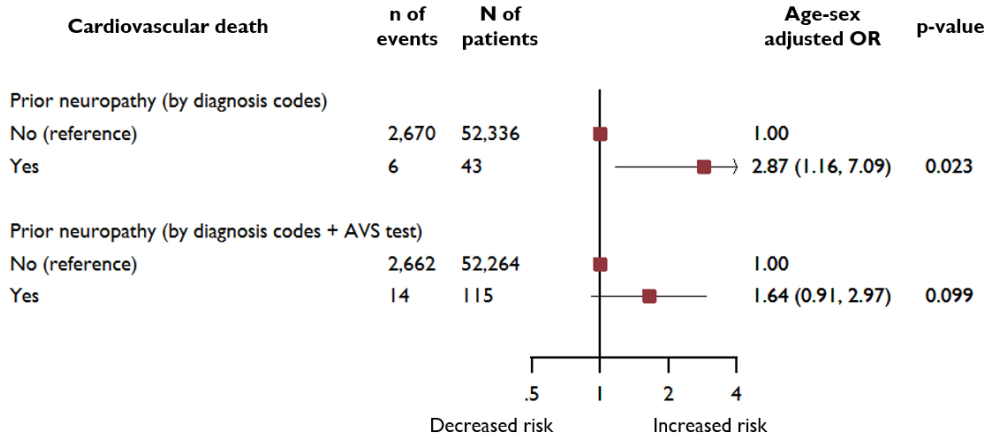


Neuropathy status defined by diagnosis codes and ankle vibration sense test											Total events*
No	468	397	381	337	301	238	201	158	91	52	2,662
	52,264	44,287	37,239	30,652	24,509	18,792	13,677	9,445	5,928	3,367	
Yes	2	3	1	3	2	1	1	1	0	0	14
	115	105	92	71	55	41	26	20	8	4	

*Included events until year 13

For each group in the risk tables, numbers in the first row denote number of events, while numbers in the second row denote number of patients at risk.

Figure 9.18 Age and sex adjusted odds ratios for the association between presence of prior neuropathy at T2D diagnosis and cardiovascular death (N=52,379)



AVS, ankle vibration sense.

The basic characteristics of patients with and without prior neuropathy are compared in **Table 9.9 below**. Patients with prior neuropathy were slightly older and the proportion of males was far higher compared with those without prior neuropathy.

Table 9.9 Demographic characteristics of patients with and without prior neuropathy at T2D diagnosis

Characteristics	With prior neuropathy (N=43)		Without prior neuropathy (N=52,336)	
Duration of GP registration before entry, median (IQR) years	13.3	(6.4-17.5)	11.1	(6.8-16.0)
Year of diagnosis, n (%)				
1998-2003	22	(51.2)	22,819	(43.6)
2004-2006	13	(30.2)	17,384	(33.2)
2007-2009	8	(18.6)	12,133	(23.2)
Age at entry, mean (SD) years	65.7	(12.6)	63.1	(13.4)
Women, n (%)	11	(25.6)	23,589	(45.1)
White ethnicity, n (%)*	22	(51.2)	26,520	(50.7)
Most deprived quintile, n (%)*	4	(9.3)	10,436	(19.9)

*Proportion of non-missing data: 57.6% for ethnicity and 99.7% for deprivation.

9.4.5 Initial presentation of microvascular diseases in incident T2D

After combining diabetic nephropathy, eye diseases and neuropathy occurring before or at T2D diagnosis, there were 2,533 patients known to have prior microvascular disease. These patients were older and more likely to be women compared with their counterparts who had no prior microvascular diseases (**Table 9.10 on page 280**).

Among patients without prior microvascular disease, incident microvascular disease was examined and its initial presentation was defined as the earliest occurrence of a microvascular disease after diagnosis of T2D. The earliest date of any microvascular outcomes was used to determine initial presentation. If multiple outcomes occurred on the same day, the hierarchical order below was used:

- CKD progression to stage G5
- CKD progression to stage G4
- CKD progression to stage G3b
- CKD progression to stage G3a
- PDR
- NPDR
- Maculopathy
- Unspecified retinopathy
- Glaucoma
- Neuropathy

Similarly to the initial presentation of CVDs (**Section 6.4.2 on pages 180-182**), the above hierarchy is ranked according to microvascular disease type followed by severity within each type.

Table 9.10 Demographic characteristics of patients with and without prior microvascular disease at T2D diagnosis

Characteristics	With prior MVD (N=2,533)		Without prior MVD (N=49,846)	
Duration of GP registration before entry, median (IQR) years	12.2	(8.5-17.3)	11.1	(6.7-15.9)
Year of diagnosis, n (%)				
1998-2003	897	(35.4)	21,944	(44.0)
2004-2006	868	(34.3)	16,529	(33.2)
2007-2009	768	(30.3)	11,373	(22.8)
Age at entry, mean (SD) years	73.3	(11.0)	62.6	(13.3)
Women, n (%)	1,334	(52.7)	22,266	(44.7)
White ethnicity, n (%)*	1,297	(51.2)	25,245	(50.7)
Most deprived quintile, n (%)*	472	(18.6)	9,968	(20.0)

*Proportion of non-missing data: 57.6% for ethnicity and 99.7% for deprivation. MVD, microvascular disease.

Among 49,846 patients without prior microvascular diseases, there were 11,766 initial presentations with microvascular outcomes after diagnosis of T2D. The most common presentations were NPDR (34.2%), unspecified retinopathy (19.1%) and CKD progression to stage G3a (12.7%) (**Figure 9.19 on page 281**).

The specific presentations will be simplified for the primary endpoints in Study 5 (**Chapter 10**) as diabetic nephropathy (CKD progressions), diabetic retinopathy (a composite of PDR, NPDR, maculopathy and unspecified retinopathy), diabetic neuropathy, microvascular triopathy (a composite of diabetic nephropathy, retinopathy and neuropathy), and all microvascular diseases (microvascular triopathy plus glaucoma). Cumulative incidence curves for these microvascular outcomes are compared in **Figure 9.20 on pages 281-282**; the highest incidence was observed for diabetic retinopathy, whilst the lowest for diabetic neuropathy. These findings somewhat contrasted with existing studies using a prevalent T2D cohort which generally showed higher incidence of diabetic nephropathy.[50,87,88] However, I used an incident T2D cohort, and microvascular diseases have been identified as initial rather than cumulative presentations with a distinctive definition for diabetic nephropathy – these may explain the difference with other studies and, importantly, add new knowledge.

Figure 9.19 Distribution of initial presentation of microvascular outcomes in patients without any microvascular diseases at T2D diagnosis (N=49,846)

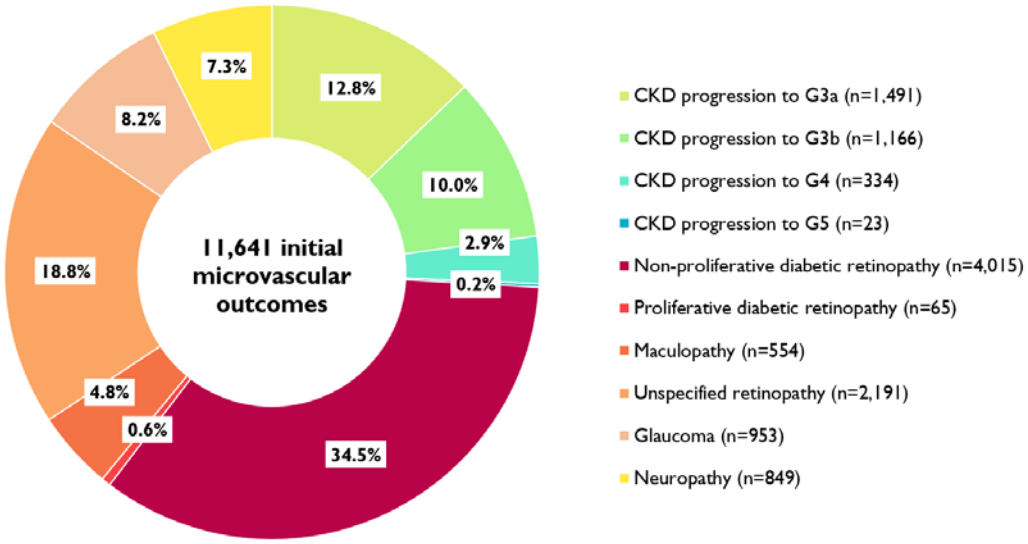
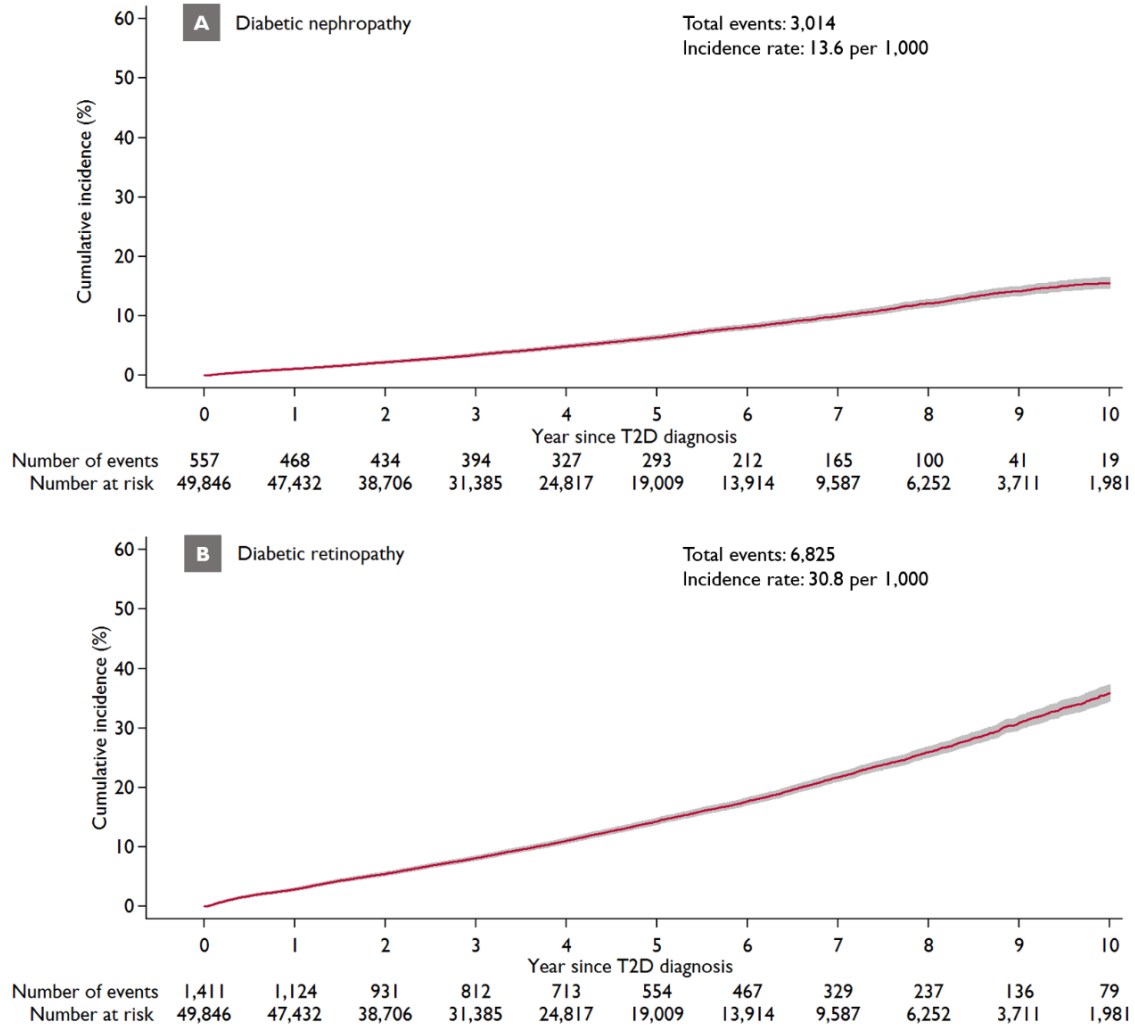
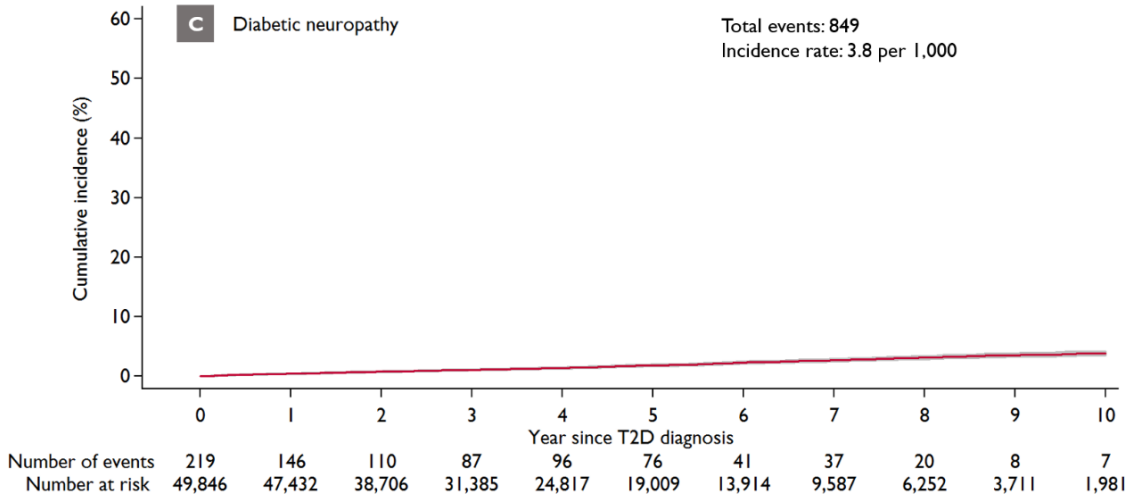
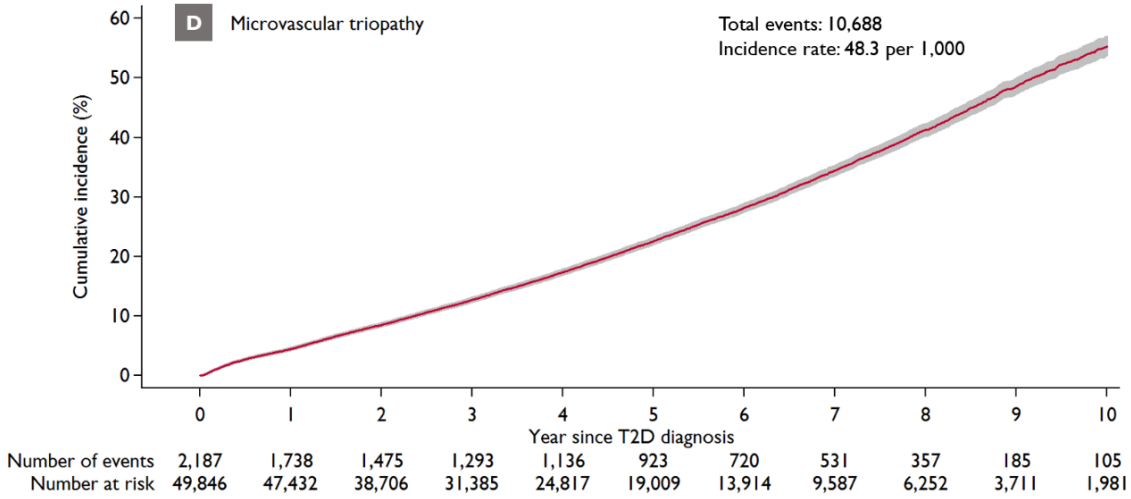
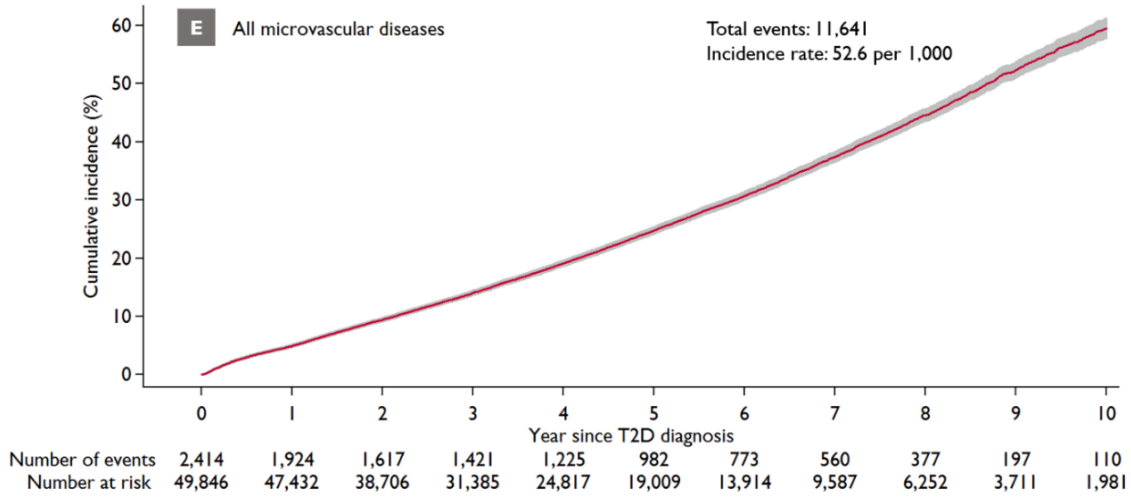


Figure 9.20 Cumulative incidence curves for simplified microvascular outcomes




C
Diabetic neuropathy
Total events: 849
Incidence rate: 3.8 per 1,000
Cumulative incidence (%)
0
10
20
30
40
50
60
0 1 2 3 4 5 6 7 8 9 10
Year since T2D diagnosis
Number of events 219 146 110 87 96 76 41 37 20 8 7
Number at risk 49,846 47,432 38,706 31,385 24,817 19,009 13,914 9,587 6,252 3,711 1,981


D
Microvascular triopathy
Total events: 10,688
Incidence rate: 48.3 per 1,000
Cumulative incidence (%)
0
10
20
30
40
50
60
0 1 2 3 4 5 6 7 8 9 10
Year since T2D diagnosis
Number of events 2,187 1,738 1,475 1,293 1,136 923 720 531 357 185 105
Number at risk 49,846 47,432 38,706 31,385 24,817 19,009 13,914 9,587 6,252 3,711 1,981


E
All microvascular diseases
Total events: 11,641
Incidence rate: 52.6 per 1,000
Cumulative incidence (%)
0
10
20
30
40
50
60
0 1 2 3 4 5 6 7 8 9 10
Year since T2D diagnosis
Number of events 2,414 1,924 1,617 1,421 1,225 982 773 560 377 197 110
Number at risk 49,846 47,432 38,706 31,385 24,817 19,009 13,914 9,587 6,252 3,711 1,981

9.5 Chapter summary

This chapter has presented microvascular phenotyping in CALIBER. Rather than being directly identified from CKD diagnosis, diabetic nephropathy could be alternatively defined as CKD progression, determined from eGFR-based CKD stage shift to a higher stage. The significant association between severity of CKD progression and cardiovascular death suggests some validity of the phenotype. Diabetic retinopathy and glaucoma were identified from diagnosis codes only and showed positive associations with cardiovascular death although they failed to reach statistical significance. Abnormal results from the AVS test could not be used to infer (and capture) diabetic neuropathy.

In the next chapter, the TITRE-HbA1c metric will be tested in the CALIBER's incident T2D cohort without prior microvascular disease in order to investigate whether long-term glycaemic control is associated with microvascular outcomes.

Chapter 10

Study 5 – Repeated measures of HbA1c, duration at glycaemic control and microvascular outcomes

> No matter what measures are taken, doctors will sometimes falter,
> and it isn't reasonable to ask that we achieve perfection.
> What is reasonable is to ask that we never cease to aim for it.
> — Atul Gawande, *Complications: A surgeon's notes on an imperfect science*

10.1 Chapter outline

This chapter presents Study 5 which sought to investigate the association between duration at glycaemic target and microvascular outcomes in CALIBER's incident T2D cohort. The TITRE-HbA1c estimation in **Chapter 7** was replicated in the cohort without prior microvascular diseases (as phenotyped in **Chapter 9**). Associations of other metrics for glycaemic control or variability with microvascular outcomes were examined for comparison.

10.2 Abstract

Background. Evidence consistently showed the benefits of snapshot glycaemic control to prevent microvascular disease in T2D patients. HbA1c routine monitoring should provide additional insights into long-term glycaemic control and how it may relate to microvascular complications, yet studies addressing such issues are lacking.

Methods. A CALIBER cohort of newly diagnosed T2D aged 30 years or older, with at least one year follow-up and without prior microvascular disease (CKD progression, DED or diabetic neuropathy) was established. Patients were followed up until censoring date or occurrence of a microvascular endpoint. Study endpoints were diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, microvascular triopathy and all microvascular outcomes. Glycaemic control was estimated longitudinally using the TITRE metric and HbA1c 48 mmol/mol as a cut-point. The risk of microvascular outcomes was estimated using logistic regressions with random effect, adjusted for baseline and follow-up covariates and weighted by duration of follow-up.

Results. The study cohort consisted of 47,432 patients with a median (IQR) follow-up of 4.2 (2.4-6.4) years during which there were 2,457 initial presentations with diabetic nephropathy, 5,414 with diabetic retinopathy and 630 with diabetic neuropathy. Compared with patients in the 3-<6 months TITRE category, those in the 0 months category had lower risk of nephropathy (OR 0.81, 95% CI 0.71-0.93) but higher risk of retinopathy (OR 1.25, 95% CI 1.12-1.39). Those in the 9-12 months TITRE category had lower risk of nephropathy (OR 0.76, 95% CI 0.64-0.90) but higher risk of retinopathy (OR 1.17, 95% CI 1.02-1.33). Non-missing TITRE categories showed marginal, linear associations with composite microvascular outcomes when the HbA1c cut-point was set higher.

Conclusions. The performance of the TITRE-HbA1c metric for risk assessment of microvascular disease did not illuminate a clear pattern of associations. An inverted J-shaped association was observed for diabetic nephropathy while a J-shaped association was observed for diabetic retinopathy. The limitations of this study were discussed.

10.3 Introduction

Evidence from clinical trials demonstrated mixed results for the association between glycaemic control and cardiovascular diseases among T2D patients, but the association with microvascular diseases has been established.[49,50,88] Glycaemic control has been commonly defined in existing studies as achieving recommended HbA1c target cross-sectionally. The availability of electronic HbA1c records from routine monitoring at primary care level for T2D patients could provide further insights into how glycaemic control is sustained over time.

It is demonstrated in Study 4 (**Chapter 8**) that duration at tighter glycaemic control was marginally associated with cardiovascular outcomes. Whether stronger association can be found with microvascular diseases – which typically occur at a later time than CVDs – is unclear. In this

chapter, the TITRE-HbA1c metric developed in **Chapter 7** to define longitudinal glycaemic control was tested for its association with microvascular outcomes.

10.4 Methods

10.4.1 Study population and inclusion criteria

The population cohort for Study 5 was drawn from CALIBER (**Section 3.9 on pages 111-113**). Newly diagnosed T2D patients aged 30 years or over with at least one year follow-up were included. Patients with microvascular disease prior to the date of T2D diagnosis were excluded. Microvascular diseases refer to CKD progression, DEDs and diabetic neuropathy as identified in **Chapter 9**.

10.4.2 Follow-up and endpoints

Eligible patients were followed-up while registered at a practice until the first occurrence of a microvascular outcome, death or transfer out of the practice.

Primary endpoints were diabetic nephropathy (CKD progressions), diabetic retinopathy (including maculopathy), diabetic neuropathy, microvascular triopathy (a composite of diabetic nephropathy, retinopathy and neuropathy) and all microvascular outcomes (a composite of diabetic nephropathy, DEDs and diabetic neuropathy). Secondary endpoints were specific CKD progressions (to stages G3a, G3b and G4/G5), NPDR, maculopathy and glaucoma.

10.4.3 Exposures

10.4.3.1 HbA1c levels

A number of existing glycaemic control metrics were used for comparison with the main exposure (**Section 10.4.3.3 on page 287**) in assessing the risk of microvascular endpoints. The metrics included baseline HbA1c (the most recent HbA1c value within a year prior to T2D diagnosis), snapshot glycaemic control within the first year since T2D diagnosis (whether HbA1c targets of 48 mmol/mol and 58 mmol/mol were achieved), the latest HbA1c value during follow-up, extended baseline (average of HbA1c values within 3 years of T2D diagnosis), mean HbA1c (average of all HbA1c values measured during follow-up) and updated mean HbA1c (re-estimation of averaged HbA1c when a new record became available). For snapshot control within the first year, patients were classified into three groups: at target (reference group), above target and unknown, whereas for other metrics patients were categorised into five groups: <48 mmol/mol, 48-<58 mmol/mol (reference group), 58-<68 mmol/mol, ≥68 mmol/mol and unknown.

10.4.3.2 Glycaemic variability

A meta-analysis demonstrated that greater glycaemic variability is independently associated with CKD progression in T2D patients.[314] Studies examining the association of glycaemic variability and peripheral neuropathy are lacking, yet CAN in T2D patients was reported to have a similar as-

sociation to CKD progression.[315] Independent association was also found for retinopathy in the T1D population but not in T2D.[316-318] Thus, as in **Chapter 8**, I analysed intrapersonal, visit-to-visit HbA1c variation in terms of its relationship with microvascular disease. Only patients with at least two HbA1c measurements after T2D diagnosis were included. Glycaemic variability metrics considered in this study were adjusted SD, CV, VIM, ARV, SV and mean absolute residual of serially measured HbA1c, the definition and calculation of which has been presented in **Section 1.1.3.2 on pages 30-35** and **Appendix B on page 325**. Distribution of glycaemic variation values measured using these metrics were inspected and transformed where necessary. Patients were classified according to quartiles of the metrics with the 1st quartile (i.e. least variability) being the reference group.

10.4.3.3 Duration at glycaemic target

The main exposure in Study 5 was duration of glycaemic control, estimated using TITRE metric from repeated HbA1c records in CPRD. The TITRE-HbA1c calculation has been detailed in **Chapter 7**. In short, the TITRE calculation time window was firstly determined from the date of the first and last HbA1c measures during patients' follow-up. The interval between two consecutive HbA1c measures was then individually calculated. Any at-target intervals exceeding one year were ignored and intervals crossing the HbA1c anniversaries were calculated separately on a yearly basis. Yearly duration at target was then averaged and expressed as a percentage, before being summed up and re-averaged over the TITRE calculation time window. The TITRE estimate was finally converted into its equivalent month and classified into six categories: missing, 0 months, <3 months, 3-<6 months, 6-<9 months and 9-12 months. The missing TITRE category referred to patients who had no HbA1c records during the follow-up period, had a single follow-up HbA1c record only without a known baseline value or had intervals which were all above one year throughout the follow-up period. The 3-<6 months category was chosen as a reference group to enable assessment of microvascular risks in patient groups with poorer and better glycaemic control at a time.

10.4.4 Covariates

Baseline covariates included demographic variables (age at T2D diagnosis, gender, ethnicity and deprivation), cardiovascular risk factors (body mass index, smoking status, blood pressure, total and HDL cholesterols) and prescriptions of cardiovascular drug. Covariates during the follow-up period were class of initial diabetes medication and time to first prescription of diabetes medication. Other variables considered in the multivariate analysis were the total number of HbA1c measures, annual frequency of hypoglycaemic events (time-varying) and snapshot glycaemic control within the first year from T2D diagnosis. All the covariates were extracted from CPRD.

10.4.5 Statistical analysis

Patient characteristics were tabulated and statistically compared, as appropriate, using one-way analysis of variance or Kruskal-Wallis non-parametric tests for continuous variables and using χ^2

tests for categorical variables. Cumulative incidence curves for microvascular outcomes by TITRE category were generated using the Fine and Gray competing risks regression model.

Mixed logistic regression was used to examine the association of duration at glycaemic target and each microvascular outcome, with GP practice being the cluster variable. Estimates were adjusted for covariates and weighted by duration of follow-up. Missing baseline covariates were 5-multiply imputed using a chained equation method (**Section 3.13.1 on pages 124-125**). Similar analysis was performed to assess the association of HbA1c levels and variability measured using different metrics. All analyses were performed using Stata 13.0.

10.4.6 Sensitivity and subgroup analysis

Sensitivity analyses were performed by excluding patients with 100% TITRE values, excluding patients whose T2D was first identified from HES, using a less stringent HbA1c target (≤58 mmol/mol) to define TITRE, addition into the model of snapshot glycaemic control within the first year, mean HbA1c and adjusted SD of HbA1c, and changing the reference group to 0 months TITRE category. Subgroup analysis was performed according to the prescription of RAAS agents at baseline.

10.5 Results

10.5.1 TITRE-HbA1c estimation in eligible patients for Study 5

Of the 49,846 patients free from prior microvascular diseases (as identified in **Section 9.4.5 on pages 279-282**), 2,414 (4.8%) were excluded due to having less than one year follow-up. Of the 47,432 patients eligible for TITRE analysis (median follow-up 4.2 (IQR 2.4-6.4) years), 7,280 (15.3%) were classified into the missing TITRE category for several reasons (**Figure 10.1 on page 290**). TITRE estimates were calculated in 40,152 patients with a median time window for TITRE calculation of 3.3 (IQR 1.7-5.4) years and a median TITRE value of 10.1% (IQR 0%-47.3%).

Similarly to TITRE analysis in the CVD-free cohort (**Chapter 7**), non-missing TITRE distribution was predominated by 0% values (N=14,884, 31.4%) and roughly J-shaped (**Appendix F, Figure F10.1A on page 375**). When a higher HbA1c cut-point (58 mmol/mol) was set for TITRE calculation, the domination of 0% values was replaced by 100% values, generating a mirrored J-shaped curve (**Figure F10.1B on page 375**).

Distribution of patients without prior microvascular disease by TITRE-HbA1c category is plotted in **Figure F10.2A on page 375** with the lowest proportions found in the 3-<6 months (12.1%) and 6-<9 months (7.6%) categories. Of those in the 9-12 months category, only 2,448 (41.3%) had less than 100% TITRE values. When a less stringent cut-point was applied, the distribution changed considerably with the 0 months and <3 months categories being the lowest proportions while the 9-12 months category predominated with nearly one-third of the proportion (**Figure F10.2B on page 375**); these features differed substantially from analysis in the patient cohort without prior CVDs (**Figure 7.10 on page 227**), particularly for non-missing and non-zero categories.

10.5.2 Characteristics of eligible patients

Characteristics of patients who were eligible for and excluded from Study 5 were compared in **Table 10.1 on page 291**. Patients who were excluded were older and more likely to be women, had higher comorbidities and were more likely to be treated with cardiovascular medication but less likely to be treated for diabetes.

Patient characteristics according to the TITRE categories are presented in **Table 10.2 on pages 292-293**. Duration of follow-up was shortest in patients in the missing category with a median (IQR) of 2.8 (1.7-4.8) years, a quarter of whom were first identified as having T2D through secondary care. Patients in the 0 months and <3 months categories were younger compared with those in the missing and higher categories. Proportions of white ethnicity were lower in the missing (43.3%) and 0 months (48.5%) categories compared with the higher TITRE categories. In contrast, the proportion of current smoker was highest in the 0 months category (10.0%). Higher comorbidities were observed in the missing category, but cardiovascular treatment was higher in the TITRE categories. Blood pressure and lipid profiles appeared to be broadly similar across the TITRE categories. Patients in the 0 months category had the highest baseline and follow-up HbA1c (77.8 and 70.1 mmol/mol, respectively) and the smallest proportion meeting glycaemic target (1.4%) and were least prescribed with diabetes medication.

Figure 10.1 Patient flow chart for TITRE-HbA1c calculation for Study 5

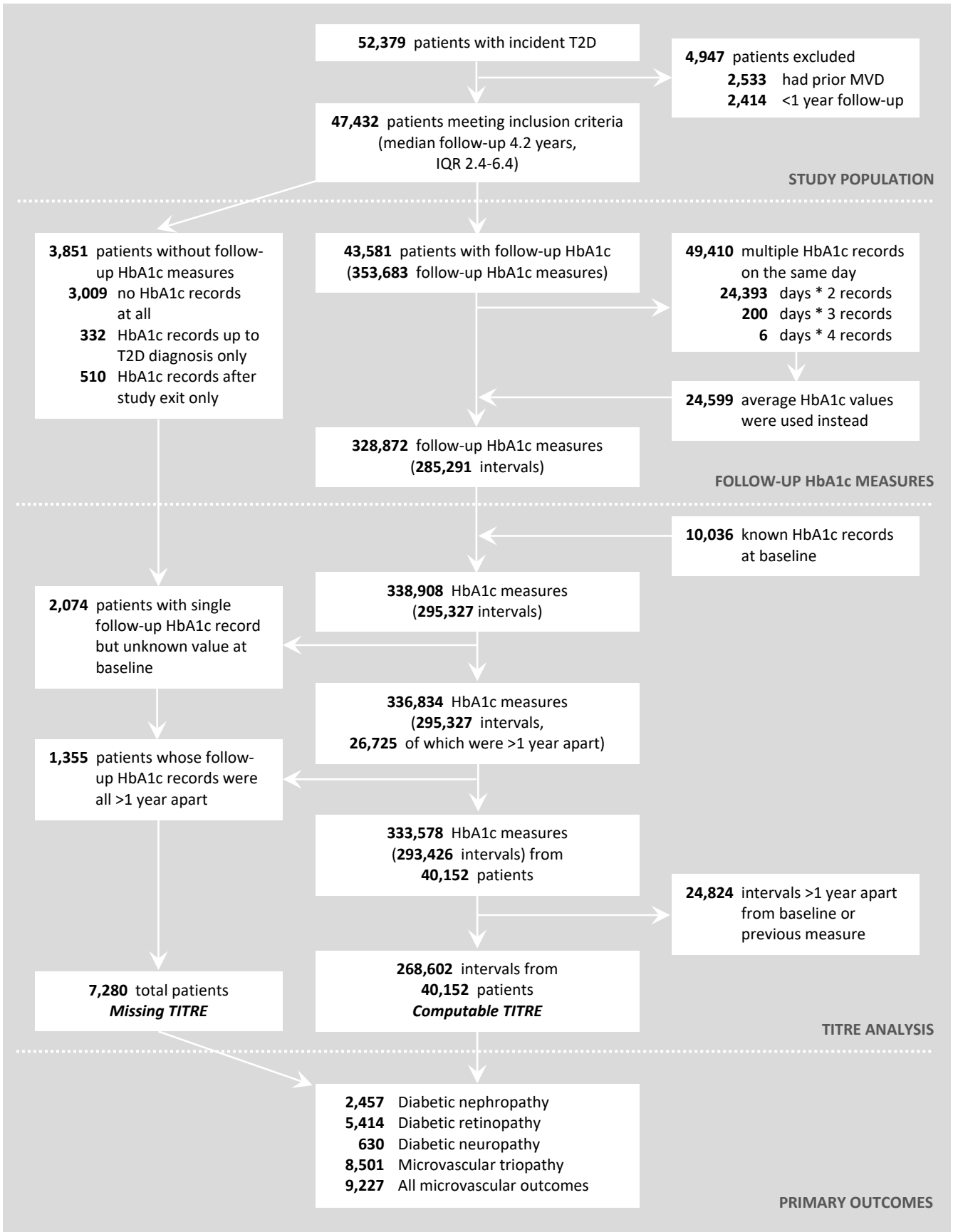


Table 10.1 Characteristics of eligible versus excluded patients for Study 5

Characteristics	Eligible patients (N=47,432)		Excluded patients (N=4,947)	
Duration of GP registration, median (IQR) years	11.0	(6.6-15.8)	11.7	(8.5-17.4)
Year of diagnosis, n (%)				
1998-2003	21,157	(44.6)	1,684	(34.0)
2004-2006	15,691	(33.1)	1,706	(34.5)
2007-2009	10,584	(22.3)	1,557	(31.5)
Age at entry, mean (SD) years	62.5	(13.4)	69.6	(12.4)
Women, n (%)	21,206	(44.7)	2,394	(48.4)
White ethnicity, n (%)*	23,964	(50.5)	2,578	(52.1)
Most deprived quintile, n (%)*	9,324	(20.1)	1,116	(18.6)
Smoking status, n (%)*				
Never	7,423	(15.7)	962	(19.5)
Ex-smoker	6,627	(14.0)	953	(19.3)
Current smoker	4,073	(8.6)	396	(8.0)
Baseline records, n (%)				
HbA1c	10,281	(21.7)	1,189	(24.0)
Blood pressure	30,395	(64.1)	3,700	(74.8)
Total cholesterol	24,199	(51.0)	2,956	(59.8)
HDL cholesterol	18,855	(39.8)	2,397	(48.5)
Body mass index	16,681	(35.2)	1,987	(40.2)
Baseline value				
HbA1c, mean (SD) mmol/mol	67.0	(24.1)	65.3	(25.0)
Systolic blood pressure, mean (SD) mmHg	145.0	(19.4)	144.9	(20.5)
Diastolic blood pressure, mean (SD) mmHg	83.6	(11.1)	81.0	(11.6)
Total cholesterol, mean (SD) mmol/L	5.5	(1.3)	5.3	(1.4)
HDL cholesterol, mean (SD) mmol/L	1.2	(0.4)	1.3	(0.4)
Body mass index, mean (SD) kg/m^2	32.0	(6.6)	30.6	(6.4)
Cardiovascular diseases, n (%)				
Coronary heart disease	8,161	(17.2)	1,290	(26.1)
Stroke	2,600	(5.5)	467	(9.4)
Peripheral arterial disease	1,406	(3.0)	298	(6.0)
Heart failure	1,727	(3.6)	460	(9.3)
COPD	3,775	(8.0)	542	(11.0)
Baseline cardiovascular medications, n (%)				
Blood pressure lowering medications	20,307	(42.8)	2,874	(58.1)
Lipid lowering medications	8,471	(17.9)	1,391	(28.1)
Antiplatelets	7,807	(16.5)	1,327	(26.8)
Class of first diabetes medication prescribed, n (%)				
Never prescribed	11,536	(24.3)	1,589	(32.1)
Insulin	539	(1.1)	56	(1.1)
Metformin†	27,176	(57.3)	2,380	(48.1)
Sulphonylureas	7,663	(16.2)	875	(17.7)
Thiazolidinediones	387	(0.8)	31	(0.6)
Acarbose	54	(0.1)	7	(0.1)
DPP4 inhibitors	7	(0.0)	1	(0.0)
GLP1 agonists	3	(0.0)	-	
Meglitinides	67	(0.1)	8	(0.2)
Time to initial diabetes medication prescription, median (IQR) months‡	4.6	(0.4-25.3)	2.2	(0.2-15.2)

*Missing values: deprivation 0.3% (142 eligible patients) and 0.2% (11 excluded patients), ethnicity 42.4% (20,098 eligible patients) and 43.0% (2,128 excluded patients), smoking status 61.8% (29,309 eligible patients) and 53.3% (2,636 patients).
†Includes combination with thiazolidinedione or DPP4 inhibitor. ‡Among patients ever prescribed: 75.7% (35,896 eligible patients) and 67.9% (3,358 excluded patients).

Table 10.2 Patient characteristics by TITRE categories (N=47,432)*

Characteristic	Missing (N=7,280)		0 months (N=14,884)		<3 months (N=9,985)		3-<6 months (N=5,754)		6-<9 months (N=3,608)		9-12 months (N=5,921)	
Duration of GP registration before entry (years)	8.4	(3.2-13.1)	10.6	(5.9-15.3)	11.6	(8.5-16.7)	11.5	(8.5-16.9)	11.4	(8.2-16.5)	11.3	(7.2-16.5)
Duration of follow-up (years)	2.8	(1.7-4.8)	4.0	(2.3-6.3)	5.3	(3.4-7.3)	4.9	(3.1-6.8)	4.3	(2.8-6.1)	2.8	(1.8-4.6)
TITRE calculation time window (years)	N/A		2.7	(1.4-4.8)	4.5	(2.7-6.4)	4.1	(2.4-5.8)	3.6	(2.1-5.4)	1.8	(1.0-3.3)
Demographic												
Age at entry**	65.3	(15.7)	59.6	(13.1)	60.9	(12.4)	62.9	(12.3)	63.7	(12.3)	65.5	(12.2)
Women	3,461	(47.3)	6,177	(41.5)	4,199	(42.1)	2,519	(43.8)	1,588	(44.0)	2,693	(45.5)
White ethnicity	3,151	(43.3)	7,214	(48.5)	4,981	(49.9)	2,944	(51.2)	1,915	(53.1)	3,080	(52.0)
Most deprived	1,629	(22.4)	2,895	(19.5)	1,791	(17.9)	1,073	(18.7)	700	(19.4)	1,092	(18.4)
Cardiovascular risk factors at baseline												
Ex-smoker	673	(9.2)	1,911	(12.8)	1,332	(13.3)	853	(14.8)	629	(17.4)	1,229	(20.8)
Current smoker	536	(7.4)	1,491	(10.0)	807	(8.1)	459	(8.0)	280	(7.8)	500	(8.4)
Body mass index**	30.7	(7.5)	32.3	(6.6)	32.3	(6.3)	32.3	(6.5)	31.9	(6.7)	31.4	(6.3)
Systolic blood pressure**	143.3	(20.4)	145.1	(19.9)	146.0	(19.4)	145.8	(18.7)	145.4	(18.9)	144.0	(18.6)
Total cholesterol**	5.3	(1.3)	5.6	(1.4)	5.6	(1.3)	5.5	(1.2)	5.4	(1.3)	5.3	(1.2)
HDL cholesterol**	1.3	(0.4)	1.2	(0.3)	1.2	(0.3)	1.2	(0.4)	1.2	(0.4)	1.2	(0.4)
Comorbidities												
Coronary heart disease	350	(4.8)	449	(3.0)	314	(3.1)	166	(2.9)	111	(3.1)	183	(3.1)
Stroke	144	(2.0)	116	(0.8)	88	(0.9)	56	(1.0)	36	(1.0)	79	(1.3)
Heart failure	106	(1.5)	91	(0.6)	60	(0.6)	38	(0.7)	21	(0.6)	41	(0.7)
Peripheral arterial disease	55	(0.8)	63	(0.4)	49	(0.5)	30	(0.5)	18	(0.5)	32	(0.5)
Chronic obstructive pulmonary disease	580	(8.0)	1,083	(7.3)	790	(7.9)	514	(8.9)	298	(8.3)	510	(8.6)
Cardiovascular medications at baseline												
Antihypertensive	2,421	(33.3)	5,412	(36.4)	4,410	(44.2)	2,911	(50.6)	1,881	(52.1)	3,272	(55.3)
Lipid lowering drug	921	(12.7)	2,410	(16.2)	1,726	(17.3)	1,153	(20.0)	749	(20.8)	1,512	(25.5)
Antiplatelet	1,149	(15.8)	2,009	(13.5)	1,574	(15.8)	1,057	(18.4)	708	(19.6)	1,310	(22.1)
Initial CKD stage												
G1†	993	(19.9)	3,281	(30.1)	1,923	(25.5)	1,006	(22.4)	615	(21.8)	882	(19.6)
G2†	2,523	(50.7)	5,843	(53.5)	4,273	(56.7)	2,615	(58.3)	1,615	(57.2)	2,631	(58.6)
G3a†	919	(18.5)	1,372	(12.6)	1,067	(14.2)	663	(14.8)	447	(15.8)	733	(16.3)
G3b†	437	(8.8)	353	(3.2)	237	(3.1)	182	(4.0)	131	(4.6)	205	(4.6)
G4/G5†	107	(2.1)	70	(0.6)	41	(0.5)	23	(0.5)	18	(0.6)	41	(0.9)
Had non-missing eGFR	4,979	(68.4)	10,919	(73.4)	7,541	(75.5)	4,489	(78.0)	2,826	(78.3)	4,492	(75.9)

HbA1c measurements												
Yearly frequency of tests**	0.2[‡]	(0.3)	1.5	(0.7)	1.6	(0.6)	1.6	(0.6)	1.6	(0.6)	1.5	(0.6)
Non-missing baseline HbA1c	479	(6.6)	3,380	(22.7)	2,460	(24.6)	1,454	(25.3)	1,017	(28.2)	1,491	(25.2)
Baseline HbA1c**	58.0	(21.7)	77.8	(23.4)	67.1	(23.3)	63.2	(22.6)	62.1	(22.8)	52.5	(18.6)
Initial follow-up HbA1c**	54.0[‡]	(19.3)	70.1	(20.1)	59.1	(19.3)	54.6	(18.6)	53.1	(180)	46.0	(13.5)
Time to initial follow-up HbA1c (months)	12.8	(3.6-30.9)	3.5	(1.4-12.2)	3.2	(1.2-8.4)	3.0	(1.2-7.4)	2.8	(1.1-6.1)	3.0	(1.2-5.9)
Non-missing follow-up HbA1c within first year	1,617[‡]	(22.2)	11,118	(74.7)	8,079	(81.9)	4,768	(82.9)	3,092	(85.7)	5,090	(86.0)
Snapshot control within first year	801[‡]	(11.0)	209	(1.4)	4,569	(45.8)	3,350	(58.2)	2,408	(66.7)	4,936	(83.4)
Initial diabetes medications during follow-up												
Never prescribed	4,178	(57.4)	964	(6.5)	1,122	(11.2)	1,195	(20.8)	1,068	(29.6)	3,009	(50.8)
Insulin	78	(1.1)	219	(1.5)	113	(1.1)	54	(1.0)	35	(1.0)	40	(0.7)
Metformin[§]	1,907	(26.2)	10,561	(71.0)	6,775	(67.9)	3,577	(62.2)	2,025	(56.1)	2,331	(39.4)
Sulphonylureas	1,060	(14.6)	2,922	(19.6)	1,866	(18.7)	876	(15.2)	440	(12.2)	499	(8.4)
Thiazolidinediones	37	(0.5)	166	(1.1)	90	(0.9)	39	(0.7)	30	(0.8)	25	(0.4)
Acarbose	6	(0.1)	149	(0.1)	11	(0.1)	8	(0.1)	5	(0.1)	10	(0.2)
DPP4 inhibitors	2	(0.0)	3	(0.0)	2	(0.0)	-		-		-	
GLP1 agonists	1	(0.0)	-		-		-		1	(0.0)	1	(0.0)
Meglitinides	11	(0.2)	35	(0.2)	6	(0.1)	5	(0.1)	4	(0.1)	6	(0.1)
Time to initial prescription (months)[¶]	8.1	(0.5-35.1)	4.5	(0.4-21.1)	7.1	(0.6-28.2)	6.3	(0.4-32.7)	3.0	(0.2-23.6)	0.9	(0-13.2)
Data source for initial T2D diagnosis												
CPRD	4,386	(60.2)	14,070	(94.5)	9,501	(95.1)	5,498	(95.5)	3,425	(94.9)	5612	(94.8)
HES	2,894	(39.8)	814	(5.5)	484	(4.9)	256	(4.5)	183	(5.1)	309	(5.2)

*Estimates are number (%) for categorical variables and median (IQR) for continuous variables unless marked with ** which are mean (SD). [†]Among patients with non-missing eGFR. [‡]Not missing due to incorporation of patients with all lengthy intervals throughout follow-up period into this category. [§]Includes combination with thiazolidinedione or DPP4 inhibitor. [¶]Among patients ever prescribed.

Proportion of non-missing data: 56.2% for ethnicity, 96.9% for deprivation, 38.2% for smoking status, 35.2% for body mass index, 64.1% for blood pressure, 51.0% for total cholesterol, 39.8% for HDL cholesterol.

10.5.3 Incidence of microvascular outcomes in eligible patients

The distribution of initial presentation with specific microvascular outcome in eligible patients for Study 5 was plotted in **Figure 10.2 below**. There were 2,457 cases (5.2%) with diabetic nephropathy, 5,414 (11.4%) with diabetic retinopathy, 630 (1.3%) with diabetic neuropathy, 8,501 (17.9%) with microvascular triopathy and 726 (1.5%) with glaucoma. These proportions differed slightly from the original cohort before applying the exclusion criteria (**Figure 9.19 on page 281**). Cumulative incidence curves for microvascular outcomes were not directly proportional to TITRE categories (**Figure 10.3 on page 295 and Figure F10.4 on page 377**).

The median time to microvascular outcomes according to TITRE category was compared in **Table F10.1 on page 376**. Patients in the <3 months and 3-<6 months TITRE categories appeared to broadly share the longest time (around 5 years) to microvascular event, whereas those in the missing and 9-12 months categories broadly shared the shortest time to event (below three years).

Figure F10.3 on page 376 compares the proportion of TITRE categories for microvascular endpoints. The proportion of missing TITRE categories was highest for diabetic neuropathy, while the proportion for 0 months was highest for diabetic retinopathy. Proportion for longer TITRE categories was higher for diabetic nephropathy.

Figure 10.2 Distribution of specific microvascular diseases in CALIBER's newly diagnosed T2D cohort without prior microvascular disease (N=47,432)

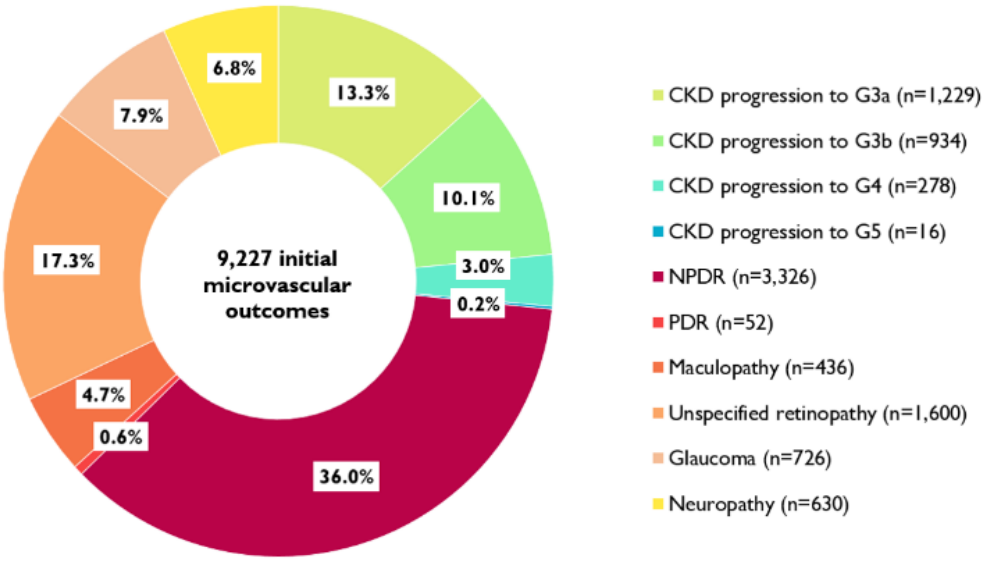
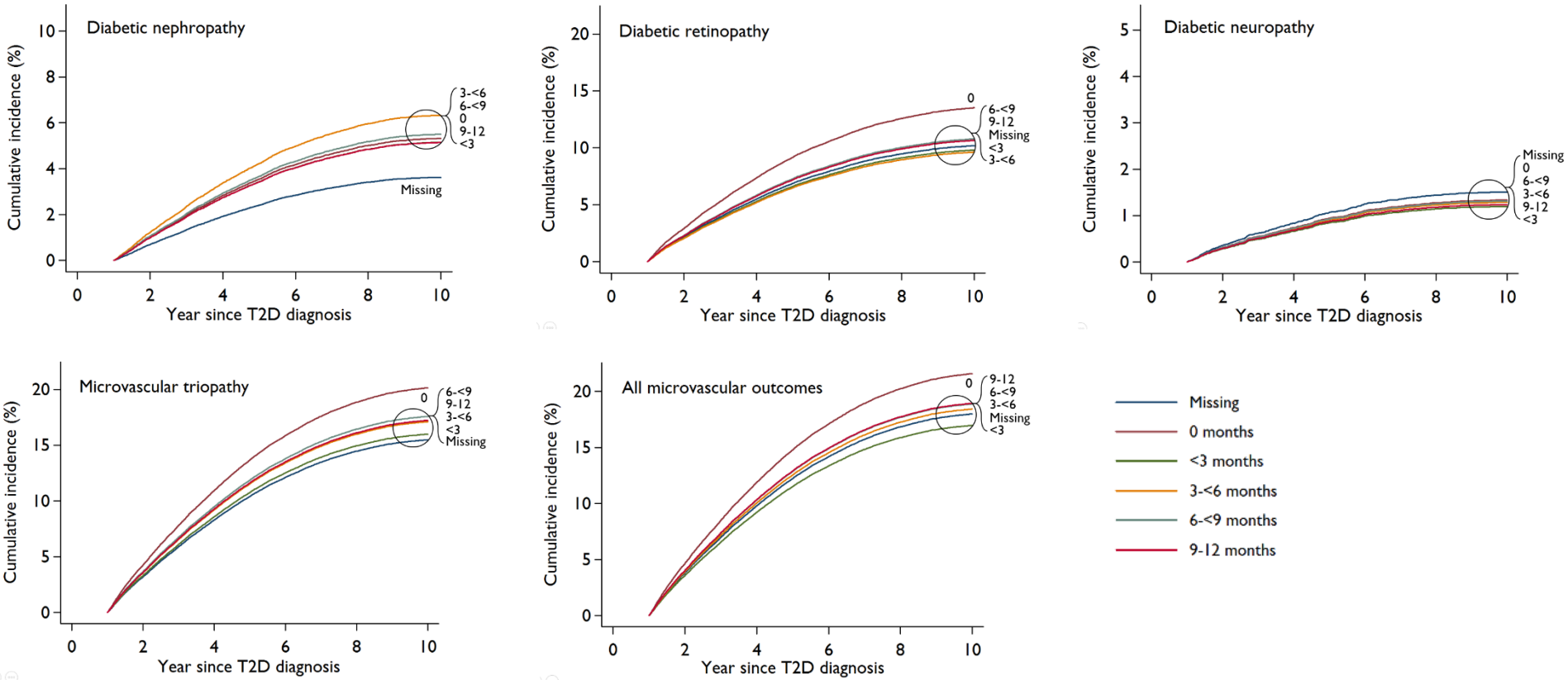


Figure 10.3 Cumulative incidence curves for primary microvascular endpoints by TITRE category



10.5.4 HbA1c levels and microvascular outcomes

Similarly to Study 4 (**Chapter 8**), HbA1c values measured using different glycaemic control metrics were approximately normally distributed with all means of above 55 mmol/mol (**Figure F10. 5 on page 378**). Unlike Study 4, however, associations between HbA1c level category and microvascular outcomes showed inconsistent results across glycaemic control metrics. Ignoring the missing category, the J-shaped association of HbA1c category was seen for diabetic neuropathy across the metrics (**Figure 10.4 on page 298**). For diabetic retinopathy and nephropathy, the measurement by baseline HbA1c value and snapshot glycaemic control within the first year still showed the anticipated results but lost its pattern with mean, updated mean and latest HbA1c values, the lowest risk being seen in the missing category (**Figure F10.6 on page 379**). With only a small number for diabetic neuropathy, the associations of HbA1c level category with microvascular triopathy and all microvascular outcomes were highly influenced by diabetic nephropathy and retinopathy; when the missing category was ignored, however, a J-shaped association was consistently observed across the metrics

Analyses for secondary endpoints provide more insights. Snapshot glycaemic control within the first year appeared to be best used to assess CKD progression at earlier stages (G3a/G3b); conversely, other glycaemic control metrics tended to give better estimates for the association with progression to final stage (**Figure F10.6 on page 379**). All glycaemic control metrics also seemed to be appropriate for estimating risk of maculopathy and glaucoma, but not NPDR unless ignoring the missing category.

10.5.5 Glycaemic variability and microvascular outcomes

Glycaemic variability was measured in 41,507 patients who had at least two HbA1c records during follow-up. Similarly to Study 4, HbA1c variation values measured using different variability metrics all showed skewed distribution with medians ranging from 6.0 to 12.7 mmol/mol and became somewhat normally distributed by square root transformation with medians ranging from 2.6 to 3.7 mmol/mol (**Figure F10.7 on page 382**).

Analyses of the association with microvascular outcomes showed no differences between quartiles of the original and transformed HbA1c variation values (data not shown). **Figure 10.5 on page 299** shows the association between quartiles of the original HbA1c variability values measured using different metrics and microvascular outcomes. Glycaemic variability measured according to adjusted SD, CV and ARV metrics showed a J-shaped pattern of association with diabetic neuropathy. For retinopathy, linear association was observed by variability measurement using adjusted SD and mean absolute residual. A small risk reduction was observed for retinopathy and nephropathy in the 4th quartile when measured using all other metrics, but the paradoxical pattern was most pronounced for retinopathy using the VIM metric. Association between glycaemic variability and composite primary endpoints was greatly influenced by diabetic retinopathy and nephropathy.

Analysis for secondary endpoints suggested that glycaemic variability measured using adjusted SD, VIM, ARV and mean absolute residual metrics was linearly associated with CKD progression to stages G4/G5. The pattern of association for diabetic retinopathy was greatly influenced by NPDR. Curvilinear pattern of association was seen for glaucoma when measured according to most metrics (**Figure F10.8 on page 384**).

10.5.6 Duration at glycaemic target and microvascular outcomes

In the analysis excluding patients with missing TITRE (N=40,152), TITRE values (in %) showed significant associations all microvascular endpoints (particularly when the less stringent HbA1c cut-point was applied), except for diabetic neuropathy. Every 1% increase of TITRE value was associated with tiny but significant risk reductions, but rescaling the estimates by a 10% or 25% increase provides more meaningful interpretation (**Figure 10.6 on page 301**). Association with individual stage of CKD progression, however, failed to reach statistical significance (**Figure F10.9 on page 386**). Risk reduction was observed for NPDR when applying a tighter HbA1c cut-point, but in contrast, was seen for maculopathy with a less stringent cut-point.

Unlike Study 4, the main analysis showed mixed results (**Figure 10.7 on page 302**). In general, risk reductions for study endpoints were documented in the missing TITRE category compared with the 3-<6 months category. Inverse a J-shaped association was seen for diabetic retinopathy with the 0 months, 6-<9 months and 9-12 months TITRE categories, showing significant excess risk by 16% to 25% when compared with the 3-<6 months category. A similar pattern of association, although non-significant, was observed for diabetic neuropathy. A significant inverse association of TITRE category was seen for diabetic nephropathy and this finding would be partly expected, particularly with higher TITRE categories (OR 0.84, 95% CI 0.70-1.01, p=0.071 in the 6-<9 months category and OR 0.76, 95% CI 0.64-0.90, p=0.002 in the 9-12 months category). No significant association was documented for glaucoma (**Figure F10.10 on page 387**).

10.5.7 Sensitivity and subgroup analysis

Sensitivity analysis. Exclusion of patients with 100% TITRE values from the analysis had only a small effect (**Figure F10.11 on page 388**). Significant excess risk of diabetic retinopathy was no longer seen in the 9-12 months TITRE category, likewise the significant risk reduction for diabetic neuropathy in the same category. For secondary endpoint, the missing and 0 months TITRE categories were now significantly associated with higher risk for maculopathy (data not shown).

Sensitivity analysis in patients whose T2D was first diagnosed in primary care also exhibited few changes (**Figure F10.12 on page 389**). Significant excess risk for diabetic retinopathy was maintained for the 0 months TITRE category only, yet the missing category was now associated with greater risk. Importantly, significant risk reduction for diabetic nephropathy remained observed in the 9-12 months TITRE category.

Figure 10.4 Association of three different measures of glycaemic control with microvascular outcomes in CALIBER's T2D cohort without prior microvascular disease (N=47,432)

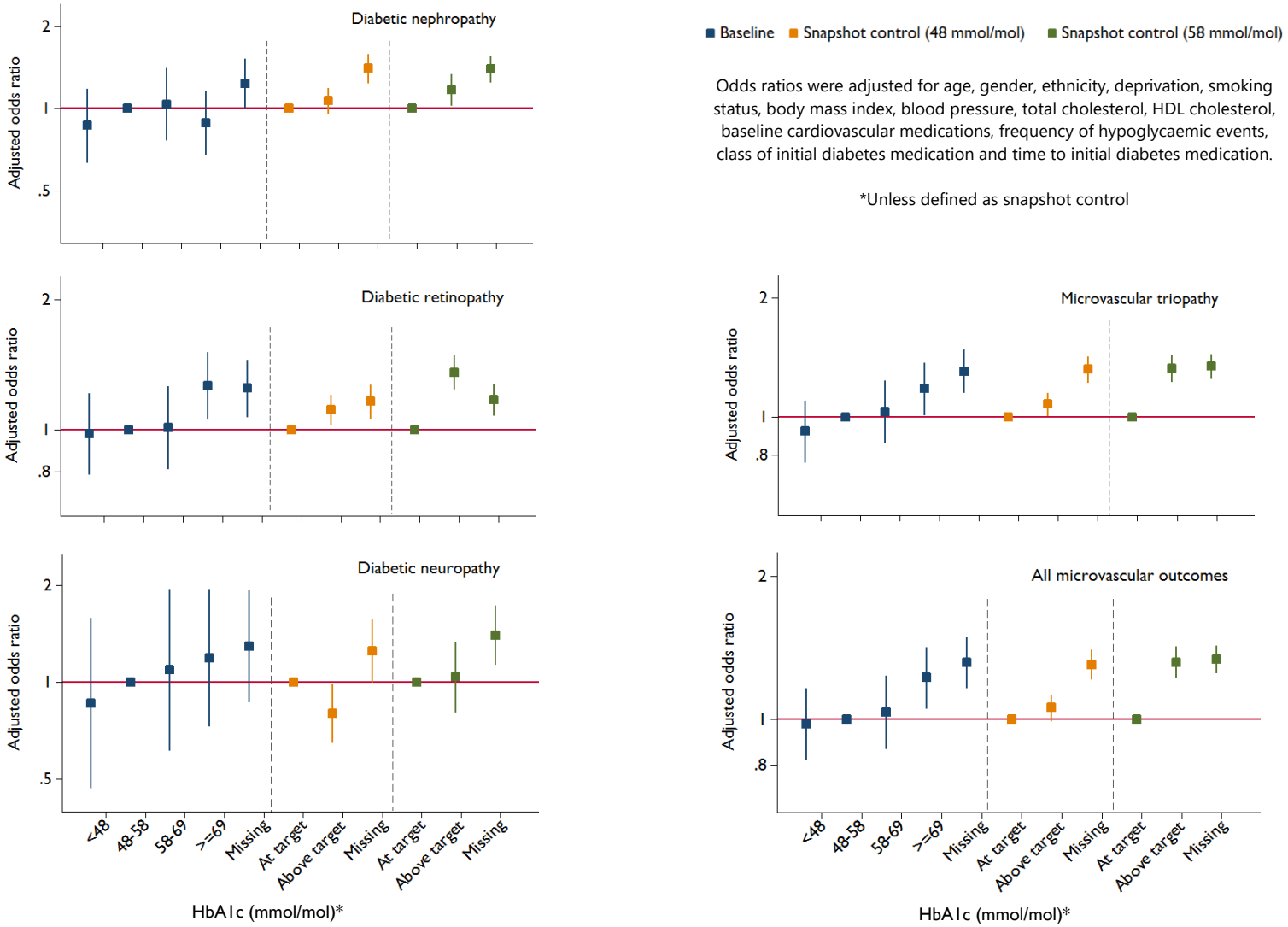
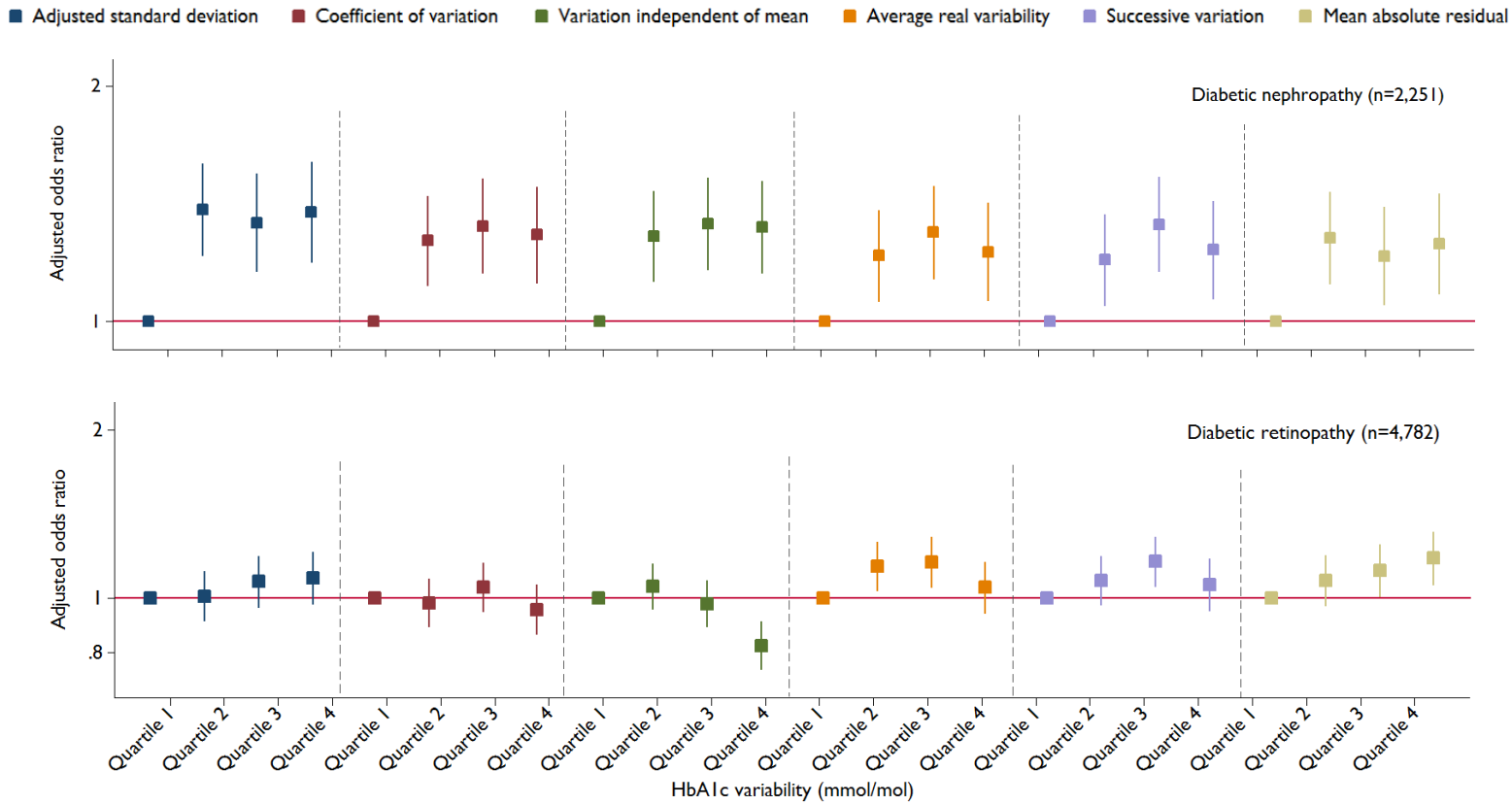


Figure 10.5 Association of six different measures of glycaemic variability* with microvascular outcomes in CALIBER's T2D cohort without prior microvascular disease (N=41,507)

Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.



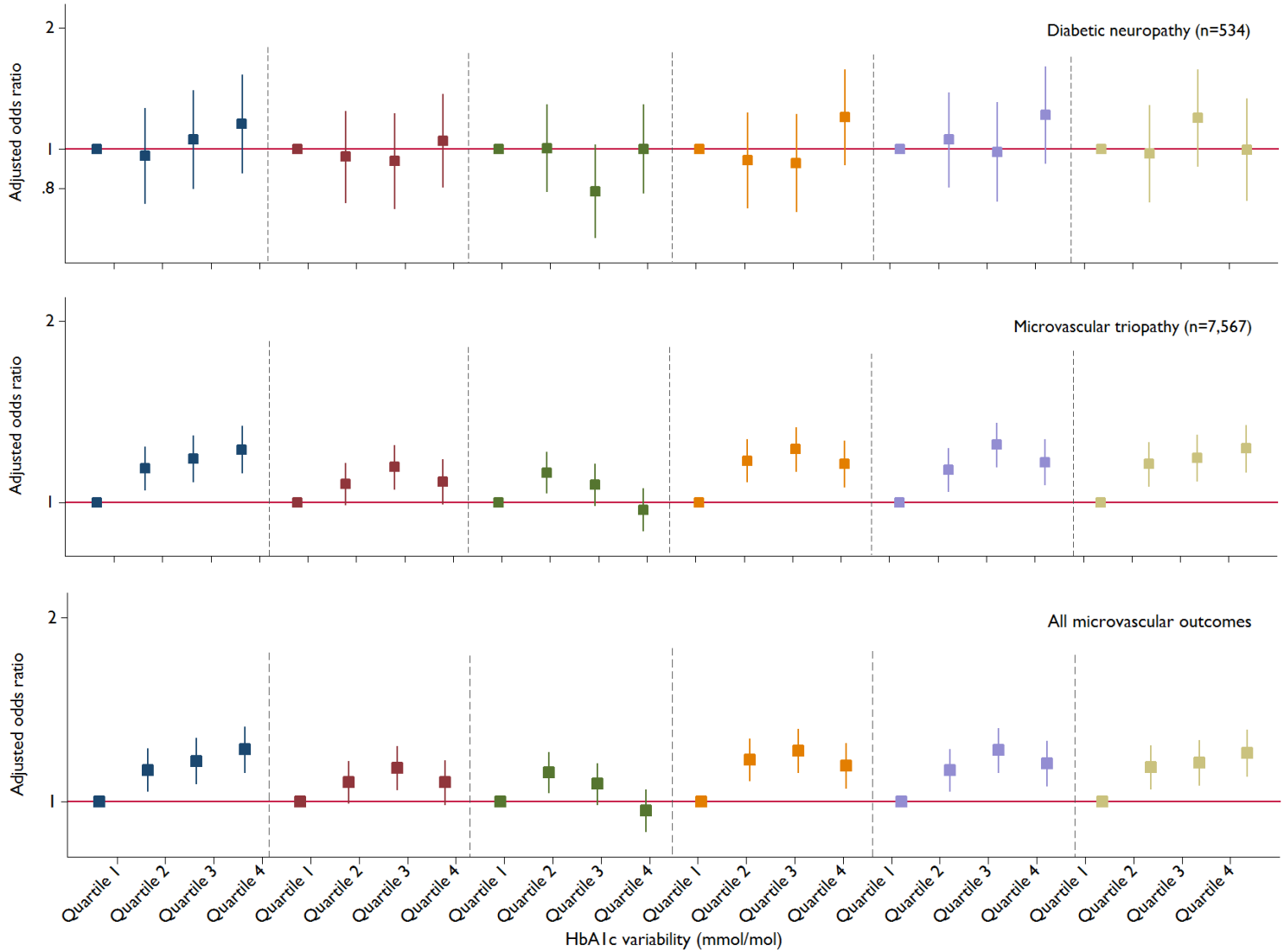
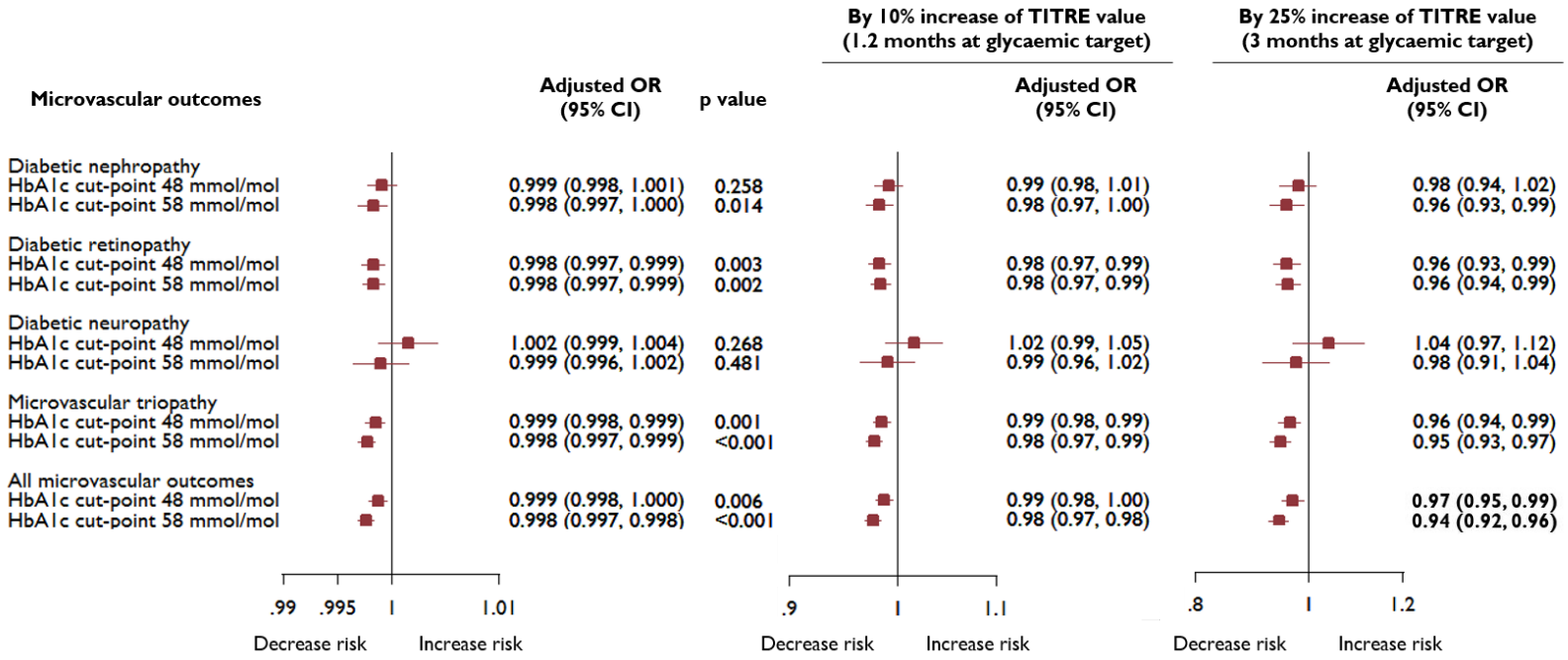
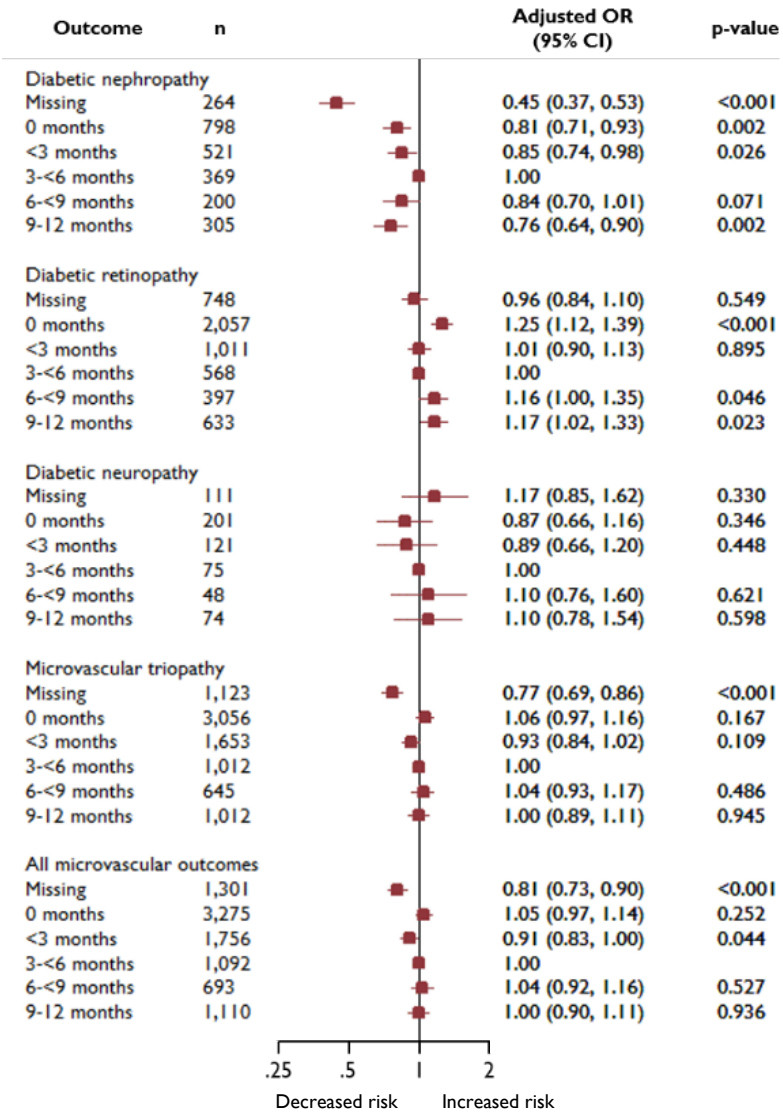

Diabetic neuropathy (n=534)
Microvascular triopathy (n=7,567)
All microvascular outcomes
Adjusted odds ratio
2
1
.8
Quartile 1
Quartile 2
Quartile 3
Quartile 4
HbA1c variability (mmol/mol)

Figure 10.6 Association between non-missing TITRE values (%) and microvascular outcomes using two different cut-points (N=40,152)



Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure 10.7 Association between TITRE category and microvascular outcomes (N=47,432)



Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Application of a higher HbA1c cut-point (58 mmol/mol) to define TITRE did not change the pattern of association for diabetic nephropathy in the 9-12 months TITRE category but altered the risk for diabetic retinopathy and neuropathy. Significant excess risk for retinopathy was only observed with the 0 months TITRE category but not with the higher categories (**Figure F10.13 on page 390**). The J-shaped association became more evident for neuropathy; the missing and 0 months TITRE categories had increased risk by over 60%, whereas the increase for the 9-12 months category was by 35% (OR 1.35, 95% CI 1.01-1.78, p-value 0.039). A linear association between non-missing TITRE categories and composite microvascular outcomes now became evident with increased risk by less than 20% in the 0 months category, although lower risks for microvascular outcomes in the higher TITRE categories were not seen.

Addition of a snapshot glycaemic control category, mean HbA1c or adjusted SD of HbA1c into a multivariate model as well as changing the reference group to the 0 months TITRE category did not greatly alter the findings from the main analysis (**Figures F10.14 to F10.17 on pages 391-394**).

Subgroup analysis. Analysis in the sub-cohort being prescribed with ACE inhibitors or ARB blockers (N=6,557, 13.8%) appeared to give a clearer pattern of association between TITRE category and diabetic nephropathy. A linear association was observed despite a lack of statistical significance which was likely due to the small number of patients on the medication (**Figure F10.18 on page 395**).

10.6 Discussion

10.6.1 Key findings

Study 5 had a larger cohort size than Study 4, indicating that more patients presented with cardiovascular complications at the time of diagnosis of T2D. It can be argued, however, that more cardiovascular than microvascular phenotypes were better identified in this thesis justifying the exclusion of a larger number of patients with prior CVDs, but this finding supports current knowledge on the natural course of T2D where microvascular complications tend to develop at a later time. In fact, initial presentation with microvascular outcomes was found in 19.5% of Study 5's cohort as compared to initial presentation with cardiovascular outcomes in 13.2% of Study 4's cohort. The most common initial presentations with microvascular outcomes were NPDR (36.0%), unspecified retinopathy (17.3%) and CKD progression to stage G3a (13.3%).

When the HbA1c cut-point was set at 48 mmol/mol, only about one-third of the cohort for Study 5 achieved adequate duration at glycaemic target (i.e. ≥3 months). The proportion doubled when a less stringent cut-point was applied (**Figure F10.2 on page 375**); in comparison, the cut-point change for TITRE calculation in Study 4 increased the proportion by about 60%. This finding implies that long-term glycaemic control with a less stringent target seems to be more achievable for T2D patients without prior microvascular disease than those without prior CVDs. In other words, once a microvascular complication occurs, glycaemic control is likely to be harder to achieve and maintain.

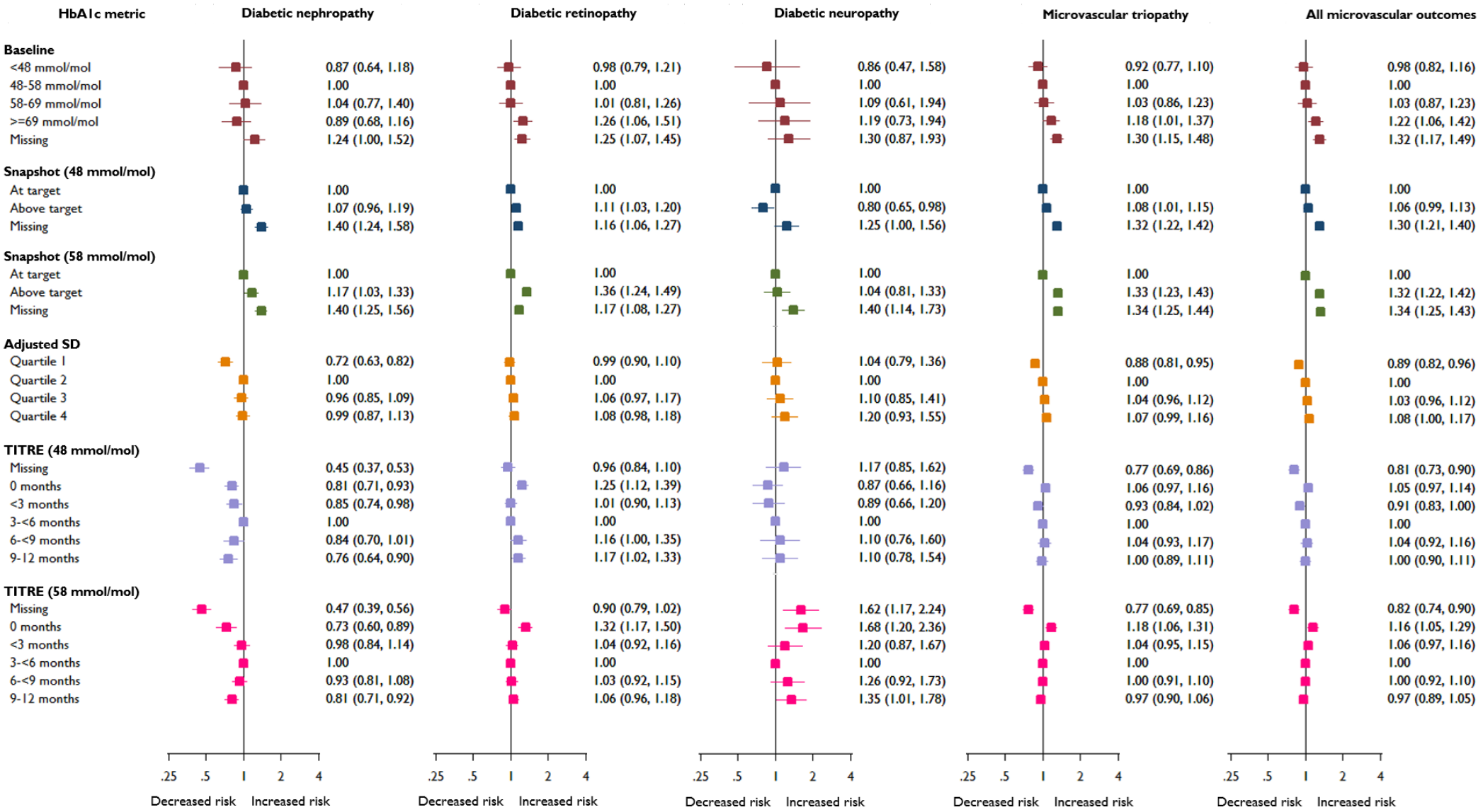
Further, Study 5 documented risk reduction for diabetic retinopathy by unit increase of duration at glycaemic target (TITRE value) measured using either HbA1c cut-point, and risk reduction for diabetic nephropathy by unit increase of TITRE value defined using a less stringent cut-point (58 mmol/mol). Analysis by TITRE category demonstrated that a longer duration at glycaemic target, relative to 3-<6 months, was associated with a lower risk for diabetic nephropathy although a shorter duration also exhibited a similar association. Application of the TITRE metric did not shed light on other microvascular risk assessments. By way of comparison, use of glycaemic control metrics in this study for assessing similar risks – particularly for diabetic retinopathy while ignoring missing HbA1c category – tended to demonstrate consistent findings with existing studies;[139,197] of note, most studies generally excluded patients without known HbA1c levels. Use of glycaemic control metrics has, however, generated counter-intuitive results for assessing nephropathy risk, by which risk reduction was observed in patients with higher (and unknown) HbA1c levels. Most glycaemic variability metrics used in this study also showed consistent findings with previous studies.[70,189,190] Although in this study nephropathy has been defined differently by harnessing eGFR data only, the finding did not differ greatly when it was defined using diagnosis codes only (data not shown). Overall, the findings from Study 5 suggest that TITRE metric does not offer much of clinical utility over existing glycaemic control metrics for assessing risk of microvascular disease. It is unclear why risk reductions for diabetic nephropathy and retinopathy were observed in patients with unknown glycaemic control.

10.6.2 Comparison with Study 4

Overall, glycaemic control measured using baseline HbA1c and snapshot control within the first year showed positive linear associations with microvascular disease (**Figure 10.8 on page 305**). When using the TITRE-HbA1c metric (particularly with removal of the missing category), a linear but non-significant association was only observed for composite microvascular outcomes, similarly when association was measured using adjusted SD-HbA1c.

As with CVDs (**Chapter 8**), linear associations were also documented by measurement using baseline HbA1c and snapshot control with greater estimates than microvascular disease in patients without measurements (**Figure 8.7 on page 249**). The pattern of associations from the TITRE-HbA1c metric, despite being non-significant, showed general concordance with other metrics, except for adjusted SD of HbA1c which did not illuminate a clear pattern of associations.

Figure 10.8 Summary plots of the associations of glycaemic control with microvascular outcomes measured using different metrics



10.6.3 Comparison with existing research

A strong association between HbA1c levels and microvascular outcomes has been long established, and unlike cardiovascular complications, studies generally reported consistent findings for microvascular complications.[49,50,87] However, my replication by a similar approach only showed consistency for diabetic retinopathy and neuropathy. The paradoxical association found between HbA1c levels and diabetic nephropathy was probably attributable to the nature of its definition in my study – this will be discussed in **Section 10.6.5 below** about study limitations. Unlike HbA1c levels, the two studies examining glycaemic variation documented a strong association with both microvascular disease and CVDs,[70,189] but one study found such a strong association with microvascular disease only.[190] When I replicated the glycaemic variability metrics in my cohort, adjusted SD of HbA1c appeared to be the most stable metric to assess microvascular outcomes, and this finding is consistent with previous research.[189,190] With the exception of VIM, other less frequently used metrics also seemed promising from my analysis for microvascular risk assessment as previously reported by a post-trial analysis.[70]

To my knowledge, there has been no previous study addressing the association of duration at glycaemic target and microvascular complications against which my findings can be compared properly.

10.6.4 Strengths

As rehearsed elsewhere in this thesis, the general strengths of CALIBER data include the large size of the population-based cohort with a sufficient follow-up period that allows identification of initial presentation with microvascular outcomes. Another strength is the availability of repeated HbA1c records which enables development of TITRE-HbA1c by which microvascular risk can be assessed. The repeat data also allow analyses using other glycaemic control and variability metrics for comparison with the TITRE metric's performance. Importantly, the overall findings of Study 5 – with some caveats to TITRE calculation and microvascular phenotyping – add some weight to the existing evidence on the importance of routine glycaemic monitoring.

10.6.5 Limitations

My study has some important limitations. Firstly, diabetic retinopathy and neuropathy have been identified using diagnosis codes only, whereas nephropathy used eGFR data only. My study lacked supporting, relevant clinical data from which retinopathy could be ascertained or further captured through data linkage. Although not used as a specific study endpoint, incident unspecified retinopathy was found to be high and was included in diabetic retinopathy as a primary study endpoint. It was among the last endpoints in the hierarchical order of initial presentation with multiple microvascular diseases, so the likelihood of unspecified retinopathy preceding other study endpoints was probably small. Incident diabetic neuropathy was the least common endpoint compared to retinopathy and nephropathy; greater capture was possible by harnessing data on the AVS test but the diagnostic test of the examination showed low sensitivity and PPV, otherwise

neuropathy potentially shifted the configuration of initial microvascular presentation and the higher number of events could have resulted in significant risk estimates. As for incident diabetic nephropathy, the way it was defined as CKD *progression* implies that my patient cohort was not truly free from microvascular disease; it might have comprised patients with stable CKD from the beginning who could not be excluded regardless of their initial stage, since, as per the definition, they never progressed to a more severe stage. To some extent, this might explain the inverse J-shaped associations of TITRE-HbA1c found. In fact, the reduced risk in lower TITRE-HbA1c categories (0 and <3 months) may be attributable to their healthier status at baseline, as indicated by a higher proportion of initial CKD stages G1 and G2 (**Table 10.2 on pages 292-293**). Additionally, I did not utilise other laboratory data (i.e. albuminuria) to define CKD progression – whilst doable, it would have generated more classification and subsequently reduced the number of events within a particular classification. A major advantage of defining nephropathy as CKD progression using eGFR data is that it captured more events compared to using diagnosis codes alone (data not shown). As the microvascular datasets I received were diagnosis summary per patient for the initial complication rather than repeat diagnosis records, utilising such a dataset could not inform on CKD progression. Overall, despite some validity of microvascular disease inferred from its relationship with cardiovascular death (**Chapter 9**), its phenotypical resolutions appeared to be lower than for the CVDs.

More recently, a probabilistic model called Hidden Absorbing Semi-Markov Modelling (HASMM) has been developed, which essentially is of latent variable models.[319] Such model is capable of predicting progression stages or generating sequences from multi clinical states manifesting only through symptoms which may or may not accurately reflect the disease's true state. In semi-Markov model, the probability of there being a change in the hidden state is not constant (which is contrary to Markov model), instead depending on the amount of time that has elapsed since entry into the current state. The reported HASMM model – applied in ICU setting – was demonstrated to perform well (and in fact outperforming discriminative models such as logistic regressions) for irregularly spaced data with short intervals between measures (i.e. within hours). While the model may be applicable to eGFR data previously being analysed in **Chapter 9**, there has been no further evidence that it may perform equally well on data with longer intervals such as eGFR. Moreover, statistical inference for hidden semi-Markov models would not be straightforward as more complex algorithms and adjustments than hidden Markov ones are required.

The limitations of Study 4 with specific reference to measurement of duration at glycaemic target using the TITRE-HbA1c metric also apply to Study 5. In brief, these include a high proportion of missing HbA1c records at baseline, a time gap between initial T2D diagnosis and index HbA1c measure for TITRE calculation, the presence of a lengthy interval between two successive HbA1c measures, low sensitivity of partial TITRE calculation during the last follow-up year and tolerance for interval calculation between two successive HbA1c measures up to one year.

Finally, the finding from subgroup analysis showed that the TITRE-HbA1c metric for diabetic retinopathy risk assessment is probably best used in a sub-cohort of those who were on RAAS agents before T2D diagnosis as indicated by the linear pattern of association observed – this,

however, would require a much larger cohort size for the significant association of long-term glycaemic control to be seen. It is not distinguishable from this study whether medication was prescribed as a secondary prevention of CVDs or as a treatment for prior nephropathy (in patients with stable CKD stage) although the latter is more likely.

10.6.6 Clinical and research implications

Clinical implications. This chapter has documented a significant association between longer duration at glycaemic target (9-12 months) and lower risk for diabetic nephropathy. With some important study limitations in mind, a similar association seen with shorter duration at target (0 months) should not justify less effort or a lower quality of care to maintain glycaemic target over time. In fact, the findings for diabetic retinopathy and neuropathy and the composite microvascular outcomes showed higher risks in patients in the 0 months category. Moreover, long-term glycaemic control has been previously demonstrated to be associated with reduced risk of MACE and cardiovascular death (**Chapter 8**). Additionally, records on simple, low cost examination such as visual acuity and AVS tests should be improved for potential early detection of microvascular complications.

Research implications. Findings from this study suggest that the CALIBER framework and future research may benefit from expanded collaboration with disease-specific institutes or registries (e.g. national kidney or eye disease registries) to enable further data linkage which would eventually help to ascertain non-cardiovascular diagnosis. The limitations of the TITRE-HBA1c metric for microvascular risk assessment imply that the metric does need further validation.

10.7 Conclusion

Risk assessment for microvascular complications using the TITRE-HbA1c metric provides a somewhat ambiguous pattern of association. Reduced risk of most microvascular outcomes was seen in patients with unknown glycaemic control, while there was an increased risk in those with 0 months glycaemic control (with the exception of diabetic nephropathy). Risk reduction for diabetic nephropathy was, however, documented in patients with glycaemic control of 9 months or longer. Despite some validity of microvascular disease phenotypes, further application of the metric for microvascular risk assessment hardly adds new information. Important limitations of this study have been discussed to explain these findings.

10.8 Chapter summary

This chapter has presented the application of the TITRE-HbA1c metric to assess microvascular risk in an incident T2D population. The indecisive findings suggest that study replication with further refinement of microvascular phenotypes as well as the TITRE-HbA1c metric in other population-based settings may be capable of addressing the drawbacks of this study.

In the last chapter, I will summarise my thesis and discuss its potential implications and recommendations for improving the quality of T2D care.

Chapter 11

Discussion

Diabetes...
It's pronounced [dye-ah-bee-teez] and NOT [die-ah-BEAT-us], because we refuse to let it BEAT us.
— Anonymous

11.1 Chapter outline

This chapter epitomises the five studies of my PhD, pulling together their objectives, methods, results, strengths, limitations, and wider implications for care and research alike.

11.2 Summary of thesis

My PhD set out to explore the quality of care after T2D presentation and, for the most part, how it relates to the onset of chronic complications. In **Chapter 1**, I described the burden of T2D and key aspects of quality of T2D care. I went on to explore the published literature on temporal trends in T2D care, predictors of care outcomes, and associations of care with chronic vascular complications (**Chapter 2**). In **Chapter 3**, I discussed the CALIBER research platform used for my research. **Chapter 7** described the development method for a novel metric to measure glycaemic control longitudinally, whereas **Chapter 9** elaborated on the refinement of microvascular disease phenotypes in CALIBER.

11.2.1 Overall approach and key findings of PhD studies

Five studies into quality of care in CALIBER's newly diagnosed T2D population have been conducted and reported in **Chapters 4, 5, 6, 8 and 10**. Objective, methods used, cohort size and period of each individual study are compared in **Table 11.1 on pages 312-314**, whereas major findings for each study are summarised below.

11.2.1.1 Key findings of Study 1

- Of over 160,000 CALIBER patients with diagnosis codes for diabetes spanning 1998-2010, only approximately one-third could be specifically phenotyped from linked CPRD and HES databases as being newly diagnosed with T2D. T2D patients identified from HES (10%) were older at diagnosis and more deprived, had lower HbA1c, blood pressure and total cholesterol levels at baseline, and had more comorbidities but received less treatments.
- HbA1c, blood pressure and total cholesterol measurements after T2D presentation showed similar trends with time. A decline in the proportion of patients measured for these care processes was immediately seen after one year but followed by a gradual rise peaking in years 5 to 6. The proportions over time were highest at 85%, 75% and 72% but never lower than 78%, 69% and 67% for blood pressure, HbA1c and total cholesterol, respectively.
- Positive trends year-by-year were seen in the proportion of patients achieving blood pressure and total cholesterol targets, peaking at around 75% and 85%, respectively towards one decade, from just 65% during year 1. In contrast, a progressive decline over time from 75% to 60% was observed for meeting HbA1c target. These indicate that achievement of HbA1c and blood pressure targets particularly fell short for their measurements over time.
- Proportion of triple measurements of HbA1c, blood pressure and total cholesterol was high at around 65% over time, but low for triple target achievements (about 25%). Only small fraction of the patients (<10%) ever achieved none of the three targets.
- Inequalities of care process measurements across demographic factors existed, leading to consequent gaps in the target achievements. In general, a lower proportion of measurements was observed year-by-year in patient groups who were younger at diagnosis, female,

non-whites or more deprived. A lower proportion of HbA1c tests – but not for blood pressure and cholesterols – was seen in patients with prior CVD. Proportion of women meeting glycaemic target was shown to be higher over time. Gender, ethnicities and deprivation were consistently associated with less measurements over time of HbA1c, blood pressure and total cholesterol either individually or combined. In contrast, older age was associated with target attainments over time of those key measurements.

- Diabetes treatment showed positive trends with multiple oral diabetes medications over time but 20% of patients remained untreated after a decade. Older age, women and deprivation were associated with receipt of diabetes treatment over time.
- Other measurements over time of care process also appeared to be suboptimal, particularly for treated albuminuria and neuropathy testing that never reached 40% over time.

11.2.1.2 Key findings of Study 2

- In the incident T2D cohort with at least two years of follow-up, the proportion of patients meeting HbA1c, blood pressure and total cholesterol target within the second year was 60%, 67% and 55%, respectively. The proportion of patients meeting all three targets, only a single target and never meeting any target were 37%, 27% and 6%, respectively.
- Ignoring any target achievements within the first year after diagnosis, the median time needed to meet the individual target was around 16 months and it took two months longer to achieve all three targets.
- About 27% of patients were never measured for either HbA1c or total cholesterol, 17% were never measured for blood pressure, and combined together 14% were never measured for all three.
- Predictors of short-term target achievement of intermediate outcomes were variable. Older age at diagnosis, baseline antiplatelet prescription and being diagnosed from 2004 onwards were consistently associated with meeting either individual or triple targets.
- Initial care processes after diagnosis of T2D were also found to be significant predictors of short-term achievement of intermediate outcomes targets. For every extra measurement of HbA1c and total cholesterol within the first year, the likelihood of meeting the respective target during the second year relative to not meeting the target increased significantly by 15% and 19%. The likelihood was marginal for blood pressure by only 2%. Only incremental number of HbA1c measurement was associated with an increased likelihood of meeting double targets by 30% and triple targets by 56% relative to meeting any single target.

Table 11.1 Overview of PhD studies

	Study 1	Study 2	Study 3	Study 4	Study 5
Study design	Serial cross-sectional	Prospective cohort	Prospective cohort	Prospective cohort	Prospective cohort
Aim	Temporal trend in processes & outcomes of care	Predictors of HbA1c, blood pressure & lipid control	Associations of glycaemic, blood pressure & lipid control with initial presentations of 12 CVDs	Associations of long-term glycaemic control with cardiovascular outcomes	Associations of long-term glycaemic control with microvascular outcomes
Study population	CALIBER's newly diagnosed T2D identified from CPRD & HES between 1998-2010				
Study period	From diagnosis until end of follow-up	From diagnosis until end of Year 2	From diagnosis until end of follow-up	From diagnosis until end of follow-up	From diagnosis until end of follow-up
Inclusion criteria	Aged ≥30 years, at least 1 year of follow-up	Aged ≥30 years, at least 2 years of follow-up	Aged ≥30 years, at least 1 year of follow-up, no prior CVDs	Aged ≥30 years, at least 1 year of follow-up, no prior CVDs	Aged ≥30 years, at least 1 year of follow-up, no prior MVDs
Main exposure	-	Frequency of HbA1c, blood pressure & total cholesterol measurements	Glycaemic control within first year	Duration at glycaemic control	Duration at glycaemic control
HbA1c target	≤7.4% (57.4 mmol/mol) - in line with the 2004 QOF indicator	≤7.4% (57.4 mmol/mol) - in line with the 2004 QOF indicator	≤7.4% (57.4 mmol/mol) - in line with the 2004 QOF indicator	≤6.5% (48 mmol/mol) - in line with the 2016 NICE guidelines	≤6.5% (48 mmol/mol) - in line with the 2016 NICE guidelines
Covariates	Gender, age at entry, ethnicity, deprivation	Gender, age at entry, ethnicity, deprivation	Gender, age at entry, ethnicity, deprivation	Gender, age at entry, ethnicity, deprivation	Gender, age at entry, ethnicity, deprivation
		Smoking status, body mass index, blood pressure, HDL-C	Smoking status, body mass index, blood pressure, HDL-C	Smoking status, body mass index, blood pressure, HDL-C	Smoking status, body mass index, blood pressure, HDL-C
	Prior CVD	Prior CVD	Renal disease	Renal disease	
		Blood pressure & lipid lowering treatments, antiplatelet	Blood pressure & lipid lowering treatments, antiplatelet	Blood pressure & lipid lowering treatments, antiplatelet, initial diabetes treatment, time to first diabetes treatment	Blood pressure & lipid lowering treatments, antiplatelet, initial diabetes treatment, time to first diabetes treatment
Primary outcomes	Proportion over time of HbA1c, blood pressure & total cholesterol measurements & attainments	Glycaemic, blood pressure & total cholesterol control within second year	Stable and unstable angina, myocardial infarction, unheralded coronary death, heart failure, arrhythmia/ sudden cardiac death, TIA, ischaemic stroke, subarachnoid and intracerebral haemorrhage, PAD, AAA	MACE, heart failure, any CVD & death	Diabetic nephropathy, retinopathy, neuropathy, microvascular triopathy, all MVDs

Secondary outcomes	Proportion over time of records on smoking status, BMI, albuminuria, serum creatinine, diabetes treatment			CAD, PAD, cardiovascular death, all-cause death	CKD progression to stages 3a, 3b, 4/5, NPDR, maculopathy, glaucoma
Data source for outcomes	CPRD	CPRD	CPRD, HES, MINAP, ONS mortality	CPRD, HES, MINAP, ONS mortality	CPRD, HES
Statistical analysis	Temporal plot with 95% CIs	Multinomial logistic regression	Cox regression	Mixed logistic regression	Mixed logistic regression
Cohort size	52,379	44,366	36,149	34,660	47,432
Median (IQR) follow-up	4.7 (2.7-7.1) years	5.4 (3.6-7.6) years (beyond period of analysis)	4.4 (2.5-6.8) years	4.4 (2.5-6.8) years	4.2 (2.4-6.4) years

AAA, abdominal aortic aneurysm; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular diseases; HES, Hospital Episodes Statistics; IQR, interquartile range; MACE, major adverse cardiovascular event; MINAP, Myocardial Ischaemia National Audit Project; MVD, microvascular diseases; NICE, National Institute for Health and Care Excellence; NPDR, non-proliferative diabetic retinopathy; ONS, Office for National Statistics; PAD, peripheral arterial disease; QOF, Quality and Outcomes Framework; TIA, transient ischaemic attack.

11.2.1.3 Key findings of Study 3

- In the incident T2D cohort without prior CVD, the proportion of patients meeting HbA1c, blood pressure and total cholesterol targets within the first year was 58%, 66% and 49%, respectively. The proportion of patients meeting all three targets, only single target and never meeting any target were 33%, 19% and 7%, respectively.
- Nearly 15% of patients developed CVDs, with the most common initial presentation of specific CVDs being heart failure, stable angina and PAD.
- Meeting HbA1c target was associated with around a 30% risk reduction for heart failure and PAD. Meeting blood pressure target was also associated with lower risk reduction for heart failure and PAD (by 20%), and for myocardial infarction and ischaemic stroke (by 30%). Meeting total cholesterol target was associated with risk reduction for myocardial infarction (30%) and TIA (40%). Meeting double or triple targets was associated with risk reduction for more CVDs.

11.2.1.4 Key findings of Study 4

- In the incident T2D cohort without prior CVD, 87.2% had repeated records on HbA1c from which duration at glycaemic target (referred to as TITRE-HbA1c) could be quantified. The majority of these patients, however, had a TITRE-HbA1c of 0 months (40%) and 3 months or less (33%).
- MACEs occurred in 5% of the cohort, heart failure in 2% and combined CVDs and death in 15%.
- TITRE-HbA1c showed stepwise associations with cardiovascular outcomes. Relative to patients in the middle TITRE category (3-6 months), those in the 0 months group had risk excess for MACE by 27% and cardiovascular death by 43%. Patients with missing (i.e. incomputable) TITRE had double the risk for all cardiovascular outcomes studied, except for PAD. Patients in the 9-12 months TITRE category did not exhibit risk reduction for cardiovascular outcomes unless a more relaxed HbA1c target was applied.
- Visual comparison with some existing metrics for glycaemic control and variability suggests that TITRE-HbA1c has the potential as both a metric for longitudinal glycaemic control and a tool for cardiovascular risk assessment.

11.2.1.5 Key findings of Study 5

- In the incident T2D cohort without prior microvascular disease, about 85% had computable TITRE-HbA1c, the majority of whom had a TITRE-HbA1c of 0 months (31.4%) and 3 months or less (21.1%).
- Diabetic nephropathy, retinopathy and neuropathy occurred in 5.2%, 11.4% and 1.3% of the cohort, respectively.

- TITRE-HbA1c showed an inverse J-shaped association with diabetic nephropathy but a J-shaped association with diabetic retinopathy. Compared with patients in the middle TITRE category, those in the 0 months category had risk reduction for nephropathy by 19% but risk excess for retinopathy by 25%. Patients in the 9-12 months TITRE category also had risk reduction for nephropathy by 24% but risk excess for retinopathy by 17%.
- TITRE-HbA1c appeared to be uninformative on microvascular risk assessment as compared to CVDs.

11.2.2 Overall strengths

- Common strengths across my studies lie in the large, nationally representative cohort size and non-selective, prospective nature of the data within CALIBER with sufficient follow-up time. These have provided a detailed picture of the patient journey over time and generated estimations for the associations sought with statistical power. Data linkage between primary and secondary care has captured more incident T2D cases by 10%. Linkage of the four data sources added strength with more capture and ascertainment of first manifestation of a wide array of specific CVDs that would not have been feasible by using a single source alone.
- The key advantage of including only incident T2D cases is that quality of care can be equally assessed from initial diagnosis, thus minimising time-related bias in estimates. Applying the same index date for all T2D patients identified will result in underestimation of survival duration since historical care in old cases is compromised while new cases after study entry are overlooked.
- Unlike other studies that generally define snapshot control for intermediate outcomes as a binary variable (target achieved or not), I added in the analysis a group of patients without measurement, thus enabling assessment of this situation which is poorer than being measured but failing to meet targets, both in terms of its predictors and influences on the initial manifestation of specific CVDs (Studies 2 and 3).
- This thesis found an important association between three major processes of care after T2D presentation and their respective targeted outcomes, and, importantly, between frequency of HbA1c measurement and combined control of glycaemia, blood pressure and total cholesterol. To my knowledge, these associations have never been documented before.
- Findings on the associations between achieving glycaemic, blood pressure and total cholesterol targets (either individually or in combination) and several specific CVDs have added weight to the importance of early intervention in reducing cardiovascular risks as demonstrated by the UKPDS.
- Another novelty of my thesis is the development of a new metric, the TITRE-HbA1c, to measure a patient's duration at glycaemic control proportionally by leveraging the avail-ability of longitudinal HbA1c records from primary care. The TITRE-HbA1c metric was shown to have potential for complication risk assessment, as suggested by positive – yet marginal –

associations observed between longer duration at glycaemic control and risk reduction for composite cardiovascular outcomes in particular. My findings – supported by my replication using other glycaemic control metrics – are consistent with analyses from other studies on heart failure using mean or updated mean HbA1c to define long-term glycaemic control.[138,188] Overall, the findings from Study 4 combined with Study 3 underline that maintaining glycaemic control over time and achieving it early are equally important for prevention of CVDs.

11.2.3 Overall limitations

- Using the existing CALIBER diagnosis-based phenotyping algorithm, I was only able to capture approximately 63% of T2D cases before applying any inclusion criteria, leaving at least 25% of all diabetes cases unclassified (**Figure 4.1 on page 131**). My final estimate for newly diagnosed T2D cases of around 52,000 is just less than half the estimates from two CPRD-based studies with a similar data period for extraction,[48,138] suggesting potentially diminished power (thus precision) of my studies. My cohort size, however, approximates to estimation in the previous CALIBER study on diabetes which projected around 51,000 new cases of T2D.[4]
- The real onset of T2D in my cohort is unknown since T2D was determined from the initial clinical presentation, but time gap between the onset and diagnosis is likely – a limitation which seems to apply to all studies on incident diseases. However, my estimates should be unaffected since the focus of my studies is quality of care, the assessments of which are only reasonably made after diagnosis.
- I used two different HbA1c thresholds across my studies; the first three studies used the 2004 QOF target of 7.4% (57.4 mmol/mol) while the last two adopted NICE's recommended target (6.5% or 48 mmol/mol) to represent more recent guidelines. In sensitivity analyses in Studies 4 and 5, however, I set a more relaxed target (7.5% or 58 mmol/mol) for convergence of the two thresholds.
- I also used two different methods across my studies to overcome considerable missing data on covariates. In Studies 2 and 3, I applied indicators of missingness in the multivariate analyses and the overall estimates derived are, therefore, more prone to bias and warrant cautious interpretation. I refined my method in Studies 4 and 5 using multiple imputation by chained equations for more robust estimations.
- The TITRE-HbA1c metric for measuring long-term glycaemic control has some drawbacks as a consequence of being developed from real data with varying longitudinal patterns and having been yet formally validated in another population (**Section 8.6.4 on pages 251-252**). The more ideal way to initially develop and validate such a metric is possibly through measurement among T2D patients recruited in an RCT where yearly frequency of HbA1c tests should be both adequate and equally spaced.

- The way microvascular diseases were redefined in Study 5 implies that my cohort was not entirely free from the complications at baseline since patients with higher but stable CKD stages (3a or above) were not excluded. Additionally, definition of DEDs and diabetic neuropathy was based on already curated diagnoses since relevant longitudinal data were unavailable to define these outcomes as a progression state, thus their definitions are not on a par with that of diabetic nephropathy.
- Whilst having shown to reasonably predict cardiovascular outcomes, the TITRE-HbA1c metric appeared to have no illuminating associations with microvascular outcomes. Some possible explanations are limitations of the metric, consequences of the methods for microvascular phenotyping, and the relatively short period for observing microvascular outcomes.

Recommendations

- CALIBER needs to expand its linkage with other primary care databases (e.g. QResearch or THIN), or the National Diabetes Audit which also holds diabetes data from specialist diabetes services, to enable ascertainment of T2D diagnosis given the importance of the disease for research (either as a main exposure or confounder).
- CALIBER and future research may also benefit from expanded collaboration with the National Diabetes Footcare Audit (NDFA) which collects data about specialist foot care services for people with diabetes as well as other national disease registries (e.g. for kidney or eye diseases) to enable further data linkage in order to facilitate ascertainment and refined phenotyping for non-cardiovascular diseases.
- A further validation study for the TITRE-HbA1c is needed, by testing the metric in another population; the most effective way is probably by using patient data from a large clinical trial.
- No clear association of duration at glycaemic target with microvascular outcomes indicates the need for replication studies using TITRE-HbA1c in a larger population with a longer study period and possibly refined methods for microvascular phenotyping.

11.2.4 Implications of findings for clinical practice and public health

- The significant proportion of diabetes patients with an unknown type who were excluded from my studies despite being potential cases of T2D suggests that practices need to improve the quality of clinical recording by specifying the type of diabetes where a diagnosis has been confirmed. Apparently, this important issue has been recognised by the NHS as reflected by its inclusion in the newest QOF indicators (**Appendix C on pages 326-330**). Identification of diabetes type can facilitate appropriate clinical and public health intervention as well as minimising selection bias in research.

- My thesis highlights missed opportunities in T2D care as early as one year from diagnosis and throughout follow-up as indicated by suboptimal examinations and treatments as well as target achievements. More frequent measurements of HbA1c, blood pressure and lipid within the first year were shown to relate to target achievements, while target achievements related to diverse cardiovascular protections. These suggest that practices need to improve these key care processes in new T2D cases given the potential cardiovascular benefits.
- To a lesser extent, my thesis also points out care disparities across demographic factors which were demonstrated to have varying effects on meeting intermediate outcome targets. These results add weight to the existing evidence about inequalities in T2D where women, younger, non-white or the most deprived patients have tended to receive fewer processes of care. Practices should, therefore, improve the quality of care for these particular groups in order to improve their intermediate outcomes.
- My thesis underlines the importance of frequent HbA1c monitoring and maintaining glycaemic control at a time following documentation of a considerable proportion of T2D patients with poor long-term glycaemic control throughout their follow-up and the consequently higher risk of CVDs. Moreover, a recent large study using laboratory data suggested a 3-monthly HbA1c testing to achieve the optimum downward trajectory (i.e. change) in HbA1c level, particularly in patients with suboptimal glycaemic control.[291] It is, therefore, suggested that practices' efforts for closer, target-based HbA1c monitoring need to be improved through diligent reminders about HbA1c tests and early, more aggressive interventions in patients showing poor adherence or poor glycaemic control. Furthermore, quality of T2D care should not be compromised by the marginal associations found in Studies 4 and 5 which were partly attributable to the limitations of TITRE-HbA1c metric. In fact, encouraging findings were reported for the risk of cardiovascular outcomes in CALIBER's population with incident hypertension where the TITRE metric was originally developed for measuring blood pressure, although no specific information was available for a sub-cohort with diabetes.[299]
- Diabetic neuropathy was shown to be somewhat ill-diagnosed in Study 5 despite its potential to cause more deleterious complications (e.g. lower extremity gangrene and amputation). Therefore, practices need to improve recording of simple, low cost investigations such as AVS tests and peripheral pulse checks to enable early detection of microvascular and foot complications. While progression to diabetes-related blindness can be detected early by visual acuity tests at consultations before confirmation from retinal examination, this has never been considered important enough to be included in the QOF indicators (**Appendix C on pages 326-330**).

Summary of recommendations

- Clinical recording on the type of diabetes needs to be improved to facilitate appropriate intervention and research.
- More frequent measurement of HbA1c, blood pressure and lipid profiles within the first year of T2D diagnosis is suggested for early target achievements.
- Care delivery for female, younger, non-white or more deprived patients needs to be improved for the cardiovascular benefits to be gained as with their counterparts.
- Action for more frequent HbA1c testing can be promoted if the current QOF to assess and incentivise GP practices' performance is revisited with an additional indicator for the minimum annual frequency of HbA1c tests for diabetes monitoring.
- Target-based HbA1c monitoring throughout patients' follow-up needs to be improved to reduce CVD risks.
- Foot examination needs to be improved to prevent diabetic peripheral neuropathy and lower extremity complications.

11.2.5 Implications of findings for future research

In addition to the recommendations listed in **Section 11.2.3 on pages 316-318**, key findings as well as limitations arising from my thesis have wider implications for future research:

- Stable angina, heart failure and PAD continue to be the most common initial cardiovascular complications in incident T2D as previously shown in the CALIBER study with prevalent T2D,[4] thus confirming that these endpoints merit consideration in diabetes-related trials in terms of providing different treatment strategies from conventional CVDs.

- My thesis has shown that the manifestation and progression of T2D complications varied markedly between patients and that quality of care alone could not fully explain the individual risk of vascular complications. Other important factors for T2D prognosis not considered in my studies include lifestyle, follow-up treatment and genetic profile. With considerable missing data on lifestyle from EHRs, future CALIBER studies on diabetes would benefit from further linkage with surveys or bespoke cohort studies that generally have more complete data in this regard. An invaluable source to leverage such linkage would be the UK Biobank study. It has recruited 500,000 participants from 2006 who will be followed prospectively for at least 25 years.[320] Data collected include lifestyle and nutritional diet, biomarkers, medication and genes – all of which are important variables for T2D research. Further linkage with the UK Biobank's genotyping data will help unravel patient heterogeneous susceptibility to T2D complications where, in the context of advances in genetics, potential genes responsible for the complications are increasingly being identified.

- Long-term glycaemic control reflects the combined effects of continuous treatment and lifestyle modifications, not just their baseline. In another words, glycaemic control could potentially be in the causal pathways (i.e. a confounder) between T2D treatments and com-

plications. To that effect, a CPRD study suggested that suboptimal glycaemic control was likely to be attributable to therapeutic inertia (i.e. delay in treatment intensification with multiple OHAs or insulin).[321] Another CPRD study further revealed that therapeutic inertia by one year in conjunction with poor glycaemic control significantly increased the risk of myocardial infarction, stroke, heart failure and MACE by 67%, 51%, 64% and 62%, respectively.[322] With limited evidence to support these studies, CALIBER would be an ideal platform to further explore the effects of therapeutic inertia on a wide range of contemporary CVDs and microvascular diseases.

- Despite the current limitations, the TITRE-HbA1c metric has shown promise for more accurately measuring long-term glycaemic control over glycaemic variability metrics (e.g. adjusted SD) provided it entails dual information (glycaemic control and its duration). Method refinement and formal validation of TITRE-HbA1c will, in time, lead to its potential clinical adoption in the future. However, the complexity of the TITRE-HbA1c calculation indicates that its prognostic utility should be facilitated in the first place by machine learning research, whereby development of sophisticated algorithms by leveraging population-wide data will automatically predict risk of T2D complications in individual patients.

Summary of recommendations

- Contemporary CVDs need to be considered as primary endpoints in diabetes-related trials.
- CALIBER linkage with UK Biobank data will be an excellent research initiative to address the lack of lifestyle data in EHRs as well as to reveal the genetic contribution to the development and progression of T2D complications.
- Long-term glycaemic control is potentially attributable to follow-up rather than baseline treatment; future CALIBER research on the quality of T2D care should, therefore, look closely into this issue.
- TITRE-HbA1c estimation and its prognostic function for T2D complications in the future will be facilitated by machine learning.

11.3 Overall conclusions and future directions

T2D is an elusive chronic disease that cannot be successfully managed using a single approach only. This thesis has documented suboptimal care in newly diagnosed T2D which has implications for both short-term and long-term intermediate outcomes as well as hard outcomes.

Limitations of the current CALIBER platform can potentially be overcome by expanding linkage with other data sources for more accurate phenotyping and richer information. Issues on medical treatments (such as adherence, therapeutic inertia, adverse drug effects) should be further explored from CALIBER (and other EHRs) to address barriers and suboptimal outcomes in T2D care. For more comprehensive care, a future model for T2D care should continue to involve patients in designing the visit experience and various aspects of care improvement. Offering geno-

type testing for early recognition of susceptibility to T2D complications and resistance to OHAs could be cost-effective for the disease management. Embracing advances in health technology – which may include but not limited to the use of non-invasive glucose sensors and adoption of T2D management apps for more independent HbA1c measurement by patients – are also worthy of exercising for potential data linkage in the future, hence reinforcing quality of T2D care and research.

Appendices

Appendix A Comparison of guidelines on cardiovascular risk management in T2D

	ESC/EASD[1]	AHA/ADA[2]	SIGN[3]	NICE[4]
Diet	Main principles: ▪ Healthy balanced eating pattern dominated by low-fat dairy products & oily fish, low-protein, low-glycaemic index & high-fibre foods ▪ Salt and alcohol intake restriction ▪ Vitamin, mineral or antioxidant supplementation is not recommended			
Physical activity	Main principles: ▪ Sedentary time reduction ▪ Moderate to vigorous physical activity of ≥150 min/week ▪ Resistance exercise, when not contraindicated, at least 2x/week ▪ Exercise programmes should be previously consulted and individually tailored			Not specifically addressed
Smoking cessation	Main principles: ▪ Structured cessation advice with strategic 5As (Ask, Advise, Assess, Assist, Arrange) ▪ Offering pharmacological therapy if needed ▪ e-Cigarettes are not supported ▪ Monitoring over smoking status			
Weight control	Main principle: ▪ Weight loss with individualised interventions (lifestyle, pharmacological or surgical) if overweight/ obese ▪ Modest initial weight loss may provide more clinical benefits			
Glycaemic control	▪ HbA1c targeted at <7% (<53 mmol/mol) or as individually agreed ▪ No apparent monitoring frequency ▪ First-line therapy: » Metformin if tolerated & not contraindicated	▪ HbA1c targeted at <7% (<53 mmol/mol) or as individually agreed ▪ 3 monthly monitoring until stable on unchanging therapy ▪ First-line therapy: » Metformin if tolerated & not contraindicated » Insulin shortly after diagnosis if markedly hyperglycaemic	▪ HbA1c targeted at <7% (<53 mmol/mol) or as individually agreed ▪ 3-6 monthly monitoring once stable on unchanging therapy ▪ First-line therapy: » Metformin if tolerated & not contraindicated » SU if intolerant or weight loss	▪ HbA1c targeted at <6.5% (<47.5 mmol/mol) or as individually agreed ▪ 2-6 monthly monitoring until stable on unchanging therapy, 6-monthly monitoring once stable on unchanging therapy ▪ First-line therapy: » Metformin if tolerated & not contraindicated » SU if intolerant or weight loss

	▪ Combination of glucose lowering drugs to achieve glycaemic target	▪ Two-drug combination: metformin plus either another OHA or add-on basal insulin or GLP-1 agonist if fail to achieve glycaemic target over 3 months ▪ Three-drug combination: metformin + either OHAs or add-on basal insulin or GLP-1 agonist if remains to fail to achieve glycaemic target over 3 months with two-drug combination at maximum tolerated dose ▪ Higher dose insulin or insulin + 1-2 non-insulin agents if HbA1c remains ≥7.5%	▪ Second-line therapy, add one of: » SU » TZD if risk of hypoglycaemia, or no heart failure » DPP-4 inhibitor if weight gain & hypoglycaemia of concerns ▪ Third-line therapy, add one/ substitute with one of: » TZD if no heart failure » DPP-4 inhibitor if weight gain a concern » Insulin if rising HbA1c or weight loss » GLP-1 agonist if obese	▪ Second-line therapy, add one of: » SU » TZD if risk of hypoglycaemia, or no heart failure » DPP-4 inhibitor if hypoglycaemia & weight gain of concerns ▪ Third-line therapy, add one/ substitute with one of: » Insulin if HbA1c remains ≥7.5% » TZD or DPP-4 inhibitor if insulin unacceptable » GLP-1 agonist if obese ▪ Higher dose insulin or insulin + TZD if HbA1c remains ≥7.5%
Blood pressure control	▪ Targeted at <140/85 mmHg with no apparent monitoring frequency ▪ ACEI/ARB as first-line therapy (particularly if protein- or microalbuminuria present) ▪ Combination of antihypertensive agents to achieve blood pressure target	▪ Targeted at <140/80 mmHg, measured at every routine visit ▪ ACEI/ARB as first-line therapy (particularly if protein- or microalbuminuria present) ▪ Combination of antihypertensive agents to achieve blood pressure target	▪ Targeted at <130 mmHg systolic and ≤80 mmHg diastolic with no apparent monitoring frequency ▪ ACEI/ARB, CCB or thiazide diuretic as first-line therapy	▪ Targeted at <140/80 mmHg with annual monitoring if normotensive or 1-2 monthly monitoring if above target until consistently below target, then 4-6 monthly monitoring once stable on unchanging therapy ▪ Targeted at <130/80 mmHg if stroke or microvascular events present ▪ ACEI/ARB as first-line therapy (particularly if protein- or microalbuminuria present) ▪ Combination with CCB or diuretic if remains above target ▪ Combination with α-blocker, β-blocker and potassium sparing diuretic if remains above target

Lipid profile	▪ Targeted at LDL <2.6 mmol/L at high risk patients (i.e. without any CV risk factor and target organ damage) ▪ Targeted at LDL <1.8 mmol/L if overt CVD or aged >40 years and ≥1 CV risk factors ▪ Combination lipid-lowering therapy are not widely recommended		▪ Primary prevention with simvastatin or atorvastatin if aged >40 years with ≥1 CV risk factors ▪ No lipid target specified ▪ Atorvastatin (or fibrate if intolerant) if ACS present or post-revascularisation	▪ Primary prevention with simvastatin if aged >40 years with ≥1 CV risk factors ▪ Targeted at total cholesterol <4 mmol/L, HDL ≤1.4 mmol/L, or LDL < 2 mmol/L with 1-3 monthly monitoring after initial treatment then annual monitoring ▪ If above target: » Increase simvastatin dose » Substitute with atorvastatin or ezetimibe if CVD present ▪ Add fibrate if high CV risk and triglyceride 2.3-4.5 mmol/L
Platelet function	▪ Low-dose aspirin, or clopidogrel if intolerant, for secondary prevention of CVD ▪ Aspirin and clopidogrel for diabetics with ACS for at least one year, prasugrel or ticagrelor if PCI is performed ▪ Tailored antiplatelet therapy for primary prevention of CV events	▪ Low-dose aspirin, or clopidogrel if intolerant, for secondary prevention of CVD ▪ Aspirin and clopidogrel for diabetics with ACS for at least one year ▪ Tailored antiplatelet therapy for primary prevention of CVD in: » Diabetics with a 10-year CVD risk of ≥10% and without increased risk of bleeding » Diabetics at intermediate risk (10-year CVD risk 5–10%)	▪ Low-dose aspirin, or clopidogrel if intolerant, for secondary prevention CVD ▪ Long-term aspirin if ACS present ▪ Add-on clopidogrel if: » NSTEMI for 3 months » STEMI up to 4 weeks	▪ Low-dose aspirin, or clopidogrel if intolerant, for secondary prevention CVD for: » Aged >50 years and blood pressure <145/90 mmHg » Aged <50 years with high CV risk

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; CV, cardiovascular; CVD, cardiovascular disease; CCB, calcium channel blocker; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; LDL, low density lipoprotein; NSTEMI, non ST elevation myocardial infarction; OHA, oral hypoglycaemic agent; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; SU, sulphonylurea; TZD, thiazolidinedione.

References:

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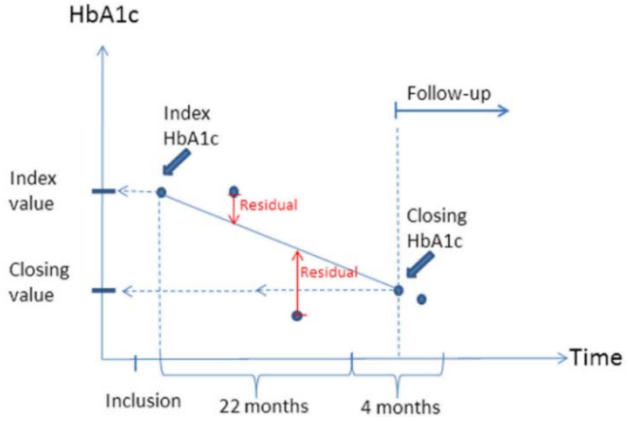
3. Scottish Intercollegiate Guidelines Network. *SIGN 116: Management of Diabetes - A National Clinical Guideline*, March 2010.
4. National Institute for Health and Care Excellence. *Type 2 Diabetes: The Management of Type 2 Diabetes, NICE Clinical Guideline 87*, modified December 2014.

Appendix B Glycaemic variability metrics and calculation

	Metric[1,2]	Formula / Method	
SD	Standard deviation	$\sqrt{\frac{\sum_{i=1}^{n}(x_i-\overline{x})^2}{(n-1)}}$	x = HbA1c value $\overline{x}$ = mean HbA1c n = number of patients
	Adjusted SD[3]	$\frac{SD}{\sqrt{\frac{n}{(n-1)}}}$	
CV	Coefficient of variation	$100 * \frac{SD}{\overline{x}}$	
VIM	Variation independent of mean	$k * \frac{SD}{\overline{x}^m}$	k = constant m is derived by fitting a curve of the form $SD = k * \overline{x}^m$ to a plot of SD against mean
ARV	Average real variability	$\frac{1}{n-1}\sum_{i=1}^{n-1}\lvert x_{i+1}-x_i\rvert$	
SV	Successive variation	$\sqrt{\frac{1}{n-1}\sum_{i=1}^{n-1}(x_{i+1}-x_i)^2}$	
Mean absolute residual[4]			

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2. Hirakawa, et al. Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: The ADVANCE Trial. *Diabetes Care* 2014, 37:2359–2365
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Appendix C Changes in the QOF indicators for diabetes

	Quality indicators	2004-2005	2006-2007	2009-2010	2011-2012		Quality indicators	2013-2014	2014-2015
DM1	The practice can produce a register of all patients with diabetes mellitus	●				**DM001**	The contractor establishes and maintains a register of all patients aged 17 or over with diabetes mellitus, which specifies the type of diabetes where a diagnosis has been confirmed	●	
DM2	The percentage of patients with diabetes whose notes record BMI in the previous 15 months	●	●	●	●	**DM002**	The percentage of patients with diabetes, on the register, in whom the last blood pressure reading (measured in the preceding 12 months) is ≤150/90 mmHg	●	●
DM3	The percentage of patients with diabetes in whom there is a record of smoking status in the previous 15 months except those who have never smoked where smoking status should be recorded once	●				**DM003**	The percentage of patients with diabetes, on the register, in whom the last blood pressure reading (measured in the preceding 12 months) is ≤140/80 mmHg	●	●
DM4	The percentage of patients with diabetes who smoke and whose notes contain a record that smoking cessation advice has been offered in the last 15 months	●				**DM004**	The percentage of patients with diabetes, on the register, whose last measured total cholesterol (measured within the preceding 12 months) is ≤5 mmol/L	●	●
DM5	The percentage of patients with diabetes who have a record of HbA1c or equivalent in the previous 15 months	●	●	●		**DM005**	The percentage of patients with diabetes, on the register, who have a record of an albumin : creatinine ratio test in the preceding 12 months	●	
DM6	The percentage of patients with diabetes in whom the last HbA1C is ≤7.4% (or equivalent test/reference range depending on local laboratory) in the last 15 months	●				**DM006**	The percentage of patients with diabetes, on the register, with a diagnosis of nephropathy (clinical proteinuria) or microalbuminuria who are currently treated with an ACEI (or ARB)	●	●
DM7	The percentage of patients with diabetes in whom the last HbA1C is ≤10% (or equivalent test/reference range depending on local laboratory) in the last 15 months	●	●			**DM007**	The percentage of patients with diabetes, on the register, in whom the last IFCC-HbA1c is ≤59 mmol/mol in the preceding 12 months	●	●
DM8	The percentage of patients with diabetes who have a record of retinal screening in the previous 15 months	●				**DM008**	The percentage of patients with diabetes, on the register, in whom the last IFCC-HbA1c is ≤64 mmol/mol in the preceding 12 months	●	●
DM9	The percentage of patients with diabetes with a record of the presence or absence of peripheral pulses in the previous 15 months	●	●	●		**DM009**	The percentage of patients with diabetes, on the register, in whom the last IFCC-HbA1c is ≤75 mmol/mol in the preceding 12 months	●	●

DM10	The percentage of patients with diabetes with a record of neuropathy testing in the previous 15 months	●	●	●	●	**DM010**	The percentage of patients with diabetes, on the register, who have had influenza immunisation in the preceding 1 September to 31 March	●	
DM11	The percentage of patients with diabetes who have a record of the blood pressure in the previous 15 months	●	●	●		**DM011**	The percentage of patients with diabetes, on the register, who have a record of retinal screening in the preceding 12 months	●	
DM12	The percentage of patients with diabetes in whom the last blood pressure is ≤145/85 mmHg	●	●	●		**DM012**	The percentage of patients with diabetes, on the register, with a record of a foot examination and risk classification: 1) low risk (normal sensation, palpable pulses), 2) increased risk (neuropathy or absent pulses), 3) high risk (neuropathy or absent pulses plus deformity or skin changes in previous ulcer) or 4) ulcerated foot within the preceding 12 month	●	●
DM13	The percentage of patients with diabetes who have a record of microalbuminuria testing in the previous 15 months (exception reporting for patients with proteinuria)	●	●	●	●	**DM013**	The percentage of patients with diabetes, on the register, who have a record of a dietary review by a suitably competent professional in the preceding 12 months	●	
DM14	The percentage of patients with diabetes who have a record of serum creatinine testing in the previous 15 months	●				**DM014**	The percentage of patients newly diagnosed with diabetes, on the register, in the preceding 1 April to 31 March who have a record of being referred to a structured education programme within 9 months after entry on to the diabetes register	●	●
DM15	The percentage of patients with diabetes with a diagnosis of proteinuria or microalbuminuria who are treated with ACE inhibitors (or ARBs)	●	●	●	●	**DM015**	The percentage of male patients with diabetes, on the register, with a record of being asked about erectile dysfunction in the preceding 12 months	●	
DM16	The percentage of patients with diabetes who have a record of total cholesterol in the previous 15 months	●	●	●		**DM016**	The percentage of male patients with diabetes on the register who have a record of erectile dysfunction with a record of advice and assessment of contributory factors and treatment options in the preceding 12 months	●	
DM17	The percentage of patients with diabetes whose last measured total cholesterol within the previous 15 months is ≤5 mmol/L	●	●	●	●	**DM017**	The contractor establishes and maintains a register of all patients aged 17 or over with diabetes mellitus, which specifies the type of diabetes where a diagnosis has been confirmed		●
DM18	The percentage of patients with diabetes who have had influenza immunisation in the preceding 1 September to 31 March	●	●	●	●	**DM018**	The percentage of patients with diabetes on the register who have had influenza immunisation in the preceding 1 August to 31 March		●

DM19	The practice can produce a register of all patients aged 17 years and over with diabetes mellitus, which specifies whether the patient has Type 1 or Type 2 diabetes	●	●	●
DM20	The percentage of patients with diabetes in whom the last HbA1C is ≤7.5% (or equivalent test/reference range depending on local laboratory) in the previous 15 months	●		
DM21	The percentage of patients with diabetes who have a record of retinal screening in the previous 15 months	●	●	●
DM22	The percentage of patients with diabetes who have a record of estimated glomerular filtration rate (eGFR) or serum creatinine testing in the previous 15 months	●	●	●
DM23	The percentage of patients with diabetes in whom the last HbA1c is ≤7% (or equivalent test/reference range depending on local laboratory) in the previous 15 months		●	
DM24	The percentage of patients with diabetes in whom the last HbA1c is ≤8% (or equivalent test/reference range depending on local laboratory) in the previous 15 months		●	
DM25	The percentage of patients with diabetes in whom the last HbA1c is ≤9% (or equivalent test/reference range depending on local laboratory) in the previous 15 months		●	
DM26	The percentage of patients with diabetes in whom the last IFCC-HbA1c is ≤59 mmol/mol (~ HbA1c of ≤7.5% in DCCT values) or equivalent test/reference range depending on local laboratory in the preceding 15 months			●
DM27	The percentage of patients with diabetes in whom the last IFCC-HbA1c is ≤64 mmol/mol (~ HbA1c of ≤8% in DCCT values) or equivalent test/reference range depending on local laboratory in the preceding 15 months			●

DM28	The percentage of patients with diabetes in whom the last IFCC-HbA1c is ≤75 mmol/mol (~ HbA1c of ≤9% in DCCT values) or equivalent test/reference range depending on local laboratory in the preceding 15 months	●	
DM29	The percentage of patients with diabetes with a record of a foot examination and risk classification: 1) low risk (normal sensation, palpable pulses), 2) increased risk (neuropathy or absent pulses), 3) high risk (neuropathy or absent pulses plus deformity or skin changes in previous ulcer) or 4) ulcerated foot within the preceding 15 months	●	
DM30	The percentage of patients with diabetes in whom the last blood pressure is ≤150/90 mmHg	●	
DM31	The percentage of patients with diabetes in whom the last blood pressure is ≤140/80 mmHg	●	

DM19 is omitted in the 2012-2013 QOF.

Reference:

NHS Employers. *Quality and Outcomes Framework.* Available at: http://www.nhsemployers.org/your-workforce/primary-care-contacts/general-medical-services/quality-and-outcomes-framework

Appendix D Read, ICD-10 and OPCS-4 codes for T2D, CVDs and microvascular diseases

Table D1 Diagnostic codes for T2D[1]

Read code	Read term
66Ao.00	Diabetes type 2 review
C100100	Diabetes mellitus, adult onset, no mention of complication
C100111	Maturity onset diabetes
C100112	Non-insulin dependent diabetes mellitus
C101100	Diabetes mellitus, adult onset, with ketoacidosis
C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
C104100	Diabetes mellitus, adult onset, with renal manifestation
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
C106100	Diabetes mellitus, adult onset, + neurological manifestation
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
C107200	Diabetes mellitus, adult with gangrene
C107400	NIDDM with peripheral circulatory disorder
C109.00	Non-insulin dependent diabetes mellitus
C109.11	NIDDM - Non-insulin dependent diabetes mellitus
C109.12	Type 2 diabetes mellitus
C109.13	Type II diabetes mellitus
C109000	Non-insulin-dependent diabetes mellitus with renal comps
C109011	Type II diabetes mellitus with renal complications
C109012	Type 2 diabetes mellitus with renal complications
C109100	Non-insulin-dependent diabetes mellitus with ophthalmic comps
C109111	Type II diabetes mellitus with ophthalmic complications
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109200	Non-insulin-dependent diabetes mellitus with neuro comps
C109211	Type II diabetes mellitus with neurological complications
C109212	Type 2 diabetes mellitus with neurological complications
C109300	Non-insulin-dependent diabetes mellitus with multiple comps
C109400	Non-insulin dependent diabetes mellitus with ulcer
C109411	Type II diabetes mellitus with ulcer
C109412	Type 2 diabetes mellitus with ulcer
C109500	Non-insulin dependent diabetes mellitus with gangrene
C109511	Type II diabetes mellitus with gangrene
C109512	Type 2 diabetes mellitus with gangrene
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C109700	Non-insulin dependent diabetes mellitus - poor control
C109711	Type II diabetes mellitus - poor control
C109712	Type 2 diabetes mellitus - poor control
C109900	Non-insulin-dependent diabetes mellitus without complication
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11	Type II diabetes mellitus with mononeuropathy
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C109B11	Type II diabetes mellitus with polyneuropathy
C109C00	Non-insulin dependent diabetes mellitus with nephropathy
C109C11	Type II diabetes mellitus with nephropathy
C109C12	Type 2 diabetes mellitus with nephropathy
C109D00	Non-insulin dependent diabetes mellitus with hypoglycaemic coma
C109D11	Type II diabetes mellitus with hypoglycaemic coma
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C109E00	Non-insulin dependent diabetes mellitus with diabetic cataract

C109E11	Type II diabetes mellitus with diabetic cataract
C109E12	Type 2 diabetes mellitus with diabetic cataract
C109F00	Non-insulin-dependent diabetes mellitus with peripheral angiopathy
C109F11	Type II diabetes mellitus with peripheral angiopathy
C109F12	Type 2 diabetes mellitus with peripheral angiopathy
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
C109G11	Type II diabetes mellitus with arthropathy
C109G12	Type 2 diabetes mellitus with arthropathy
C109H00	Non-insulin dependent diabetes mellitus with neuropathic arthropathy
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C109J00	Insulin treated Type 2 diabetes mellitus
C109J11	Insulin treated non-insulin dependent diabetes mellitus
C109J12	Insulin treated Type II diabetes mellitus
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10C.11	Maturity onset diabetes in youth
C10D.00	Diabetes mellitus autosomal dominant type 2
C10D.11	Maturity onset diabetes in youth type 2
C10ER00	Latent autoimmune diabetes mellitus in adult
C10F.00	Type 2 diabetes mellitus
C10F.11	Type II diabetes mellitus
C10F000	Type 2 diabetes mellitus with renal complications
C10F011	Type II diabetes mellitus with renal complications
C10F100	Type 2 diabetes mellitus with ophthalmic complications
C10F200	Type 2 diabetes mellitus with neurological complications
C10F211	Type II diabetes mellitus with neurological complications
C10F300	Type 2 diabetes mellitus with multiple complications
C10F311	Type II diabetes mellitus with multiple complications
C10F400	Type 2 diabetes mellitus with ulcer
C10F411	Type II diabetes mellitus with ulcer
C10F500	Type 2 diabetes mellitus with gangrene
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
C10F700	Type 2 diabetes mellitus - poor control
C10F711	Type II diabetes mellitus - poor control
C10F900	Type 2 diabetes mellitus without complication
C10F911	Type II diabetes mellitus without complication
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FA11	Type II diabetes mellitus with mononeuropathy
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10FB11	Type II diabetes mellitus with polyneuropathy
C10FC00	Type 2 diabetes mellitus with nephropathy
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11	Type II diabetes mellitus with hypoglycaemic coma
C10FE00	Type 2 diabetes mellitus with diabetic cataract
C10FE11	Type II diabetes mellitus with diabetic cataract
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
C10FJ00	Insulin treated Type 2 diabetes mellitus
C10FJ11	Insulin treated Type II diabetes mellitus
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FL00	Type 2 diabetes mellitus with persistent proteinuria
C10FL11	Type II diabetes mellitus with persistent proteinuria
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
C10FM11	Type II diabetes mellitus with persistent microalbuminuria
C10FN00	Type 2 diabetes mellitus with ketoacidosis
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy

C10FR00	Type 2 diabetes mellitus with gastroparesis
C10y100	Diabetes mellitus, adult, + other specified manifestation
C10z100	Diabetes mellitus, adult onset, + unspecified complication
L180600	Pre-existing diabetes mellitus, non-insulin-dependent
ZC2CA00	Dietary advice for type II diabetes

ICD-10 code*	ICD-10 term
E11	Non-insulin-dependent diabetes mellitus

*Includes all codes below the 3-digit code

Table D2 Diagnostic and procedure codes for specific CVDs in CALIBER[2]

CVD	Primary care CPRD - Read codes	Disease Registry MINAP - Registry specific	Hospital procedures HES - OPCS-4	Hospital diagnoses[a] HES - ICD-10	Causes of death[b] ONS - ICD-10
Acute myocardial infarction	G30X000 Acute ST segment EMI, G307100 Acute non-ST segment EMI, G30.14 Heart attack, G30.15 MI Acute myocardial infarction + 60 other codes as acute myocardial infarction not otherwise specified	MI with or without ST elevation based on initial ECG findings, raised troponins and clinical diagnosis	Not used (there is no code that is specific to primary coronary intervention)	I21 Acute myocardial infarction, I23 Current complications of acute myocardial infarction	I21 Acute myocardial infarction, I23 Current complications of acute myocardial infarction
Unstable angina	G311.13/G311100 Unstable angina, G233200 Angina at rest, G311400 Worsening angina + 13 other codes	Discharge diagnosis of unstable angina, no raised ST elevation, no raised troponin levels	nu	I20.0 Unstable or worsening angina, I24 Acute ischaemic heart disease, I24.0 Coronary thrombosis not resulting in myocardial infarction, I24.8 Other forms of ischaemic heart disease, I24.9 Acute ischaemic heart disease, unspecified	nu
Stable angina	G33..00 Stable angina, G33z.00 Angina pectoris NOS + 25 other codes for diagnosis of stable angina pectoris, 30 codes for evidence of coronary artery disease at angiography (CT, MR, invasive or not specified), 151 Read codes for evidence of myocardial ischaemia (resting ECG, exercise ECG,	nu	K40-K46 Coronary Artery Bypass Graft (CABG) or K49, K50, K75 Percutaneous Coronary Intervention (PCI), not within 30 days of an ACS	I20 Stable angina pectoris excluding unstable angina I20.0	nu

	stress echo, radioisotope scan), Two or more successive prescriptions for anti-anginals				
Coronary heart disease not otherwise specified	G3...00 Ischaemic heart disease + 90 other codes including CHD NOS, chronic ischaemic heart disease, silent myocardial infarction	nu	nu	I25 CHD NOS, chronic ischaemic heart disease, silent myocardial infarction excluding old myocardial infarction I25.2	nu
Heart failure	G58.00 Heart Failure + 92 other Read codes for heart failure diagnosis	nu	nu	I50 Heart failure (including all sub), I11.0 Hypertensive heart disease with (congestive) heart failure, I13.0 Hypertensive heart and renal disease with (congestive) heart failure, I13.2 Hypertensive heart and renal disease with both (congestive) heart failure and renal disease	I50 Heart failure, I11.0 Hypertensive heart disease with (congestive) heart failure, I13.0 Hypertensive heart and renal disease with (congestive) heart failure, I13.2 Hypertensive heart and renal disease with both (congestive) heart failure and renal disease
Ventricular arrhythmia, cardiac arrest and sudden cardiac death	G574.00 Ventricular fibrillation and flutter, G757.00 Cardiac arrest + 35 other Read codes for ventricular fibrillation, asystole, cardiac arrest, cardiac resuscitation, electro-mechanical dissociation, G575100 Sudden cardiac death, so described	nu	X50 Implanted cardiac defibrillation device, K59 Implantation, revision and renewal of cardiac defibrillator	I46 (cardiac arrest) I47.0 (re-entry ventricular arrhythmia) I47.2 (ventricular tachycardia)	I46 (cardiac arrest, including sudden cardiac death I46.1), I47.0 (re-entry ventricular arrhythmia) I47.2 (ventricular tachycardia)
Unheralded coronary death	Any CVD excluded	Any CVD excluded	Any CVD excluded	Any CVD excluded	I20 Angina Pectoris, I21 Acute myocardial infarction, I22 Subsequent myocardial infarction,

					I23 Certain current complications following acute myocardial infarction, I24 Other acute ischaemic heart diseases and I25 Chronic ischaemic heart disease not preceded by any other CVD presentation
Ischaemic stroke	G64.11 CVA – cerebral artery occlusion, G64.13 Stroke due to cerebral arterial occlusion, G6W.00 Cerebral infarction due unspecified occlusion/stenosis of precerebral arteries, G6X.00 cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries + 8 other codes	nu	nu	I63 cerebral infarction	I63 cerebral infarction
Haemorrhagic stroke	93 codes for subarachnoid haemorrhage, intracerebral haemorrhage, and intracranial haemorrhage not otherwise specified	nu		I60 Subarachnoid haemorrhage, I61.0 Intracerebral haemorrhage in hemisphere, subcortical, I61.1 Intracerebral haemorrhage in hemisphere, cortical, I61.2 Intracerebral haemorrhage in hemisphere unspecified, I61.3 Intracerebral haemorrhage in brain stem, I61.4 Intracerebral haemorrhage in cerebellum, I61.5 Intracerebral haemorrhage intraventricular, I61.6 Intracerebral	nu

				haemorrhage, multiple localized, I61.8 Other intracerebral haemorrhage, I61.9 Intracerebral haemorrhage	
Peripheral arterial disease	72 codes for lower limb peripheral arterial disease diagnosis (including diabetic peripheral arterial disease, gangrene and intermittent claudication, evidence of atherosclerosis of iliac and lower limb arteries based on angiography or Dopplers)	nu	L50-L54 Bypass, reconstruction and other open operations on iliac artery L58-L60, L62 Bypass, reconstruction, transluminal operations or other open operations of femoral artery, L65 Revision of reconstruction of artery	I70.2 atherosclerosis of arteries of extremities, I73.9 peripheral vascular disease intermittent claudication, peripheral complications of diabetes including gangrene 0.5 suffix of E10 Insulin dependent diabetes mellitus, E11 Non-insulin-dependent diabetes mellitus, E12 Malnutrition-related diabetes mellitus, E13 Other specified diabetes mellitus, E14 Unspecified diabetes mellitus	I70.2 atherosclerosis of arteries of extremities, I73.9 peripheral vascular disease intermittent claudication, peripheral complications of diabetes including gangrene 0.5 suffix of E10 Insulin dependent diabetes mellitus, E11 Non-insulin-dependent diabetes mellitus, E12 Malnutrition-related diabetes mellitus, E13 Other specified diabetes mellitus, E14 Unspecified diabetes mellitus
Abdominal aortic aneurysm (AAA)	G714.00 Abdominal aortic aneurysm without mention of rupture + 11 more codes for AAA diagnosis. 13 codes for evidence of AAA on ultrasound or CT scan	nu	L16 Extra anatomic bypass of aorta, L18-L23 Replacement of aneurysmal segment of aorta, bypass of segment of aorta, plastic repair of aorta, L25-L28 Transluminal or endovascular insertion of stent on aneurysmal segment of aorta	I71.3 Abdominal aortic aneurysm, ruptured. 171.4 AAA, without rupture	I71.3 Abdominal aortic aneurysm, ruptured. 171.4 AAA, without rupture

[a]Primary cause of admission; [b]Underlying cause of death; nu, not used in definition.

Table D3 Diagnostic codes for microvascular diseases[1]

Microvascular disease	Read code	Read term
Kidney - diabetic nephropathy	C104.00	Diabetes mellitus with renal manifestation
	C104.11	Diabetic nephropathy
	C104000	Diabetes mellitus, juvenile type, with renal manifestation
	C104100	Diabetes mellitus, adult onset, with renal manifestation
	C104y00	Other specified diabetes mellitus with renal complications
	C104z00	Diabetes mellitus with nephropathy NOS
	C108000	Insulin-dependent diabetes mellitus with renal complications
	C108011	Type I diabetes mellitus with renal complications
	C108012	Type 1 diabetes mellitus with renal complications
	C108D00	Insulin dependent diabetes mellitus with nephropathy
	C108D11	Type I diabetes mellitus with nephropathy
	C109000	Non-insulin-dependent diabetes mellitus with renal comps
	C109011	Type II diabetes mellitus with renal complications
	C109012	Type 2 diabetes mellitus with renal complications
	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
	C109C11	Type II diabetes mellitus with nephropathy
	C109C12	Type 2 diabetes mellitus with nephropathy
	C10E000	Type 1 diabetes mellitus with renal complications
	C10ED00	Type 1 diabetes mellitus with nephropathy
	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
	C10F000	Type 2 diabetes mellitus with renal complications
	C10F011	Type II diabetes mellitus with renal complications
	C10FC00	Type 2 diabetes mellitus with nephropathy
	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
	C10FL11	Type II diabetes mellitus with persistent proteinuria
	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
	C314.11	Renal diabetes
	K01x100	Nephrotic syndrome in diabetes mellitus
	K01x111	Kimmelstiel - Wilson disease
Neurological complications of diabetes	C106.00	Diabetes mellitus with neurological manifestation
	C106.11	Diabetic amyotrophy
	C106.12	Diabetes mellitus with neuropathy
	C106.13	Diabetes mellitus with polyneuropathy
	C106000	Diabetes mellitus, juvenile, + neurological manifestation
	C106100	Diabetes mellitus, adult onset, + neurological manifestation
	C106y00	Other specified diabetes mellitus with neurological comps
	C106z00	Diabetes mellitus NOS with neurological manifestation
	C108200	Insulin-dependent diabetes mellitus with neurological comps
	C108211	Type I diabetes mellitus with neurological complications
	C108212	Type 1 diabetes mellitus with neurological complications
	C108B00	Insulin dependent diabetes mellitus with mononeuropathy
	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
	C108J00	Insulin dependent diabetes mellitus with neuropathic arthropathy
	C108J11	Type I diabetes mellitus with neuropathic arthropathy
	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
	C109211	Type II diabetes mellitus with neurological complications
	C109212	Type 2 diabetes mellitus with neurological complications
	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
	C109A11	Type II diabetes mellitus with mononeuropathy
	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
	C109B11	Type II diabetes mellitus with polyneuropathy
	C109H00	Non-insulin dependent diabetes mellitus with neuropathic arthropathy
	C109H11	Type II diabetes mellitus with neuropathic arthropathy
	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
	C10E200	Type 1 diabetes mellitus with neurological complications
	C10EB00	Type 1 diabetes mellitus with mononeuropathy
	C10EC00	Type 1 diabetes mellitus with polyneuropathy

	C10EC11	Type I diabetes mellitus with polyneuropathy
	C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
	C10EQ00	Type 1 diabetes mellitus with gastroparesis
	C10F200	Type 2 diabetes mellitus with neurological complications
	C10F211	Type II diabetes mellitus with neurological complications
	C10FA00	Type 2 diabetes mellitus with mononeuropathy
	C10FA11	Type II diabetes mellitus with mononeuropathy
	C10FB00	Type 2 diabetes mellitus with polyneuropathy
	C10FB11	Type II diabetes mellitus with polyneuropathy
	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
	C10FR00	Type 2 diabetes mellitus with gastroparesis
	F171100	Autonomic neuropathy due to diabetes
	F345000	Diabetic mononeuritis multiplex
	F35z000	Diabetic mononeuritis NOS
	F372.00	Polyneuropathy in diabetes
	F372.11	Diabetic polyneuropathy
	F372.12	Diabetic neuropathy
	F372000	Acute painful diabetic neuropathy
	F372100	Chronic painful diabetic neuropathy
	F372200	Asymptomatic diabetic neuropathy
	F381300	Myasthenic syndrome due to diabetic amyotrophy
	F381311	Diabetic amyotrophy
	F3y0.00	Diabetic mononeuropathy
	M271100	Neuropathic diabetic ulcer - foot
	N030100	Diabetic Charcot arthropathy
Eye complications of diabetes apart from retinopathy (e.g. cataract, or unspecified)	C105.00	Diabetes mellitus with ophthalmic manifestation
	C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
	C105y00	Other specified diabetes mellitus with ophthalmic complications
	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
	C108F00	Insulin dependent diabetes mellitus with diabetic cataract
	C108F11	Type I diabetes mellitus with diabetic cataract
	C109100	Non-insulin-dependent diabetes mellitus with ophthalmic complications
	C109111	Type II diabetes mellitus with ophthalmic complications
	C109112	Type 2 diabetes mellitus with ophthalmic complications
	C109E00	Non-insulin dependent diabetes mellitus with diabetic cataract
	C109E11	Type II diabetes mellitus with diabetic cataract
	C109E12	Type 2 diabetes mellitus with diabetic cataract
	C10E100	Type 1 diabetes mellitus with ophthalmic complications
	C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
	C10EF00	Type 1 diabetes mellitus with diabetic cataract
	C10F100	Type 2 diabetes mellitus with ophthalmic complications
	C10FE00	Type 2 diabetes mellitus with diabetic cataract
	C10FE11	Type II diabetes mellitus with diabetic cataract
	F464000	Diabetic cataract
Retinopathy - retinal disease with no details of severity	2BBF.00	Retinal abnormality - diabetes related
	C108700	Insulin dependent diabetes mellitus with retinopathy
	C108711	Type I diabetes mellitus with retinopathy
	C108712	Type 1 diabetes mellitus with retinopathy
	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
	C109611	Type II diabetes mellitus with retinopathy
	C109612	Type 2 diabetes mellitus with retinopathy
	C10E700	Type 1 diabetes mellitus with retinopathy
	C10E711	Type I diabetes mellitus with retinopathy
	C10E712	Insulin dependent diabetes mellitus with retinopathy
	C10F600	Type 2 diabetes mellitus with retinopathy
	C10F611	Type II diabetes mellitus with retinopathy
	F420.00	Diabetic retinopathy
	F420z00	Diabetic retinopathy NOS
R1 - background diabetic retinopathy	2BBP.00	O/E - right eye background diabetic retinopathy
	2BBQ.00	O/E - left eye background diabetic retinopathy
	F420000	Background diabetic retinopathy

R2 - preproliferative diabetic retinopathy	2BBR.00	O/E - right eye preproliferative diabetic retinopathy
	2BBS.00	O/E - left eye preproliferative diabetic retinopathy
	F420200	Preproliferative diabetic retinopathy
	F420500	Advanced diabetic retinal disease
	F420600	Non proliferative diabetic retinopathy
	F420800	High risk non proliferative diabetic retinopathy
RSa - active proliferative diabetic retinopathy	2BBT.00	O/E - right eye proliferative diabetic retinopathy
	2BBV.00	O/E - left eye proliferative diabetic retinopathy
	2BBo.00	O/E - sight threatening diabetic retinopathy
	F420100	Proliferative diabetic retinopathy
	F420700	High risk proliferative diabetic retinopathy
R3s - treated or stable proliferative diabetic retinopathy	2BBk.00	O/E - right eye stable treated proliferative diabetic retinopathy
	2BBl.00	O/E - left eye stable treated proliferative diabetic retinopathy
	7276	Pan retinal photocoagulation for diabetes
Maculopathy	2BBL.00	O/E - diabetic maculopathy present both eyes
	2BBW.00	O/E - right eye diabetic maculopathy
	2BBX.00	O/E - left eye diabetic maculopathy
	C10EP00	Type 1 diabetes mellitus with exudative maculopathy
	C10EP11	Type I diabetes mellitus with exudative maculopathy
	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
	F420300	Advanced diabetic maculopathy
	F420400	Diabetic maculopathy

Microvascular disease	ICD10 code	ICD10 term
Kidney - diabetic nephropathy	E102	Insulin-dependent diabetes mellitus; With renal complications
	E112	Non-insulin-dependent diabetes mellitus; With renal complications
	E122	Malnutrition-related diabetes mellitus; With renal complications
	E132	Other specified diabetes mellitus; With renal complications
	E142	Unspecified diabetes mellitus; With renal complications
	N083	Glomerular disorders in diabetes mellitus
Neurological complications of diabetes	E104	Insulin-dependent diabetes mellitus; With neurological complications
	E114	Non-insulin-dependent diabetes mellitus; With neurological complications
	E124	Malnutrition-related diabetes mellitus; With neurological complications
	E134	Other specified diabetes mellitus; With neurological complications
	E144	Unspecified diabetes mellitus; With neurological complications
	G590	Diabetic mononeuropathy
	G632	Diabetic polyneuropathy
Eye complications of diabetes apart from retinopathy (e.g. cataract, or unspecified)	E103	Insulin-dependent diabetes mellitus; With ophthalmic complications
	E113	Non-insulin-dependent diabetes mellitus; With ophthalmic complications
	E123	Malnutrition-related diabetes mellitus; With ophthalmic complications
	E133	Other specified diabetes mellitus; With ophthalmic complications
	E143	Unspecified diabetes mellitus; With ophthalmic complications
Retinopathy with no details of severity	H360	Diabetic retinopathy

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Appendix E Definition of microvascular diseases according to clinical guidelines and diabetes outcome trials

	Retinopathy	Nephropathy	Neuropathy
Clinical guidelines			
AACE/ACE[1]	Not clearly defined	**CKD:** ▪ Abnormalities of kidney structure or function, pre-sent for >3 months, with implications for health: • Markers of kidney damage (one or more): ✓ Albuminuria (AER ≥30 mg/day; ACR ≥30 mg/g [≥3 mg/mmol]) ✓ Urine sediment abnormalities ✓ Electrolyte and other abnormalities due to tubular disorders ✓ Abnormalities detected by histology ✓ Structural abnormalities detected by imaging ✓ History of kidney transplantation • Decreased GFR (<60 ml/min/1.73 m^2) ▪ **CKD by GFR category:** • **G1** – GFR ≥90 – Normal or high* • **G2** – 60-89 – Mildly decreased* • **G3a** – 45-59 – Mildly/moderately decreased • **G3b** – 30-44 – Moderately/severely decreased • **G4** – 15-29 – Severely decreased • **G5** – <15 – Kidney failure **In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfil the criteria for CKD* ▪ **CKD by albuminuria category:** • **A1** – AER <30 mg/day, ACR <3 mg/mmol or <30 mg/g – Normal to mildly increased • **A2** – AER 30-300 mg/day, ACR 3-30 mg/mmol or 30-300 mg/g – Moderately increased* • **A3** – AER >300 mg/day, ACR >30 mg/mmol or >300 mg/g – Severely increased**	Not clearly defined

ADA[2]	▪ **NPDR** ▪ **PDR** ▪ **ME** None above is clearly defined.	▪ **Microalbuminuria** – ACR 30-300 mg/g ▪ **Macroalbuminuria** – ACR >300 mg/g ▪ **Diabetic CKD:** • Macroalbuminuria, or • Microalbuminuria + diabetic retinopathy ▪ **CKD stages:** • **Stage 1** – Kidney damage* with normal or increased eGFR (≥90 mL/min/1.73 m^2) • **Stage 2** – Kidney damage* with mildly decreased eGFR (60-89) • **Stage 3** – Moderately decreased eGFR (30-59) • **Stage 4** – Severely decreased eGFR (15-29) • **Stage 5** – Kidney failure (<15 or dialysis) **ACR ≥30 mg/g*	Diagnosis of exclusion - nondiabetic neuropathies may be present in patients with diabetes. ▪ **Diabetic peripheral neuropathy** – pain and dysesthesias, numbness and loss of protective sensation (distal sensorimotor polyneuropathy). ▪ **Diabetic autonomic neuropathy** – hypoglycaemia unawareness, resting tachycardia, orthostatic hypotension, esophageal dysmotility, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, retrograde ejaculation, neurogenic bladder, and sudomotor dysfunction (increased or decreased sweating). ▪ **Cardiac autonomy neuropathy** – decreased HR variability with deep breathing, resting tachycardia (>100 bpm), and orthostatic hypotension (a fall in SBP/DBP by >20/>10 mmHg, respectively, on standing without an appropriate HR increase).
ESC/EASD[3]	▪ **NPDR** ▪ **PDR** ▪ **ME** None above is clearly defined.	Not clearly defined	Not clearly defined
KDOQI[4,5]	N/A	▪ **Microalbuminuria** – ACR 30-299 mg/g ▪ **Macroalbuminuria** – ACR ≥300 mg/g ▪ **Diabetic CKD:** • Macroalbuminuria, or • Microalbuminuria + diabetic retinopathy	N/A
NICE[6,7]	▪ **NPDR –** cotton wool spots plus: • Any venous beading • Any venous reduplication • Any intraretinal microvascular abnormalities • Multiple deep, round or blot haemorrhages	Idem with AACE/ACE	Not clearly defined

	▪ **Maculopathy:** • Exudate or retinal thickening within 1 disc diameter of the centre of fovea • Circinate or group of exudates within macula (a circle centred on the fovea, with a diameter the distance between temporal border of optic disc and fovea) • Any microaneurysm or haemorrhage within 1 disc diameter of the centre of fovea, only if associated with deterioration of best visual acuity to 6/12 or worse		
SIGN[8]	▪ **PDR** – neovascularisation of the disc or neovascularisation elsewhere with vitreous haemorrhage	▪ **Microalbuminuria:** • Urinary albumin loss to 30- 300 mg/day • ACR >2.5 (men) and >3.5 mg/mmol (women) • Albumin concentration >20 mg/L ▪ **Diabetic CKD**: • AER >300 mg/ day (clinical proteinuria) with or without a raised serum creatinine level • ACR > 30 mg/mmol in a spot urine, provi-ding other causes have been excluded • Can occur in the absence of retinopathy ▪ **CKD stages:** • **Stage 1** – Kidney damage* with normal or increased eGFR (≥90 mL/min/1.73 m^2) • **Stage 2** – Kidney damage* with mildly decreased eGFR (60-89) • **Stage 3A** – Moderately decreased eGFR (45-59) • **Stage 3B** – Moderately decreased eGFR (30-44) • **Stage 4** – Severely decreased eGFR (15-29) • **Stage 5** – Kidney failure (<15) **ACR ≥30 mg/g*	N/A

Landmark randomised controlled trials			
UKPDS[9,10]	▪ **Blindness in one eye:** • WHO criteria with Snellen-chart visual acuity of 6/60 or worse • ETDRS logMAR 1.0 or worse, for 3 months ***Subclinical endpoints:*** ▪ **Retinopathy** – ≥1 microaneurysm in one eye or worse retinopathy ▪ **Progression of retinopathy** – a two-step change in grade ▪ **Poor visual acuity**: • logMAR >0.3 (unable to drive a car) • logMAR >0.7 (US definition of blindness) • logMAR ≥1.0 (WHO definition of blindness) ▪ **Deterioration of vision** – a three-line deterioration in reading an ETDRS chart	▪ **Renal failure** – dialysis or plasma creatinine >250 µmol/L not related to any acute intercurrent illness ***Subclinical endpoints:*** ▪ **Microalbuminuria** – urinary albumin concentration >50 mg/L ▪ **Clinical proteinuria** – urinary albumin concentration >300 mg/L	***Subclinical endpoints:*** ▪ **Neuropathy** – loss of both ankle or both knee reflexes or mean biothesiometer reading from both toes ≥25V ▪ **Autonomic neuropathy** – R-R interval less than the age-adjusted normal range (ratio <1.03 of longest R-R interval at approximately beat 30 to shortest at approximately beat 15) ▪ **Orthostatic hypotension** – systolic fall of ≥30 mmHg, or diastolic fall of ≥10 mmHg ▪ **Impotence** – no ejaculation or erection
PROActive[11]	Not clearly defined	Not clearly defined - urinary albumin concentration measured locally using Micral test strips.	Not clearly defined
ADVANCE[12]	▪ **New or worsening retinopathy:** • Development of PDR • ME • Diabetes-related blindness • Retinal photocoagulation therapy ▪ **Visual deterioration –** not clearly defined	▪ **New or worsening nephropathy:** • Development of macroalbuminuria (ACR >300 µg/mg or 33.9 mg/mmol, or doubling of serum creatinine level to ≥200 µmol/L or 2.26 mg/dL) • The need for renal replacement therapy • Death due to renal disease ▪ **Development of microalbuminuria** – ACR 30-300 µg/mg or 0.34-33.9 mg/mmol	▪ **New or worsening neuropathy –** not clearly defined
ACCORD[13]	▪ **Eye-1** – Retinal photocoagulation or vitrectomy ▪ **Eye-2** – Eye surgery for cataract extraction ▪ **Eye-3** – Three-line change in visual acuity (measured using LogMAR visual acuity chart) ▪ **Eye-4** – Severe vision loss (Snellen fraction <20/200)	▪ **Neph-1** – Development of microalbuminuria (ACR ≥3.4 mg/mmol) ▪ **Neph-2** – Development of macroalbuminuria (ACR ≥33.9 mg/mmol) ▪ **Neph-3** – Development of renal failure (initiation of dialysis or ESRD, renal transplantation, or rise of serum creatinine >291.72 µmol/L in the absence of an acute reversible cause)	▪ **Neuro-1** – New score of >2.0 on MNSI* ▪ **Neuro-2** – New loss of vibratory sensation (tested with 128 Hz tuning fork) ▪ **Neuro-3** – New loss of ankle jerk during Jendrassik manoeuvre ▪ **Neuro-4** – New loss of light touch (10 g force monofilament test) **MNSI examination comprises a structured assessment of the feet to identify deformities, dry*

		▪ **Neph-4** – Doubling of baseline serum creatinine or >20 mL/min per 1.73 m2 decrease in eGFR. ▪ **Neph-5** – Development of Neph-2, Neph-3, or Neph-4	*skin, calluses, infec-tion, fissure, or ulcers, and evaluation of ankle reflexes and vibration sensation in the great toe.*
VADT[14]	▪ **Progression to new PDR** – a 2-point increase on the 23-point ETDRS grading scale ▪ **New, clinically important ME** – retinal thickening that involves or threatens the center of macula (even if visual acuity is not yet reduced), assessed by stereo contact lens biomicroscopy or stereo photography	▪ **Severe nephropathy** – doubling of serum creatinine level, creatinine level >3 mg/dL (265 µmol/L), or GFR <15 ml/min ▪ **Progression of albuminuria** – increase of albuminuria for ≥2 successive yearly visits without reversion to an improved level	▪ **Mononeuropathies** – mononeuropathy, mononeuropathy multiplex, or femoral neuropathy ▪ **Peripheral neuropathies** – radiculoneuropathy, polyneuropathy, diabetic amyotrophy, or neuropathic ulcer ▪ **Autonomic neuropathies** – symptomatic orthostatic hypotension, gastroparesis, neurogenic bladder, or diabetic diarrhea *Type of neuropathy – defined as the first outcome reached*

ACR, albumin creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease; DBP, diastolic blood pressure; ESRD, end-stage renal disease; ETDRS, Early Treatment of Diabetic Retinopathy Study; eGFR, estimated glomerular filtration rate; ME, macular edema; MNSI, Michigan neuropathy screening instrument; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; SBP, systolic blood pressure.

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Appendix F Results from sensitivity and subgroup analyses

Chapter 4

Figure F4.1 Proportion of incident T2D cases by year of diagnosis and age group at diagnosis

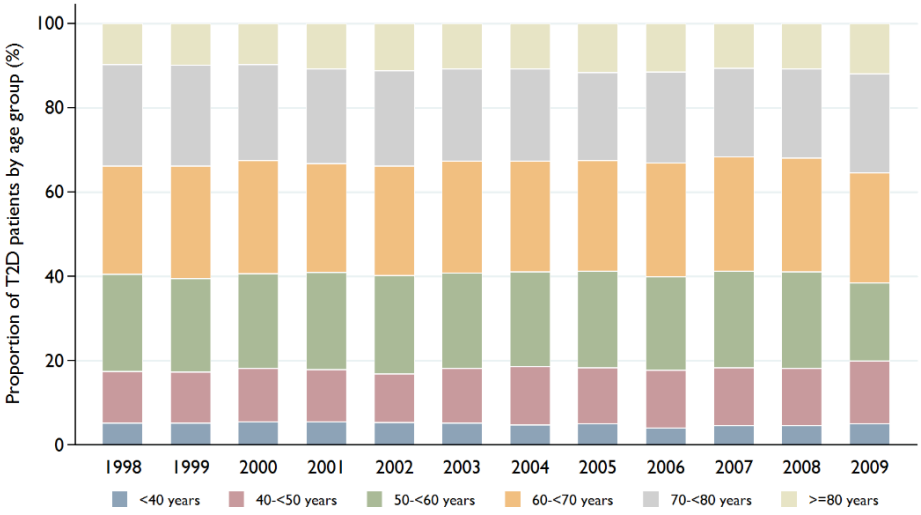


Figure F4.2 Proportion of incident T2D cases by year of diagnosis and gender

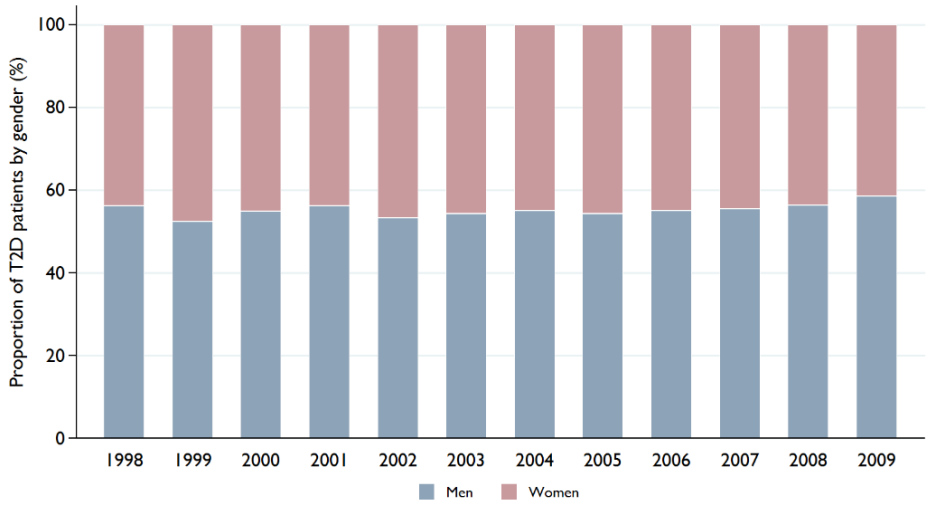


Figure F4.3 Proportion of incident T2D cases by year of diagnosis and ethnicity

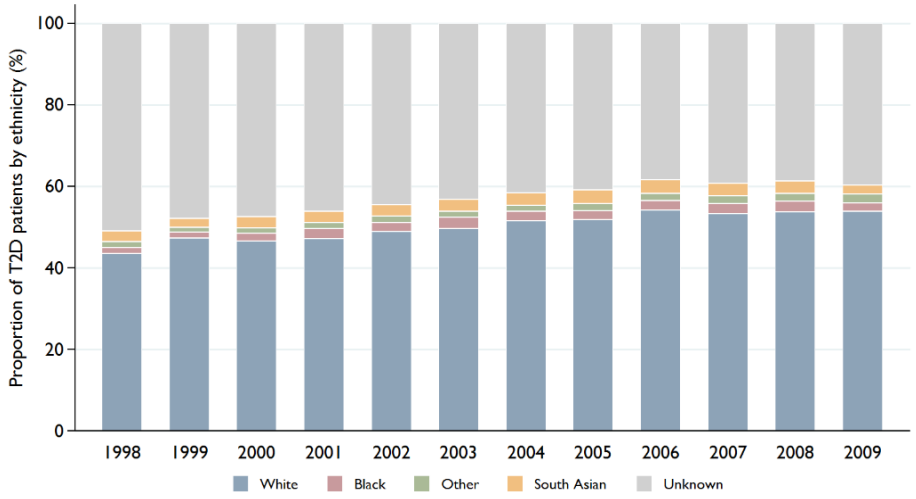


Figure F4.4 Proportion of incident T2D cases by year of diagnosis and deprivation status

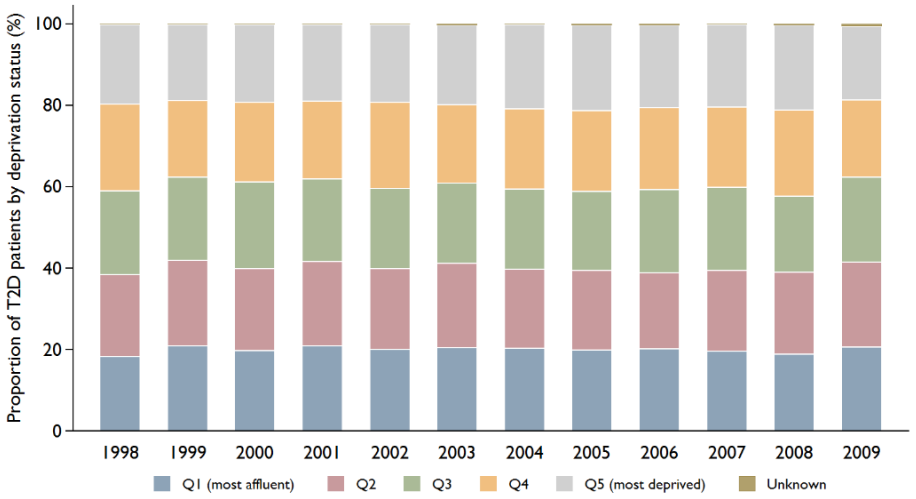


Figure F4.5 Proportion of incident T2D cases by year of diagnosis and prior CVD status

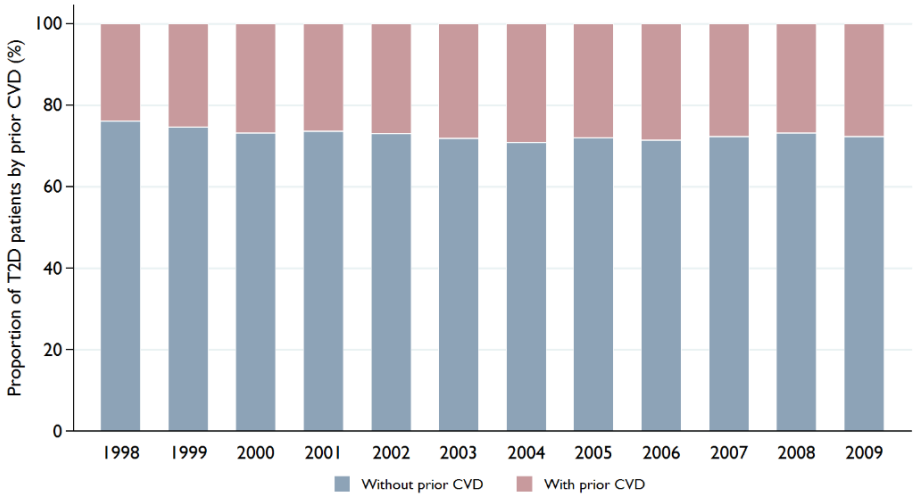


Figure F4.6 Proportion over time of incident T2D cases by diabetes treatment and EHR source

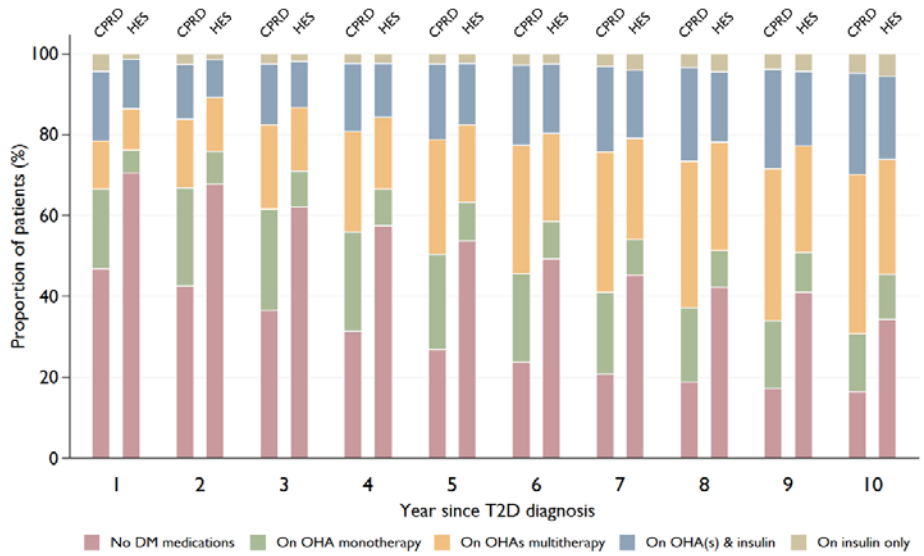


Figure F4.7 Proportion over time of incident T2D cases by diabetes treatment and age group at diagnosis

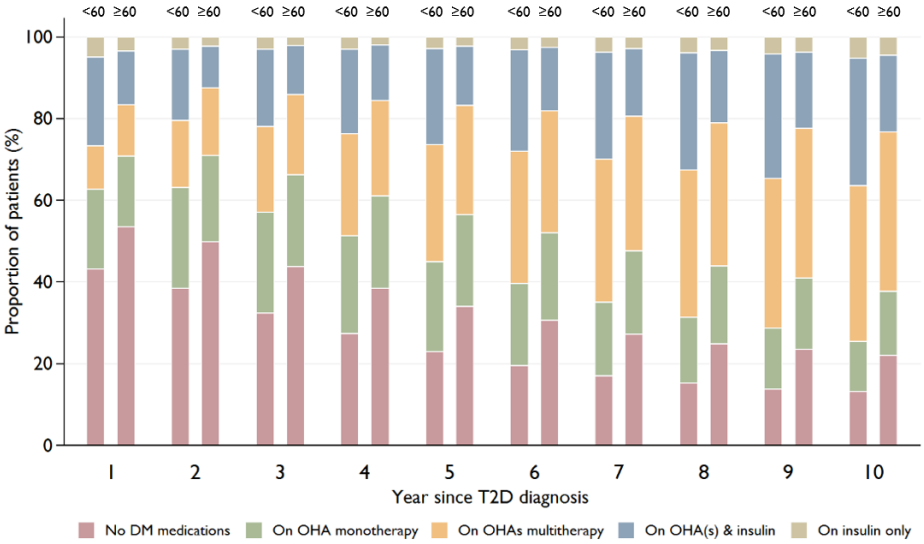


Figure F4.8 Proportion over time of incident T2D cases by diabetes treatment and gender

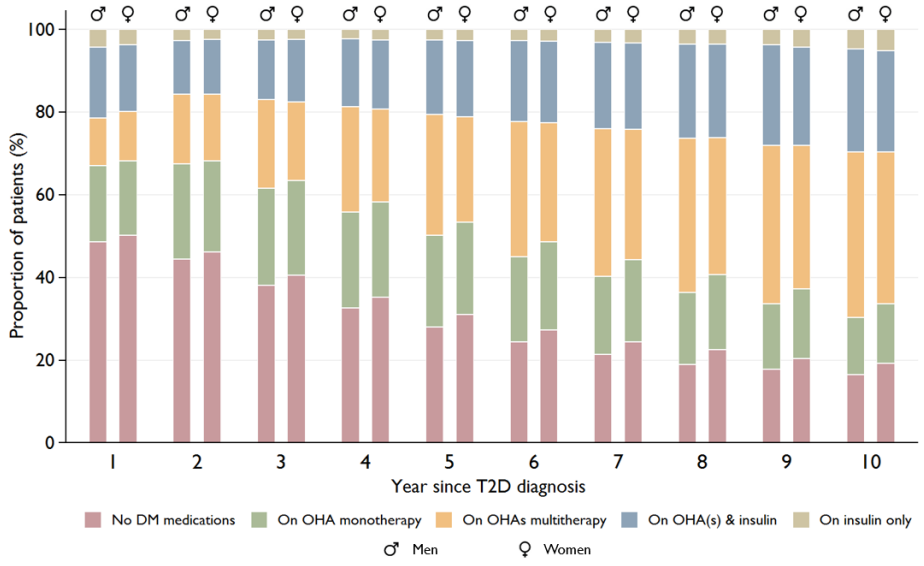


Figure F4.9 Proportion over time of incident T2D cases by diabetes treatment and ethnicity

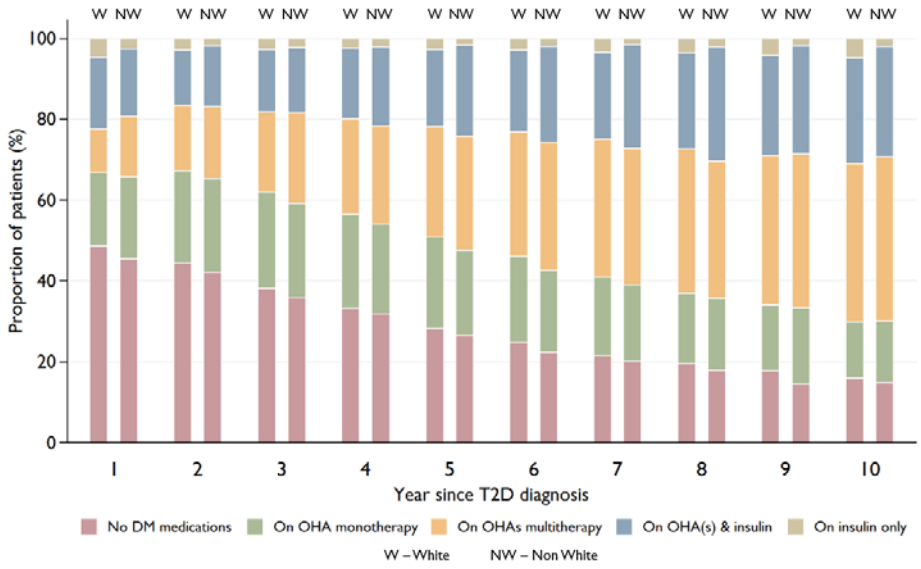


Figure F4.10 Proportion over time of incident T2D cases by diabetes treatment and deprivation status

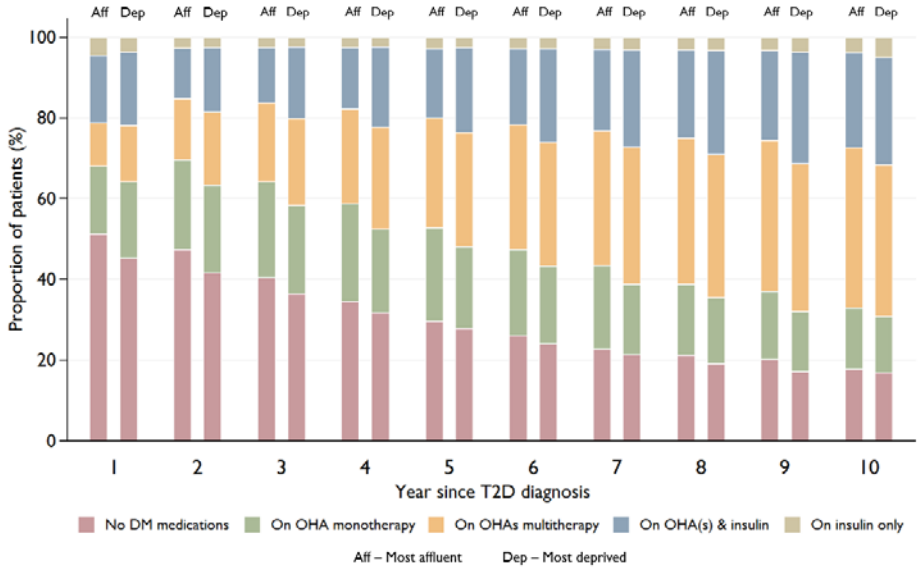


Figure F4.11 Proportion over time of incident T2D cases by diabetes treatment and prior CVD status

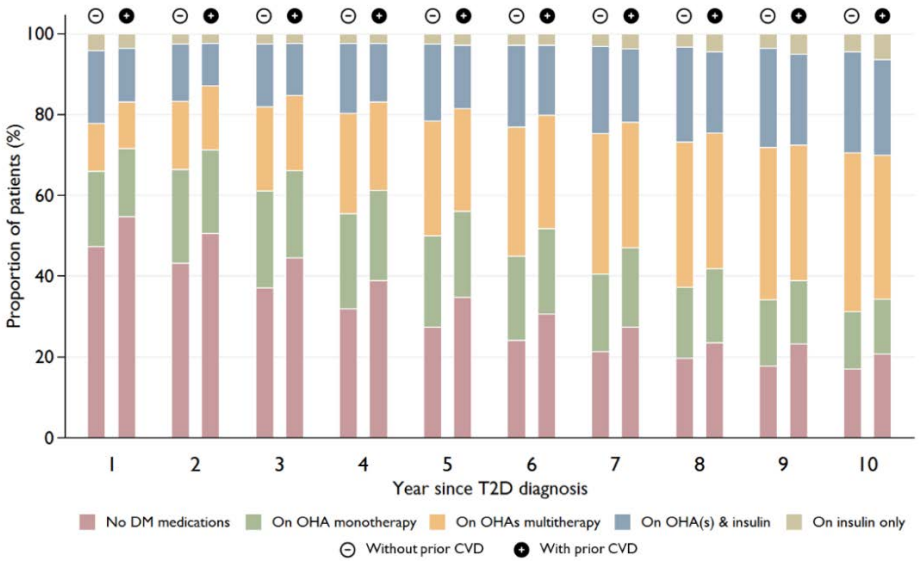
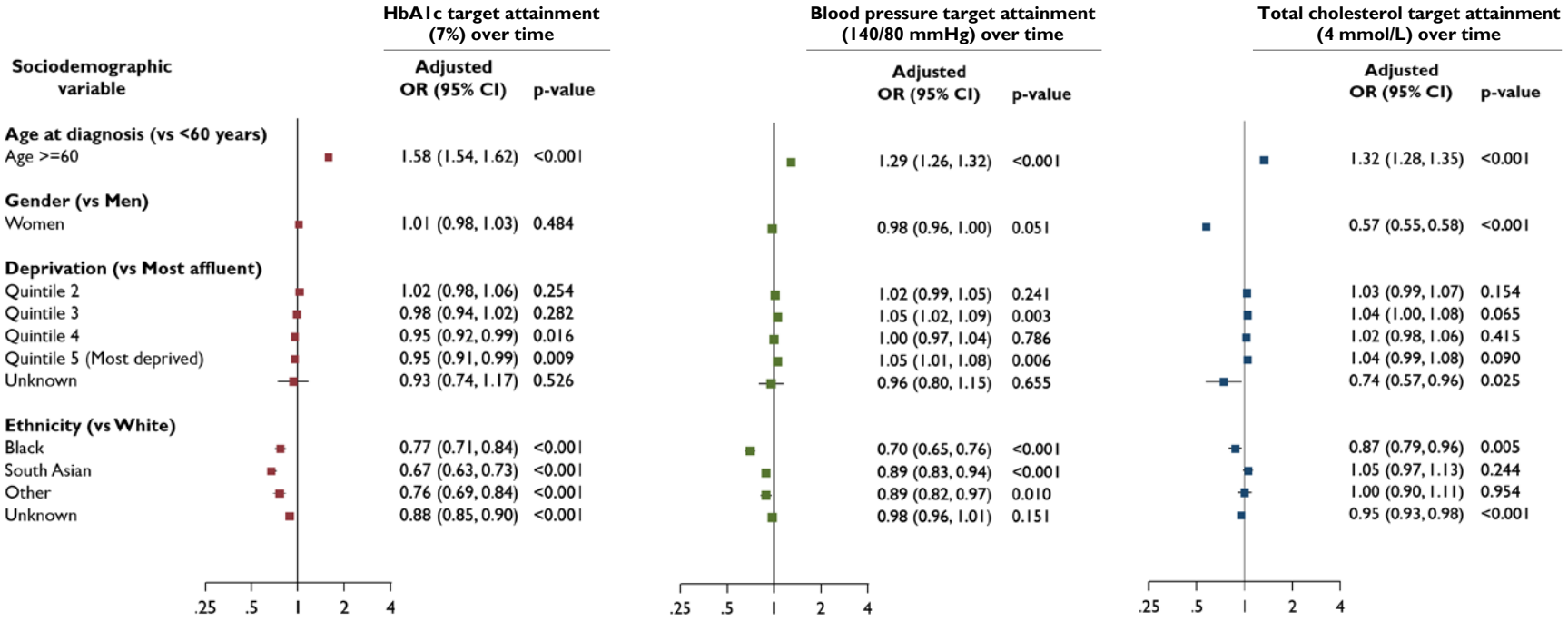


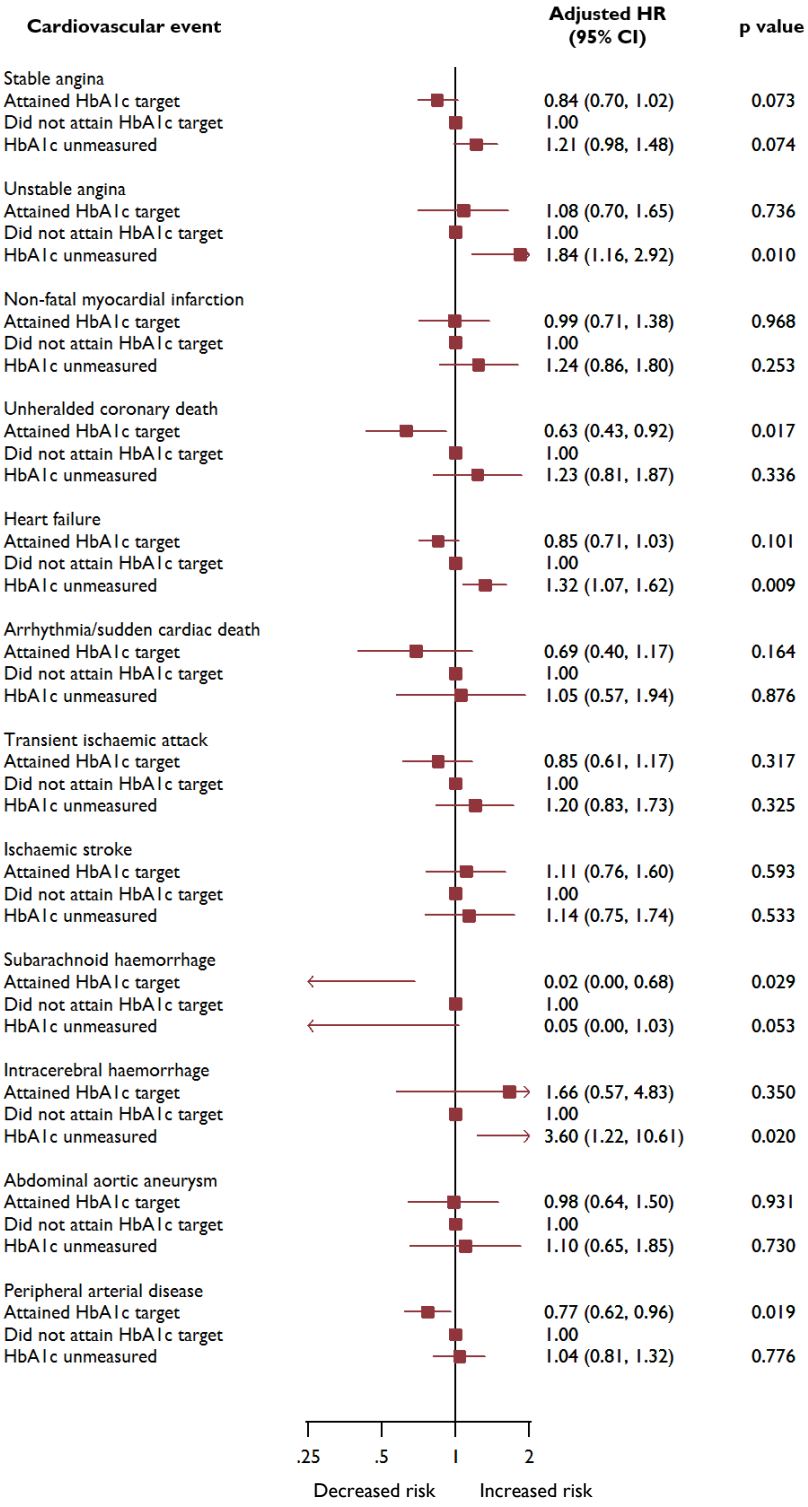
Figure F4.12 Associations between sociodemographic factors and attainment of less stringent targets over time



*Population-averaged estimates from generalised estimating equations logistic (n=52,379), within-patient correlations (r) = 0.301 (HbA1c), 0.196 (blood pressure) and 0.261 (total cholesterol).

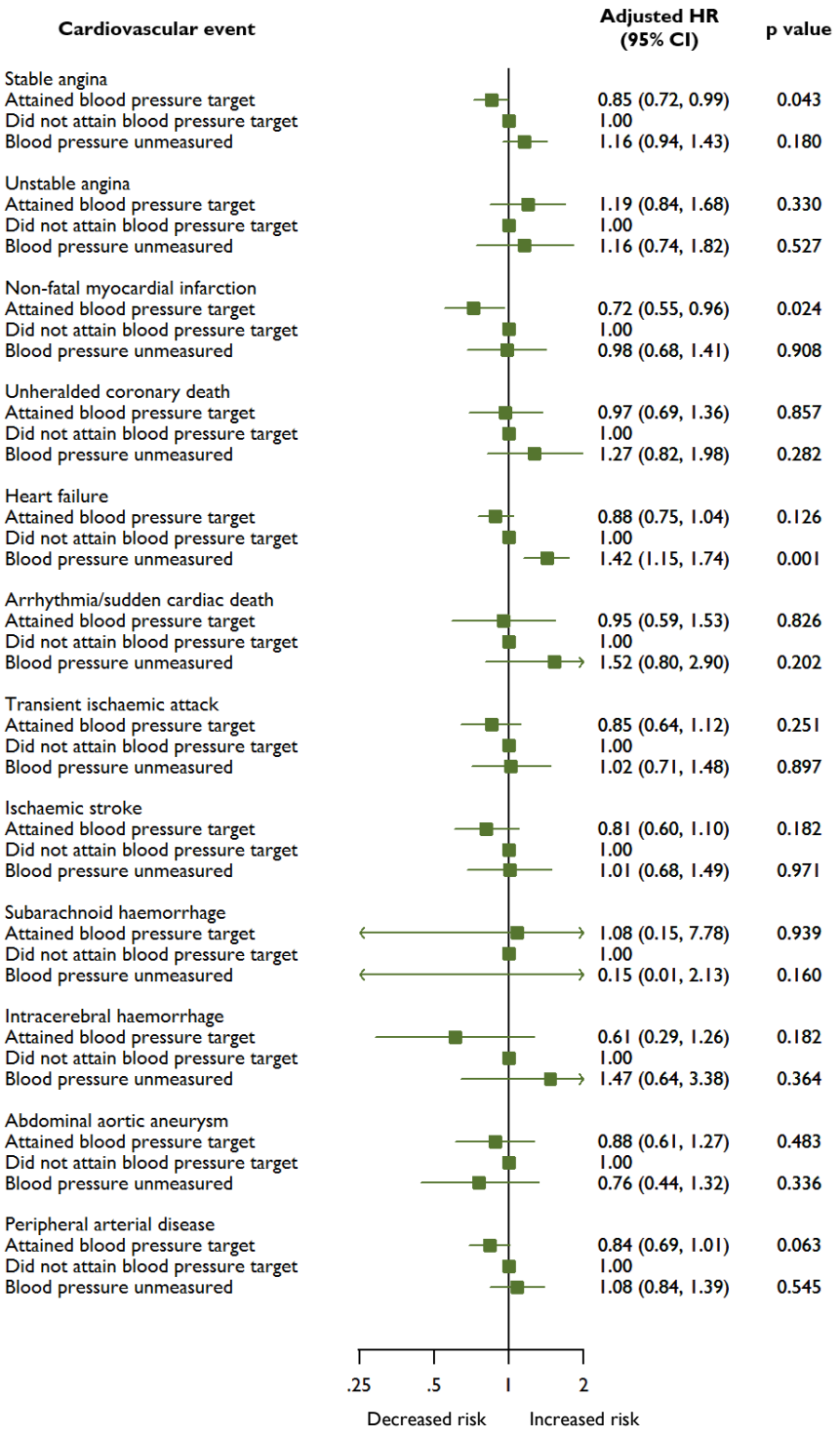
Chapter 6

Figure F6.1 Adjusted hazard ratios for meeting tighter HbA1c target*



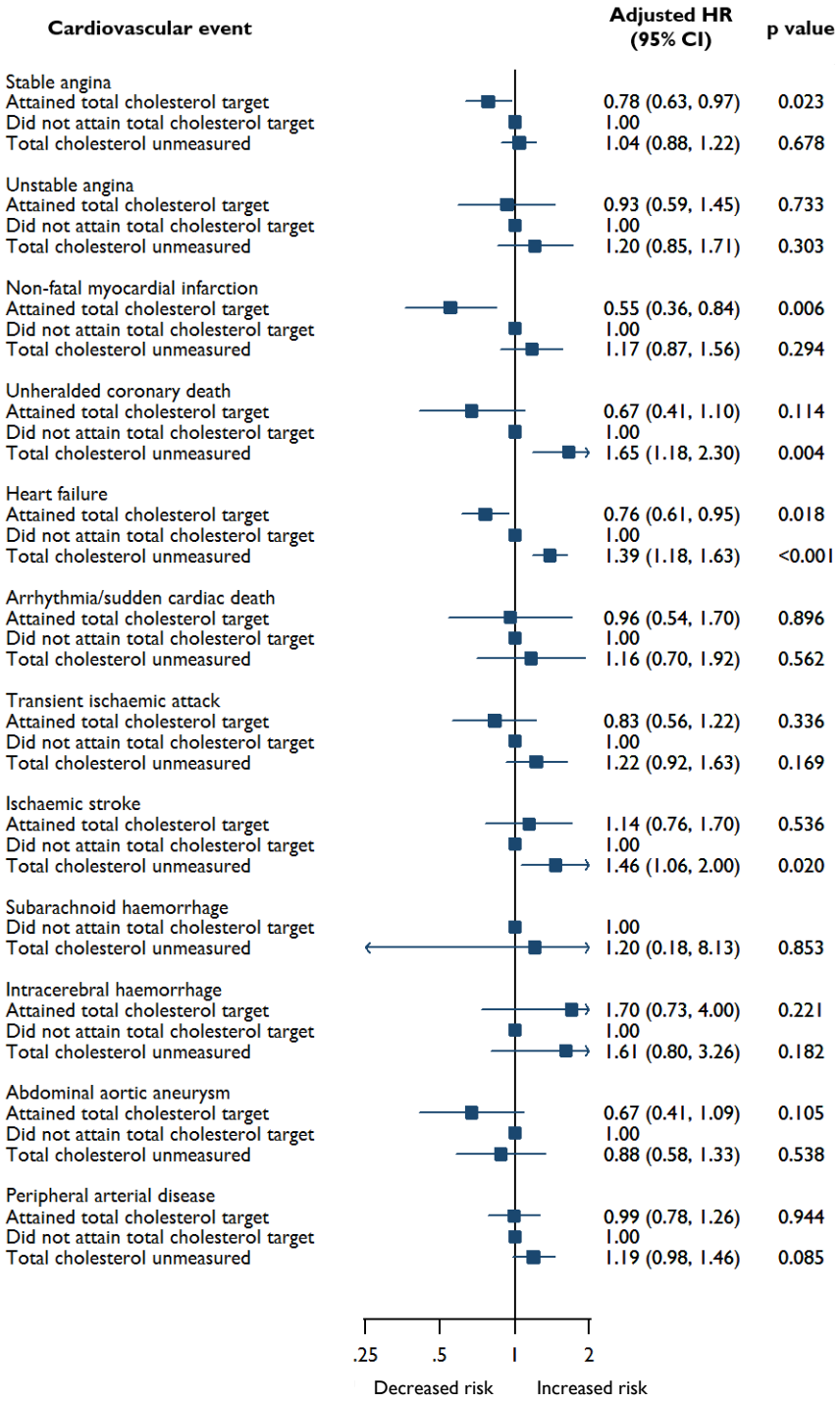
Risk estimates were adjusted for baseline factors (age, sex, social deprivation, ethnicity, body mass index category, smoking status, systolic blood pressure category, total cholesterol category, HDL cholesterol category, renal disease, blood pressure lowering medication, lipid lowering medication and antiplatelet) and initial diabetes treatment, and stratified by GP practice.
*HbA1c target is ≤7%.

Figure F6.2 Adjusted hazard ratios for meeting tighter blood pressure target*



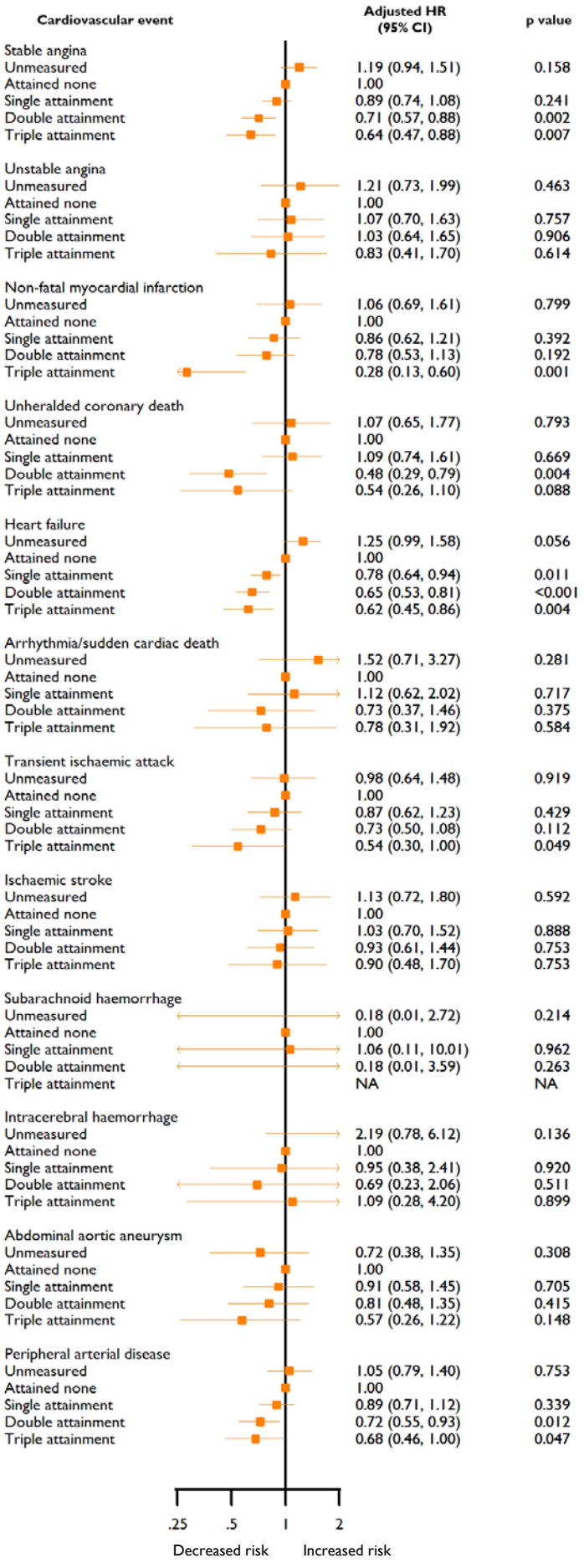
Risk estimates were adjusted for baseline factors (age, sex, social deprivation, ethnicity, body mass index category, smoking status, systolic blood pressure category, total cholesterol category, HDL cholesterol category, renal disease, blood pressure lowering medication, lipid lowering medication and antiplatelet) and initial diabetes treatment, and stratified by GP practice.
*Blood pressure target is ≤140/80 mmHg.

Figure F6.3 Adjusted hazard ratios for meeting tighter total cholesterol target*



Risk estimates were adjusted for baseline factors (age, sex, social deprivation, ethnicity, body mass index category, smoking status, systolic blood pressure category, total cholesterol category, HDL cholesterol category, renal disease, blood pressure lowering medication, lipid lowering medication and antiplatelet) and initial diabetes treatment, and stratified by GP practice.
*Total cholesterol target is ≤4 mmol/L.

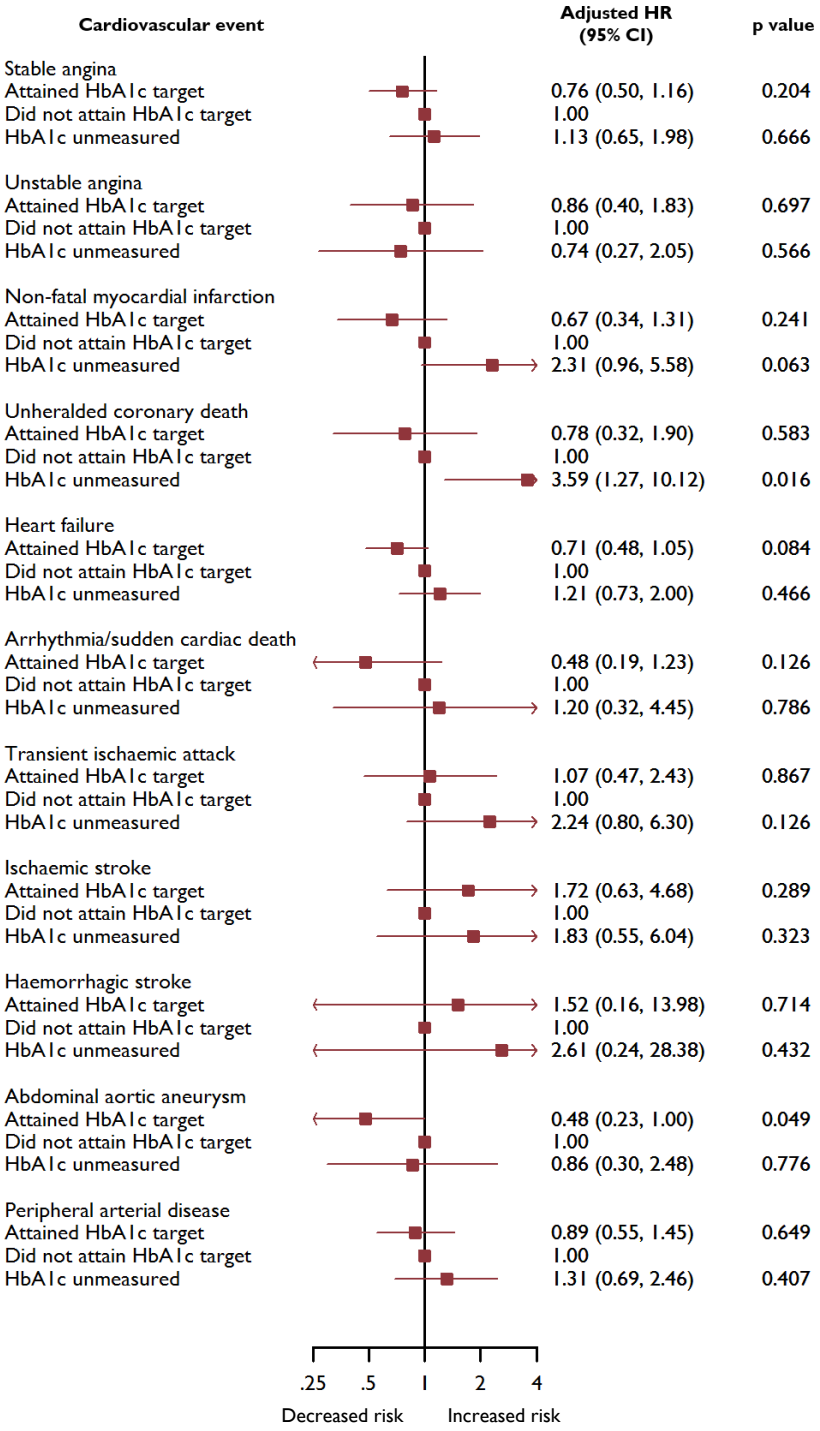
Figure F6.4
Adjusted hazard ratios for attainment of tighter composite targets*



Risk estimates were adjusted for baseline factors (age, sex, social deprivation, ethnicity, body mass index category, smoking status, systolic blood pressure category, total cholesterol category, HDL cholesterol category, renal disease, blood pressure lowering medication, lipid lowering medication and antiplatelet) and initial diabetes treatment, and stratified by GP practice.

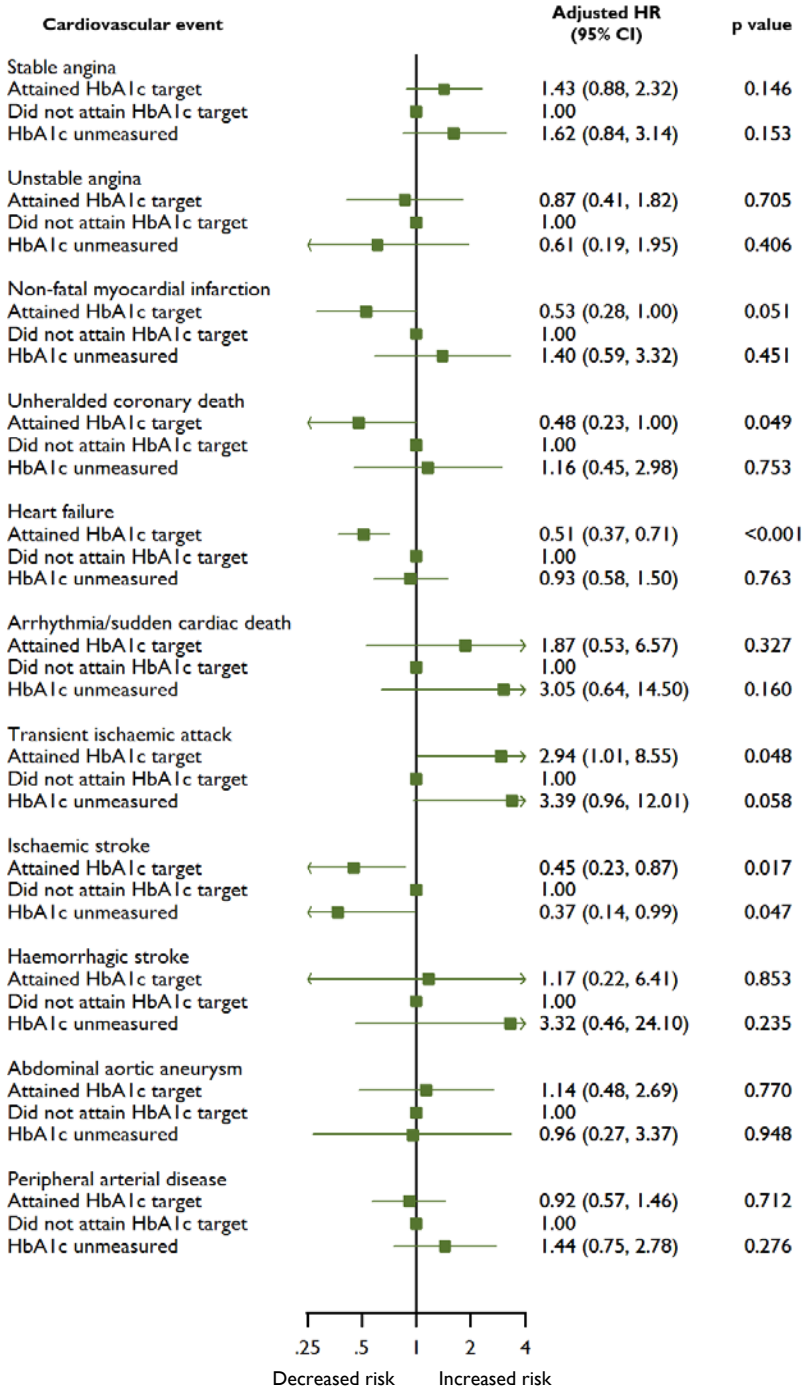
*Intermediate outcome targets are HbA1c ≤7%, blood pressure ≤140/80 mmHg and total cholesterol ≤4 mmol/L.

Figure F6.5 Adjusted hazard ratios for meeting HbA1c target in CALIBER's incident T2D sub-cohort entering study after 1 January 2004 (N=20,341)



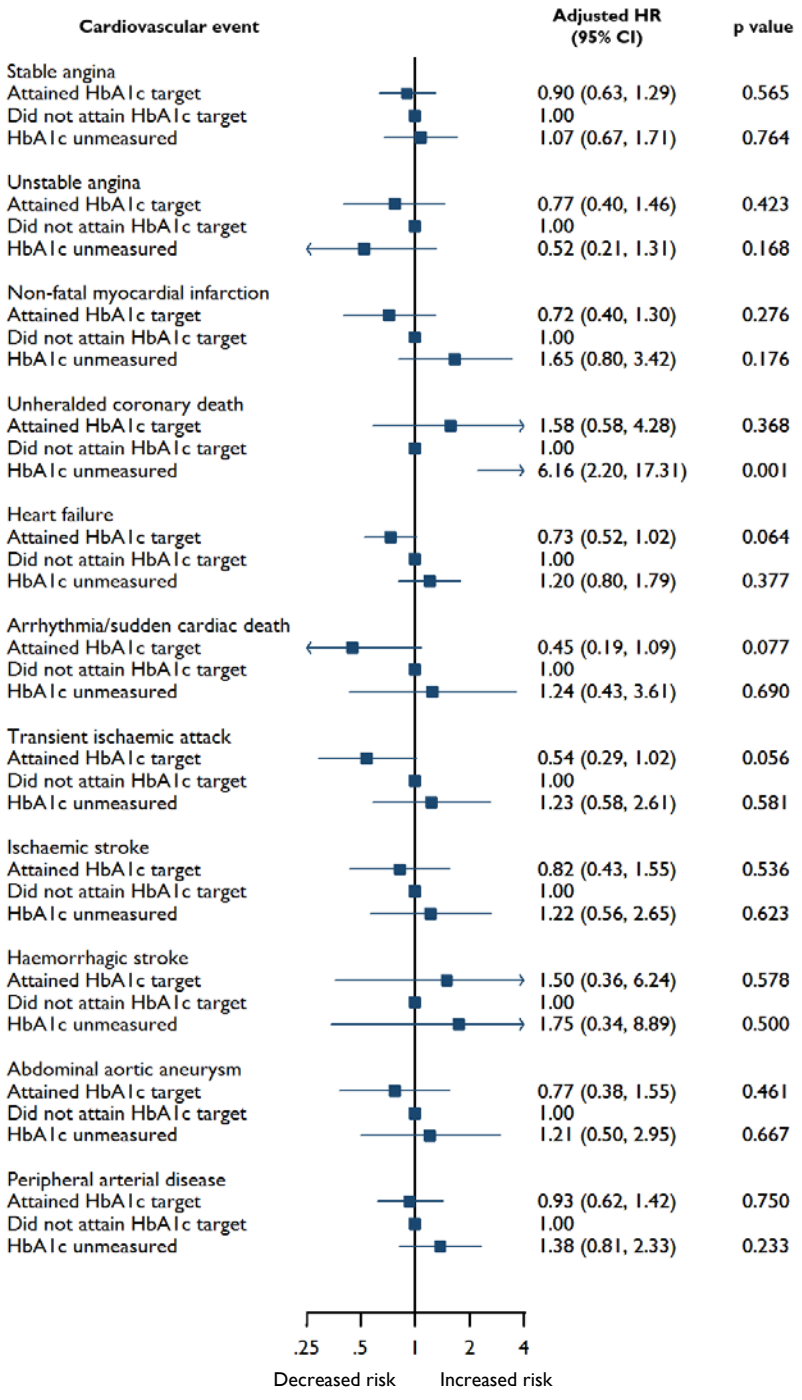
Risk estimates were adjusted for baseline factors (age, sex, social deprivation, ethnicity, body mass index category, smoking status, systolic blood pressure category, total cholesterol category, HDL cholesterol category, renal disease, blood pressure lowering medication, lipid lowering medication and antiplatelet) and initial diabetes treatment, and stratified by GP practice.

Figure F6.6 Adjusted hazard ratios for meeting blood pressure target in CALIBER's incident T2D sub-cohort entering study after 1 January 2004 (N=20,341)



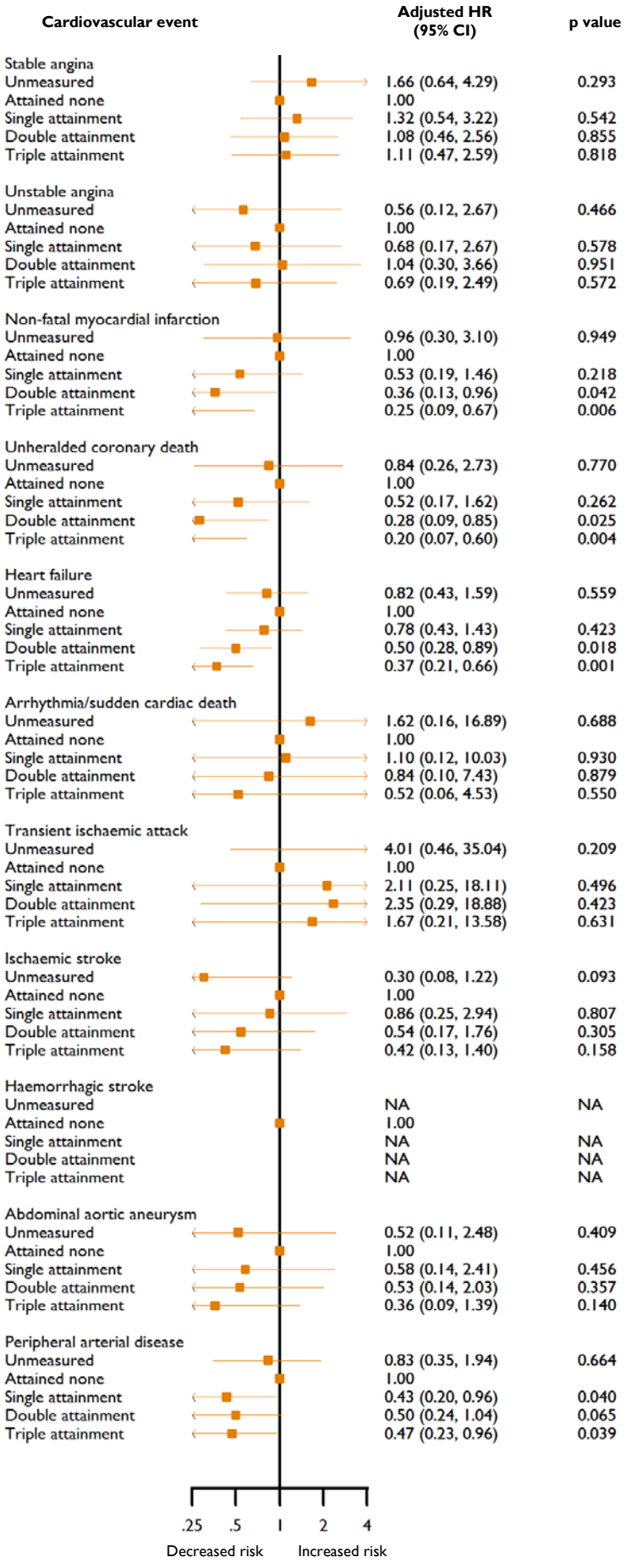
Risk estimates were adjusted for baseline factors (age, sex, social deprivation, ethnicity, body mass index category, smoking status, systolic blood pressure category, total cholesterol category, HDL cholesterol category, renal disease, blood pressure lowering medication, lipid lowering medication and antiplatelet) and initial diabetes treatment, and stratified by GP practice.

Figure F6.7 Adjusted hazard ratios for meeting total cholesterol target in CALIBER's incident T2D sub-cohort entering study after 1 January 2004 (N=20,341)



Risk estimates were adjusted for baseline factors (age, sex, social deprivation, ethnicity, body mass index category, smoking status, systolic blood pressure category, total cholesterol category, HDL cholesterol category, renal disease, blood pressure lowering medication, lipid lowering medication and antiplatelet) and initial diabetes treatment, and stratified by GP practice.

Figure F6.8
Adjusted hazard ratios for attainment of composite targets in CALIBER's incident T2D sub-cohort entering study after 1 January 2004 (n=20,341)



Risk estimates were adjusted for baseline factors (age, sex, social deprivation, ethnicity, body mass index category, smoking status, systolic blood pressure category, total cholesterol category, HDL cholesterol category, renal disease, blood pressure lowering medication, lipid lowering medication and antiplatelet) and initial diabetes treatment, and stratified by GP practice.

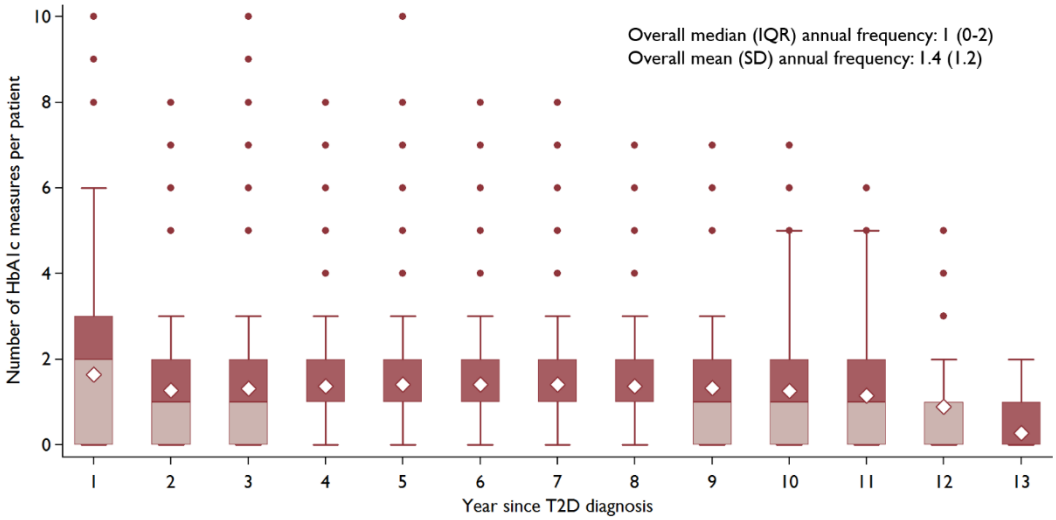
Chapter 7

Table F7.1 Characteristics of patients with non-zero TITRE values (N=18,031)

Characteristics	100% TITRE (N=1,319)				TITRE between 0-100% (N=16,712)	
	With known baseline HbA1c (N=635)		Without known baseline HbA1c (N=684)			
Duration of practice registration before entry, median (IQR) years	12.1	(8.2-16.3)	11.0	(7.6-16.3)	9.3	(5.7-13.5)
Duration of follow-up, median (IQR) years	2.5	(1.7-3.9)	1.6	(1.2-2.6)	5.0	(3.1-7.2)
Time window for TITRE calculation, median (IQR) years	1.6	(0.8-2.9)	0.7	(0.5-0.9)	4.0	(2.2-6.0)
TITRE, median (IQR) %	100	(100-100)	100	(100-100)	18.5	(7.1-37.5)
Age at entry, mean (SD) years	65.0	(12.2)	63.2	(13.9)	60.5	(12.2)
Women, n (%)	315	(49.6)	331	(48.4)	7,814	(46.8)
Ethnicity, n (%)*						
White	371	(58.4)	395	(57.8)	9,900	(59.2)
South Asian	8	(1.3)	22	(3.2)	526	(3.2)
Black	9	(1.4)	7	(1.0)	452	(2.7)
Other	8	(1.3)	7	(1.0)	300	(1.8)
Most deprived quintile, n (%)*	110	(17.3)	138	(20.2)	3,185	(19.1)
HbA1c measurements						
Baseline HbA1c, mean (SD) mmol/mol	41.5	(4.6)	-		67.4	(23.6)†
Baseline HbA1c at target, n (%)	635	(100)	-		847	(5.1)†
Initial follow-up HbA1c, mean (SD) mmol/mol	40.3	(4.6)	41.0	(4.6)	56.0	(20.3)
Initial follow-up HbA1c at target, n (%)	635	(100)	684	(100)	7,539	(45.1)
Time to initial follow-up HbA1c, median (IQR) months	3.1	(1.4-5.6)	3.4	(1.5-10.0)	2.7	(0.9-6.2)
Data source for initial T2D diagnosis						
CPRD	625	(98.4)	647	(94.6)	16,227	(97.1)
HES	10	(1.6)	37	(5.4)	485	(2.9)
Frequency of GP consultation over follow-up years, median (IQR)	25	(16-41)	17	(12-26)	47	(29-74)

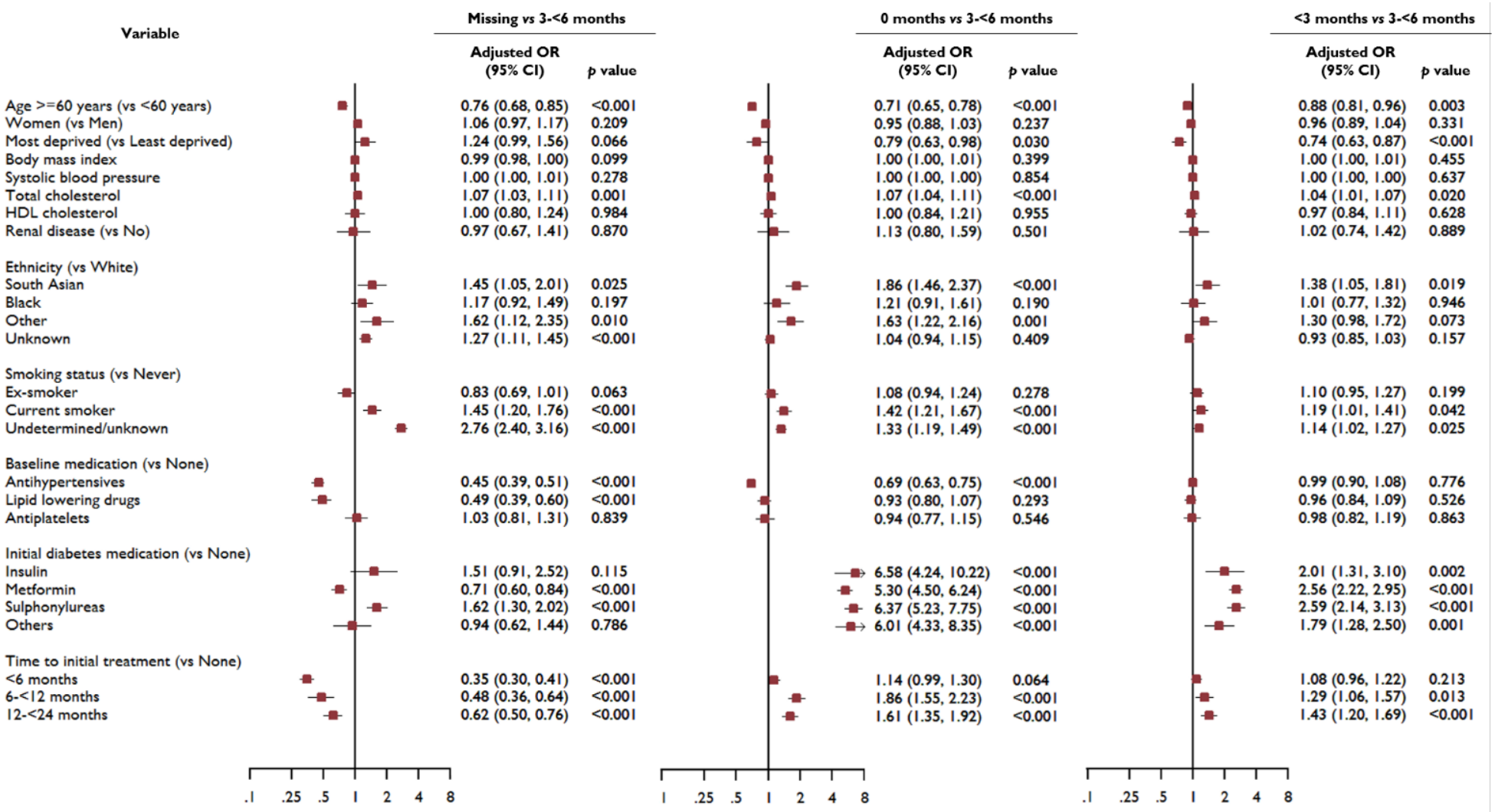
*Missing values: ethnicity 37.3% (492 patients with 100% TITRE) and 33.1 (5,534 patients with 0-100% TITRE), deprivation 0.4% (5 patients with 100% TITRE) and 0.3% (47 patients with 0-100% TITRE).
†Among patients with known baseline HbA1c (N=4,297, 25.7%).

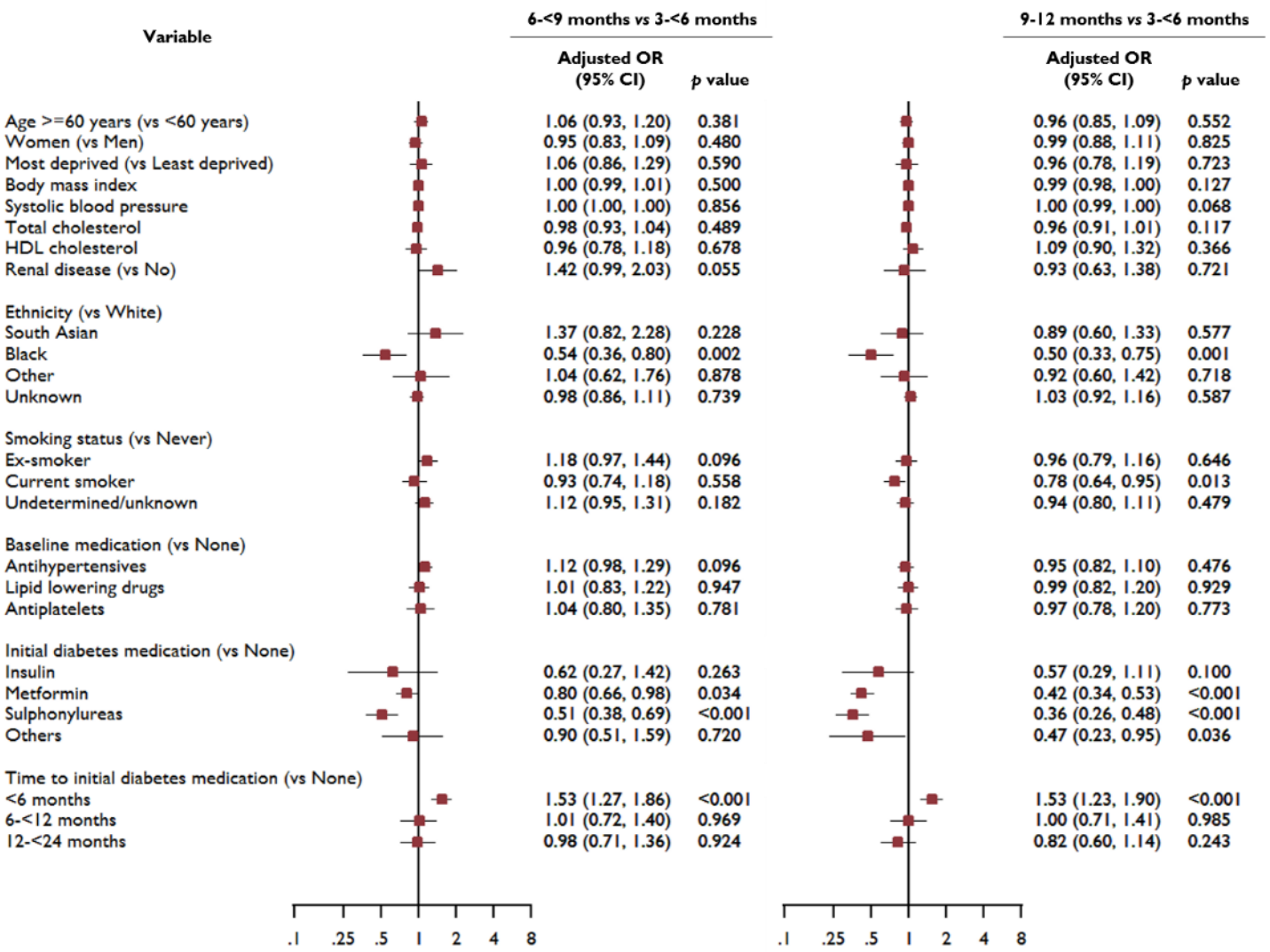
Figure F7.1 Number of follow-up HbA1c tests per patient over years of follow-up* (N=34,660)



**Mean (diamonds) and median (boxplots)*

Figure F7.2 Associations of patient characteristics and TITRE categories




Variable
6-<9 months vs 3-<6 months
Adjusted OR (95% CI)
p value
9-12 months vs 3-<6 months
Adjusted OR (95% CI)
p value
Age >=60 years (vs <60 years) 1.06 (0.93, 1.20) 0.381 0.96 (0.85, 1.09) 0.552
Women (vs Men) 0.95 (0.83, 1.09) 0.480 0.99 (0.88, 1.11) 0.825
Most deprived (vs Least deprived) 1.06 (0.86, 1.29) 0.590 0.96 (0.78, 1.19) 0.723
Body mass index 1.00 (0.99, 1.01) 0.500 0.99 (0.98, 1.00) 0.127
Systolic blood pressure 1.00 (1.00, 1.00) 0.856 1.00 (0.99, 1.00) 0.068
Total cholesterol 0.98 (0.93, 1.04) 0.489 0.96 (0.91, 1.01) 0.117
HDL cholesterol 0.96 (0.78, 1.18) 0.678 1.09 (0.90, 1.32) 0.366
Renal disease (vs No) 1.42 (0.99, 2.03) 0.055 0.93 (0.63, 1.38) 0.721
Ethnicity (vs White)
South Asian 1.37 (0.82, 2.28) 0.228 0.89 (0.60, 1.33) 0.577
Black 0.54 (0.36, 0.80) 0.002 0.50 (0.33, 0.75) 0.001
Other 1.04 (0.62, 1.76) 0.878 0.92 (0.60, 1.42) 0.718
Unknown 0.98 (0.86, 1.11) 0.739 1.03 (0.92, 1.16) 0.587
Smoking status (vs Never)
Ex-smoker 1.18 (0.97, 1.44) 0.096 0.96 (0.79, 1.16) 0.646
Current smoker 0.93 (0.74, 1.18) 0.558 0.78 (0.64, 0.95) 0.013
Undetermined/unknown 1.12 (0.95, 1.31) 0.182 0.94 (0.80, 1.11) 0.479
Baseline medication (vs None)
Antihypertensives 1.12 (0.98, 1.29) 0.096 0.95 (0.82, 1.10) 0.476
Lipid lowering drugs 1.01 (0.83, 1.22) 0.947 0.99 (0.82, 1.20) 0.929
Antiplatelets 1.04 (0.80, 1.35) 0.781 0.97 (0.78, 1.20) 0.773
Initial diabetes medication (vs None)
Insulin 0.62 (0.27, 1.42) 0.263 0.57 (0.29, 1.11) 0.100
Metformin 0.80 (0.66, 0.98) 0.034 0.42 (0.34, 0.53) <0.001
Sulphonylureas 0.51 (0.38, 0.69) <0.001 0.36 (0.26, 0.48) <0.001
Others 0.90 (0.51, 1.59) 0.720 0.47 (0.23, 0.95) 0.036
Time to initial diabetes medication (vs None)
<6 months 1.53 (1.27, 1.86) <0.001 1.53 (1.23, 1.90) <0.001
6-<12 months 1.01 (0.72, 1.40) 0.969 1.00 (0.71, 1.41) 0.985
12-<24 months 0.98 (0.71, 1.36) 0.924 0.82 (0.60, 1.14) 0.243
.1 .25 .5 1 2 4 8
.1 .25 .5 1 2 4 8

Chapter 8

Table F8.1 Median time to cardiovascular events by TITRE categories

Cardiovascular event	Median time to event (years) by TITRE categories					
	Missing	0 months	<3 months	3-<6 months	6-<9 months	9-12 months
Overall	2.8	4.4	5.8	4.3	3.6	2.4
MACE	2.6	3.8	5.0	3.4	3.2	2.6
Heart failure	3.0	4.1	5.0	4.2	3.8	2.4
Any CVD and death	2.7	3.8	4.9	3.7	3.2	2.4
Coronary artery disease	2.5	3.7	4.7	3.5	3.1	2.2
Peripheral arterial disease	2.7	3.5	5.0	4.1	2.3	2.3
Cardiovascular death	2.5	3.7	4.8	3.4	3.1	2.8
All-cause death	2.4	4.0	4.9	3.6	3.2	2.5

Figure F8.1 Distribution of TITRE categories for cardiovascular endpoints

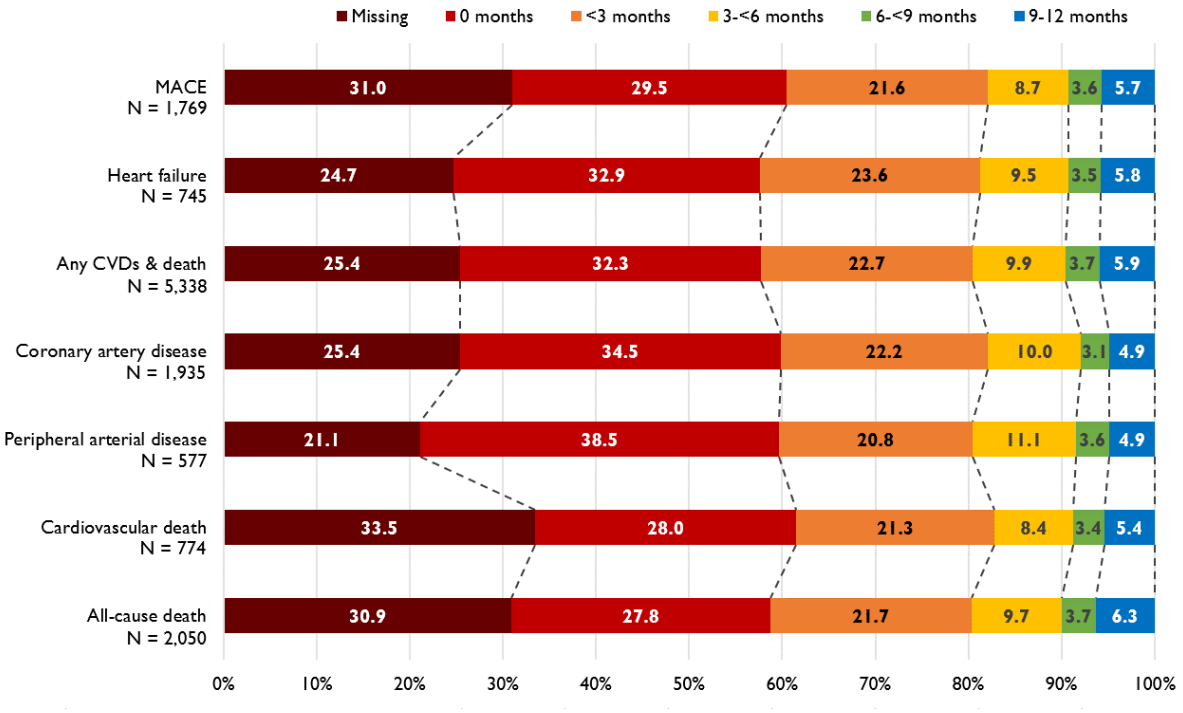


Figure F8.2
Distribution of HbA1c levels measured using different glycaemic control metrics in CALIBER's T2D cohort without prior CVD

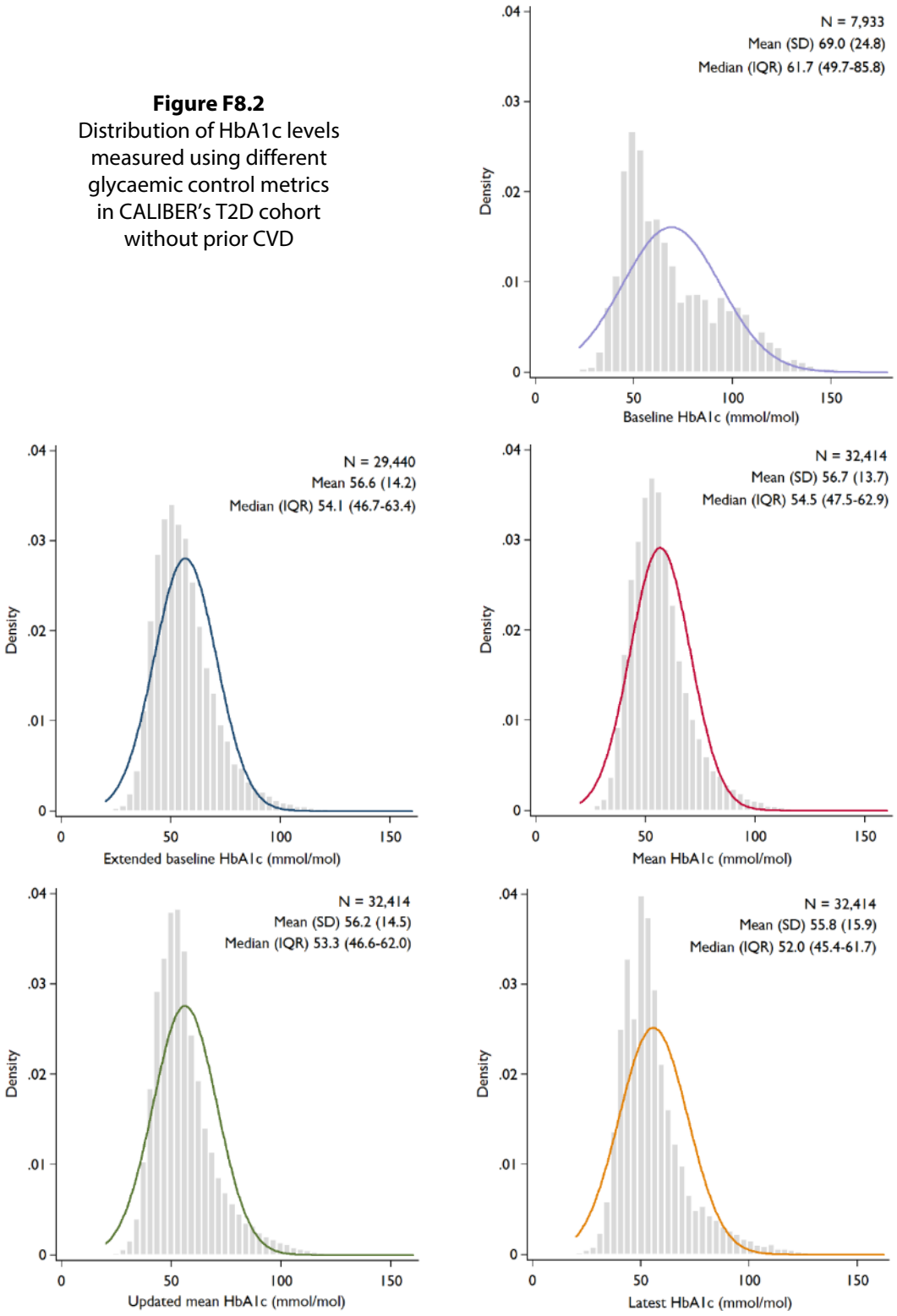
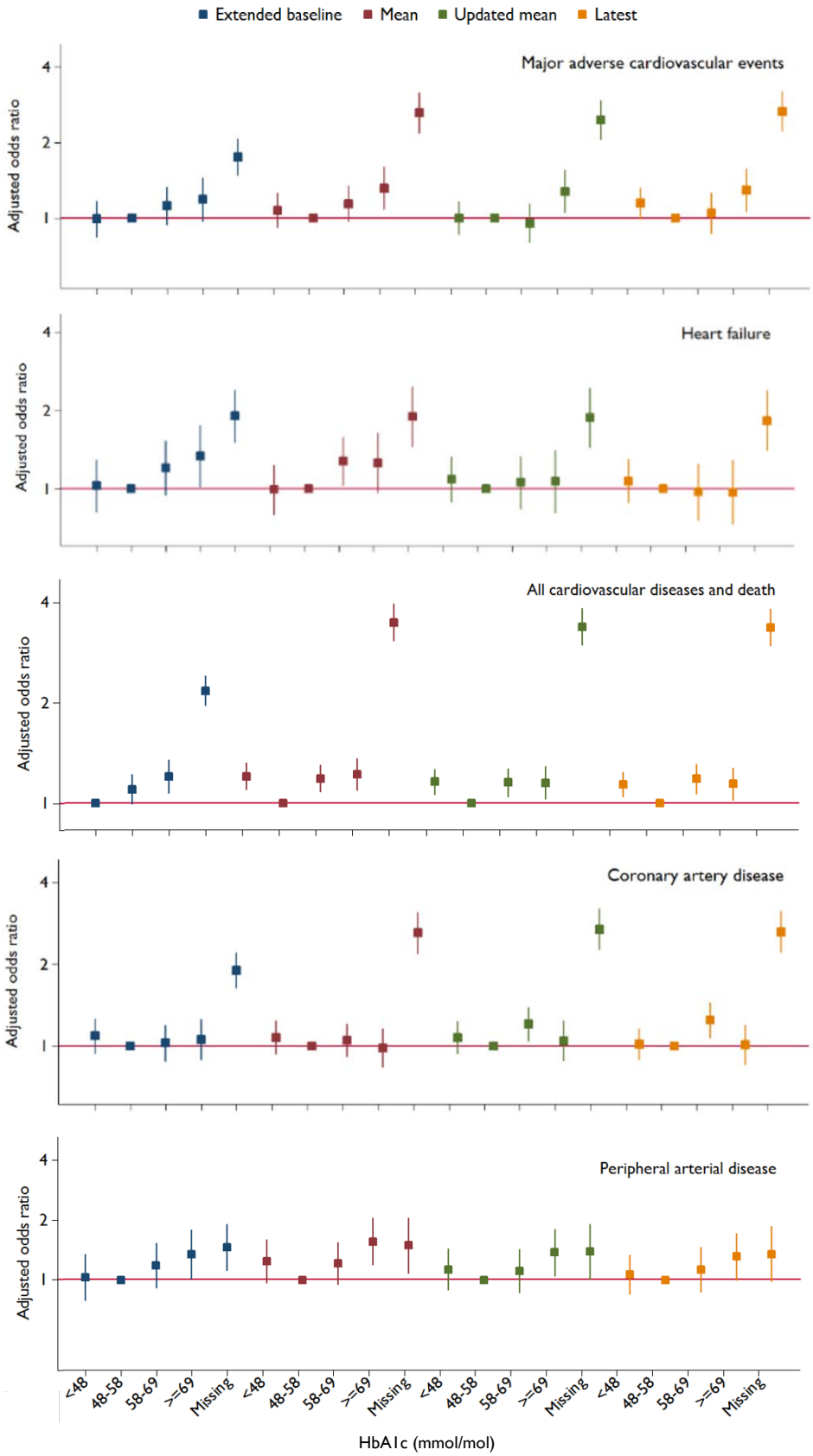
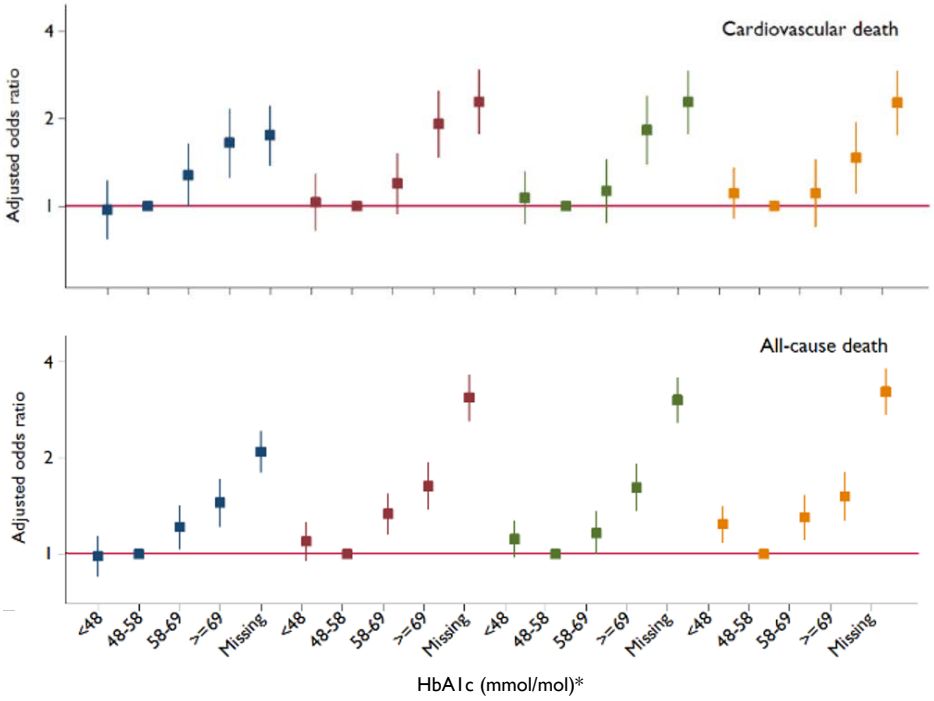


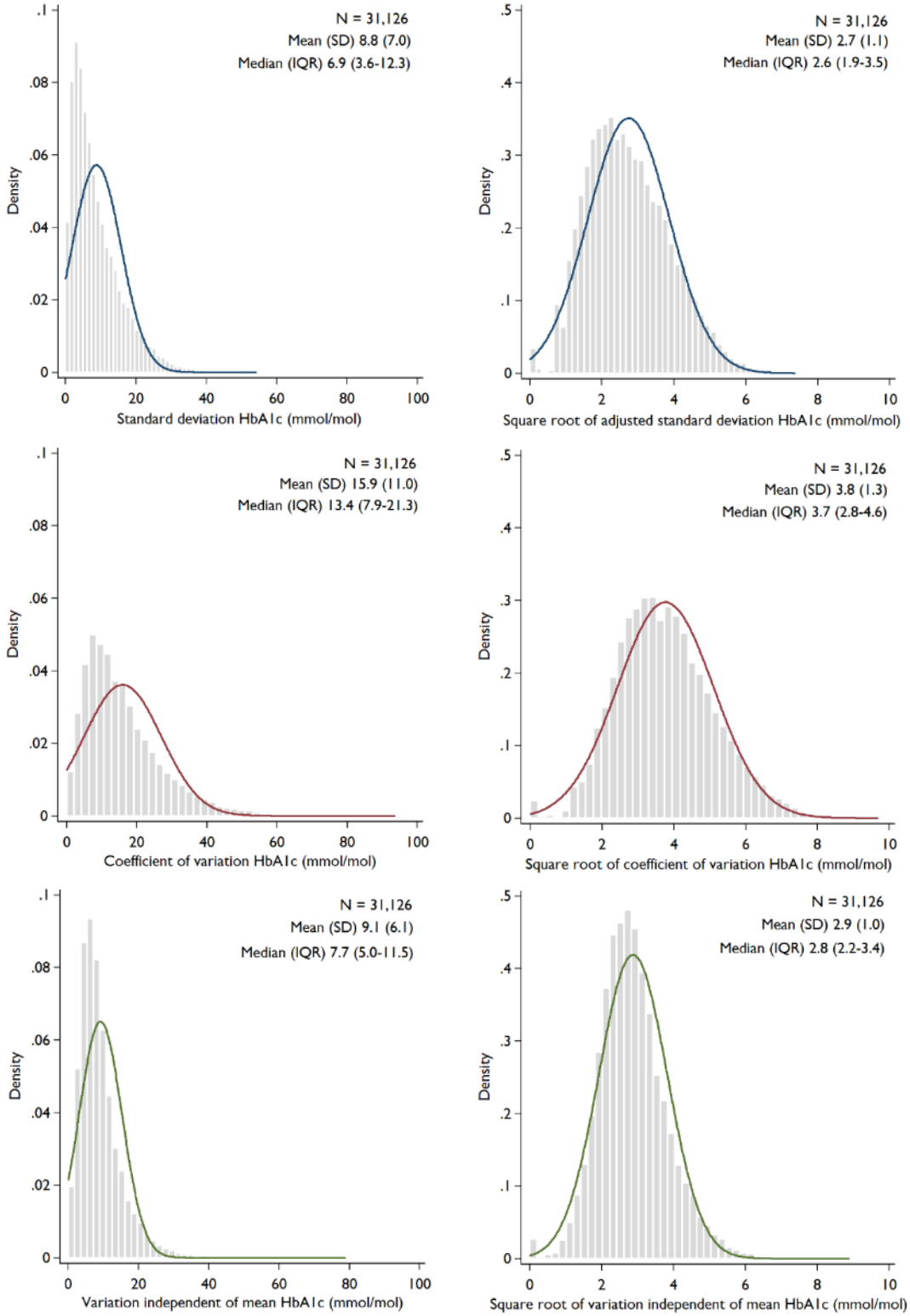
Figure F8.3 Association of HbA1c levels measured using other glycaemic control metrics and cardiovascular outcomes in CALIBER's T2D cohort without prior CVD

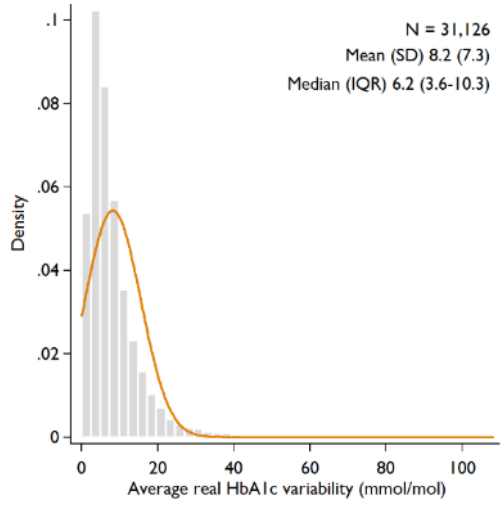


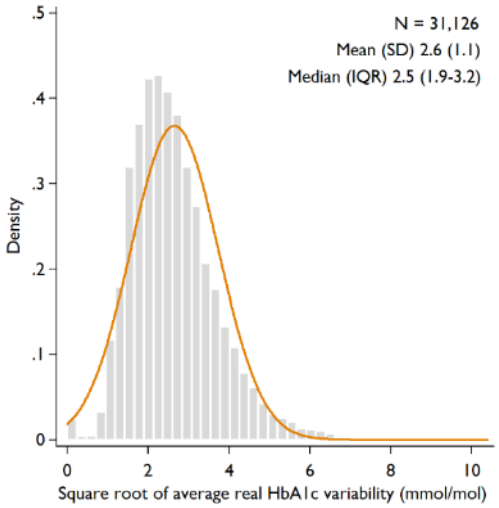


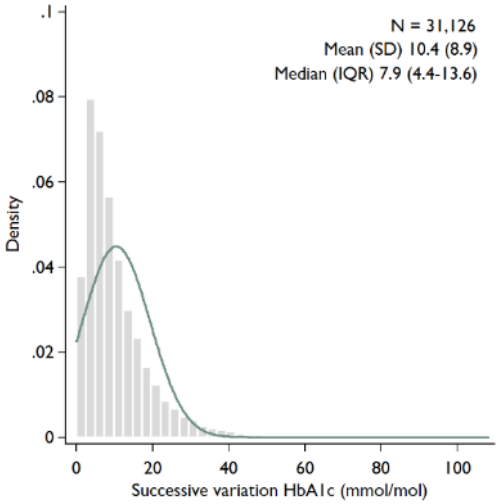
Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, baseline cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

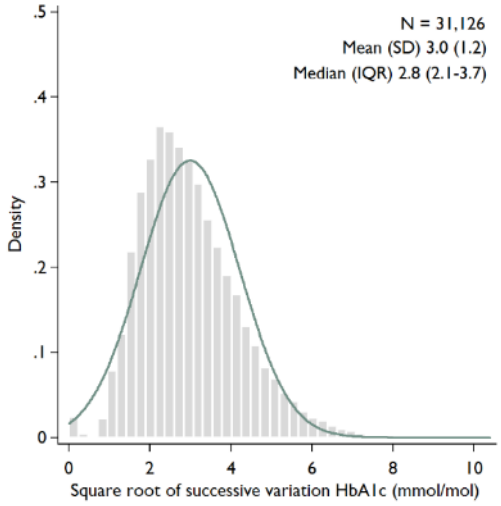
Figure F8.4 Distribution of HbA1c variation values measured using different glycaemic variability metrics in CALIBER's T2D cohort without prior CVD

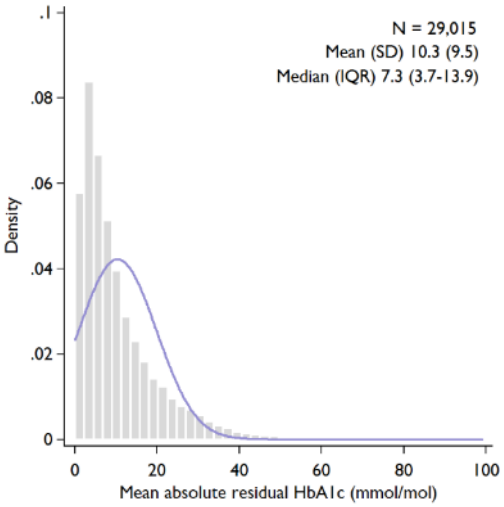



N = 31,126
Mean (SD) 8.2 (7.3)
Median (IQR) 6.2 (3.6-10.3)
Density
Average real HbA1c variability (mmol/mol)


N = 31,126
Mean (SD) 2.6 (1.1)
Median (IQR) 2.5 (1.9-3.2)
Density
Square root of average real HbA1c variability (mmol/mol)


N = 31,126
Mean (SD) 10.4 (8.9)
Median (IQR) 7.9 (4.4-13.6)
Density
Successive variation HbA1c (mmol/mol)


N = 31,126
Mean (SD) 3.0 (1.2)
Median (IQR) 2.8 (2.1-3.7)
Density
Square root of successive variation HbA1c (mmol/mol)


N = 29,015
Mean (SD) 10.3 (9.5)
Median (IQR) 7.3 (3.7-13.9)
Density
Mean absolute residual HbA1c (mmol/mol)

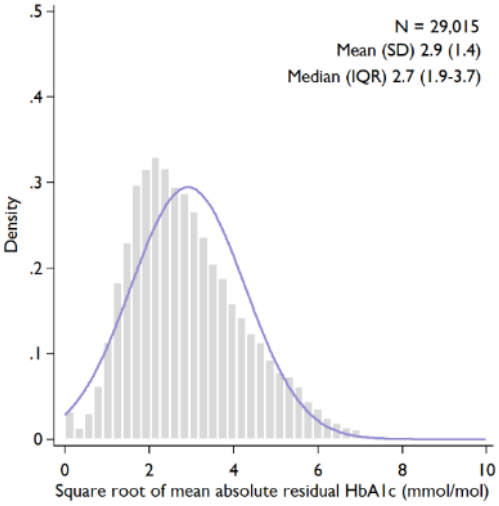
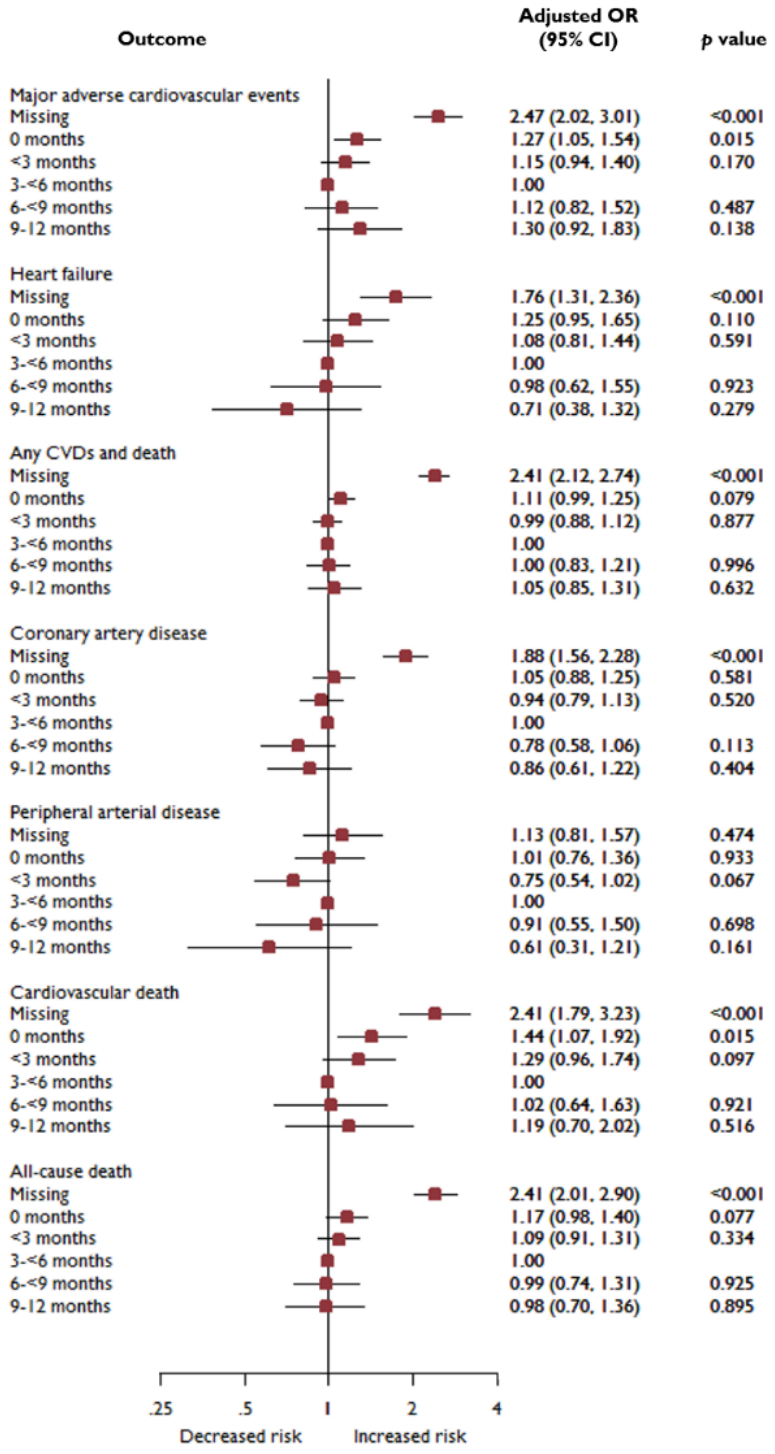
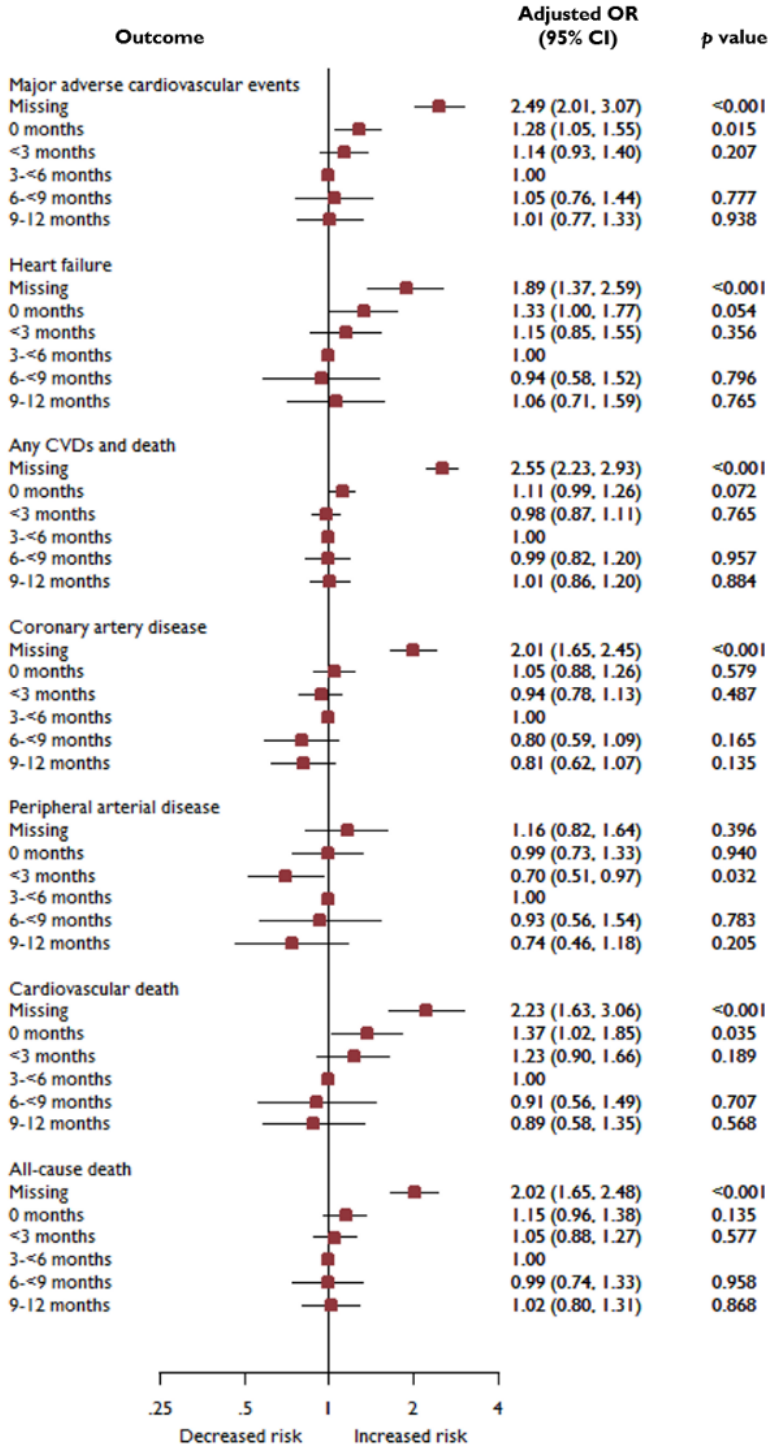

N = 29,015
Mean (SD) 2.9 (1.4)
Median (IQR) 2.7 (1.9-3.7)
Density
Square root of mean absolute residual HbA1c (mmol/mol)

Figure F8.5 Adjusted odds ratios for association between TITRE categories and cardiovascular outcomes by excluding patients with 100% TITRE (N=33,341)



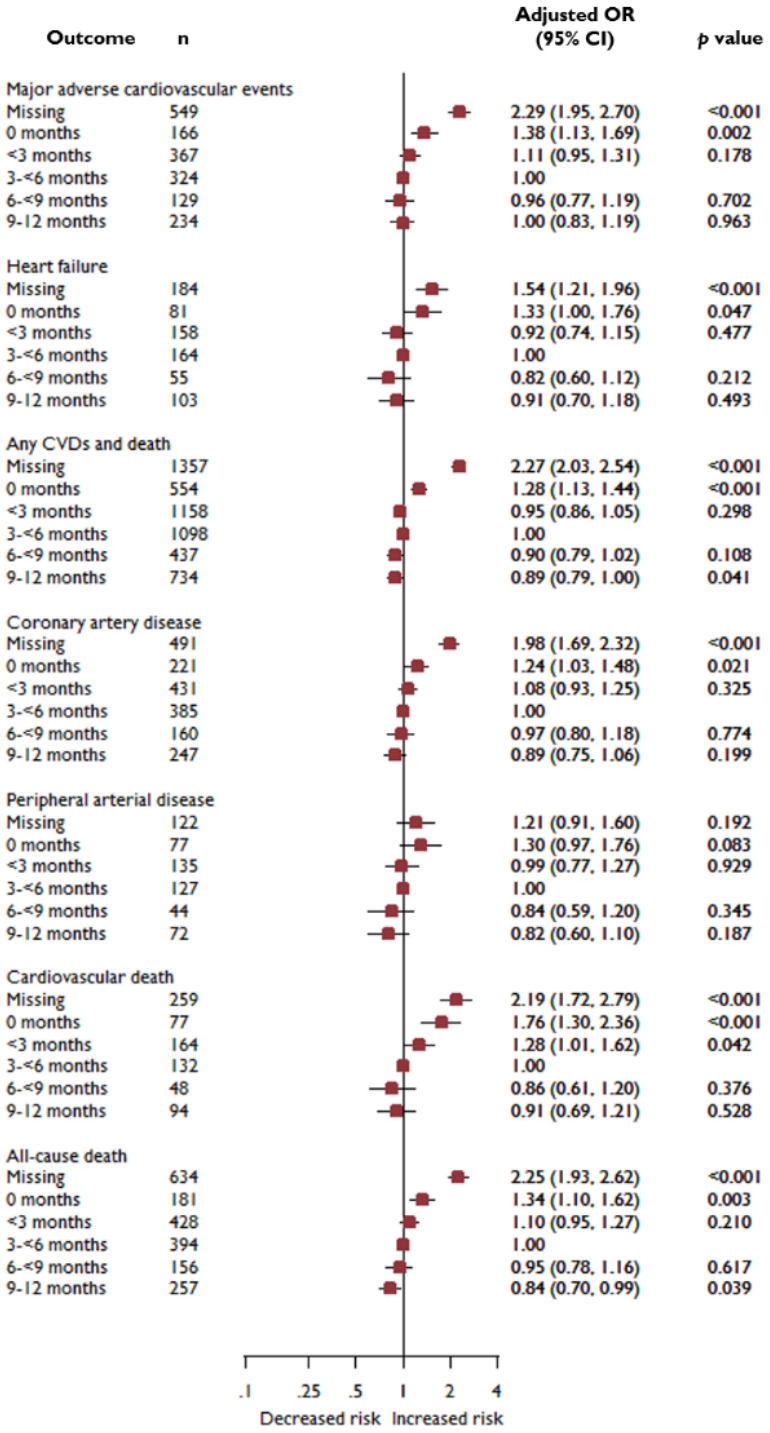
Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure F8.6 Adjusted odds ratios for association between TITRE category and cardiovascular outcomes in patients whose T2D was first diagnosed in primary care (N=32,521)



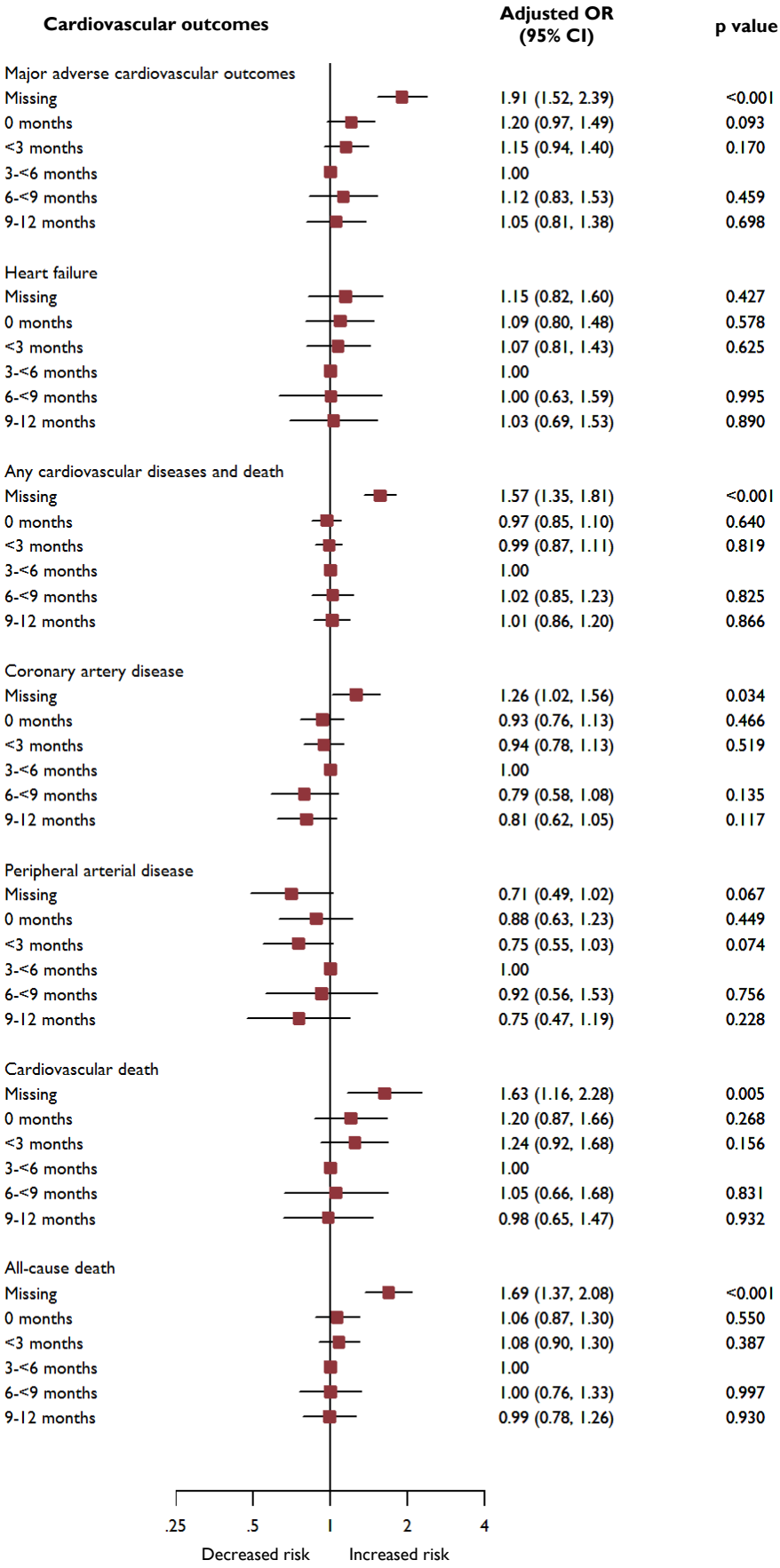
Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure F8.7 Adjusted odds ratios for association between TITRE category and cardiovascular outcomes using higher HbA1c cut-point (58 mmol/mol) (N=34,660)



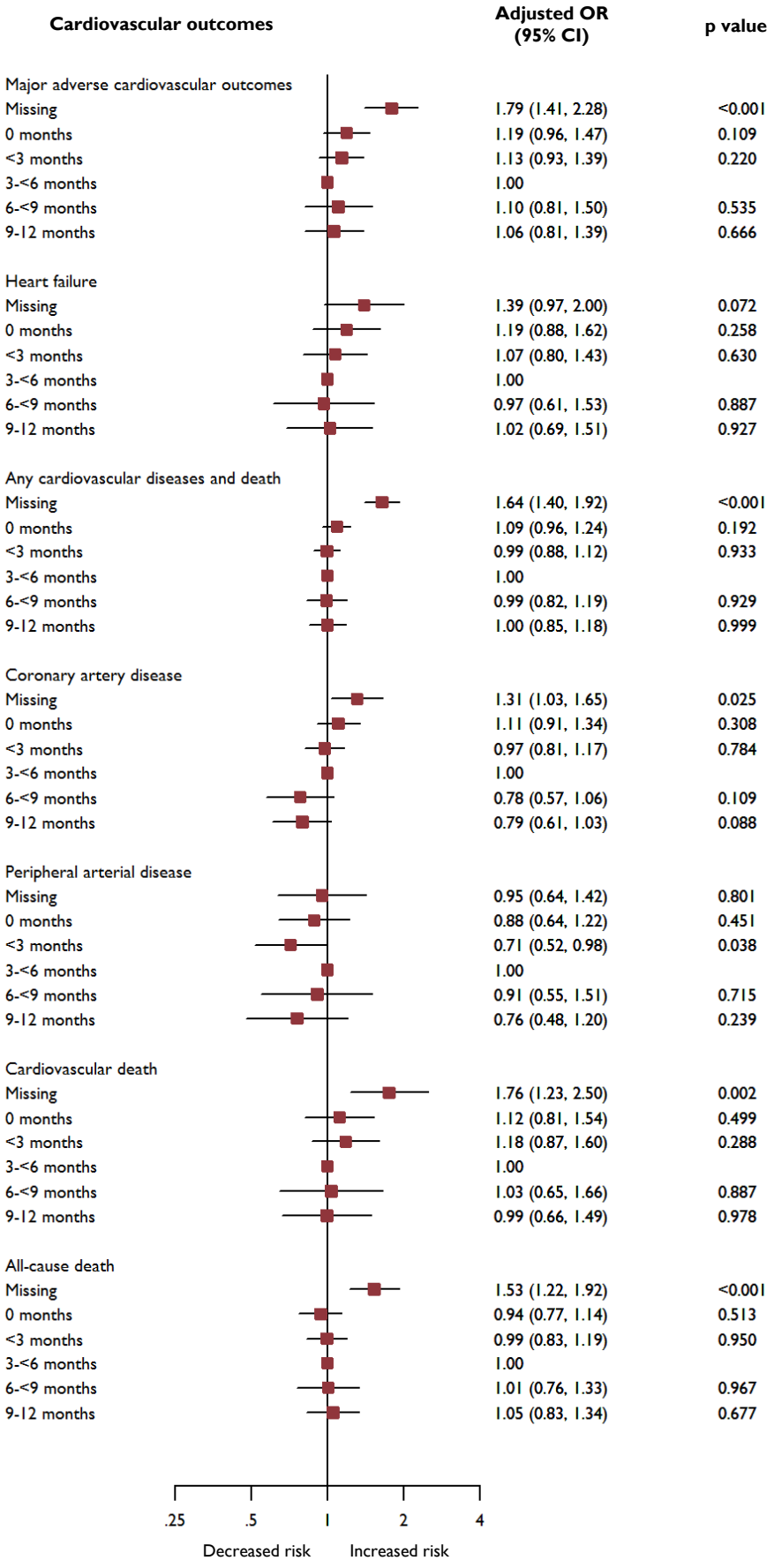
Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure F8.8
Adjusted odds ratios for the association between TITRE categories and cardiovascular outcomes by adding snapshot glycaemic control within the first year into the multivariate analysis (N=34,660)



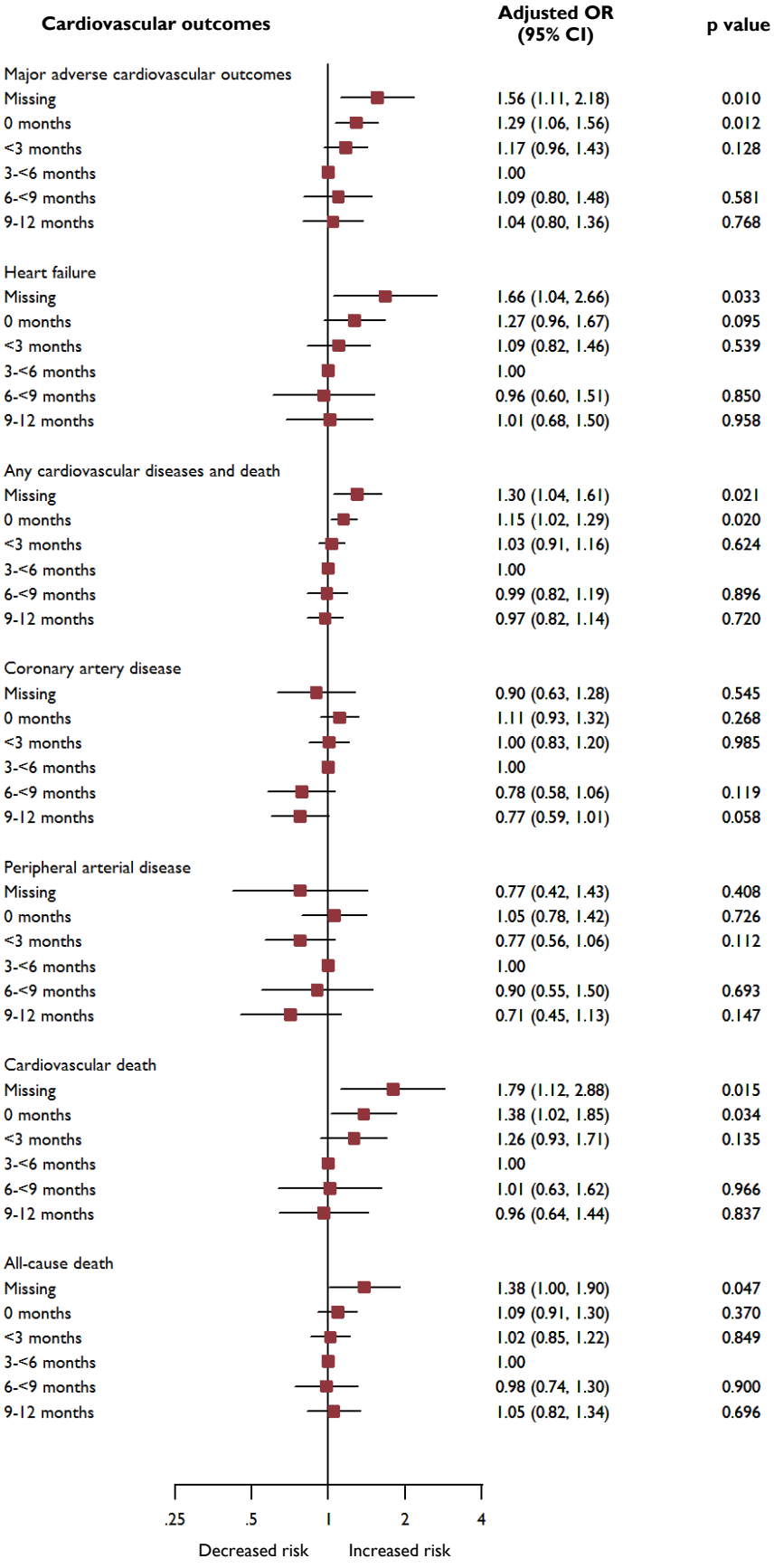
Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure F8.9
Adjusted odds ratios for the association between TITRE categories and cardiovascular outcomes by adding mean HbA1c into the multivariate analysis (N=32,414)



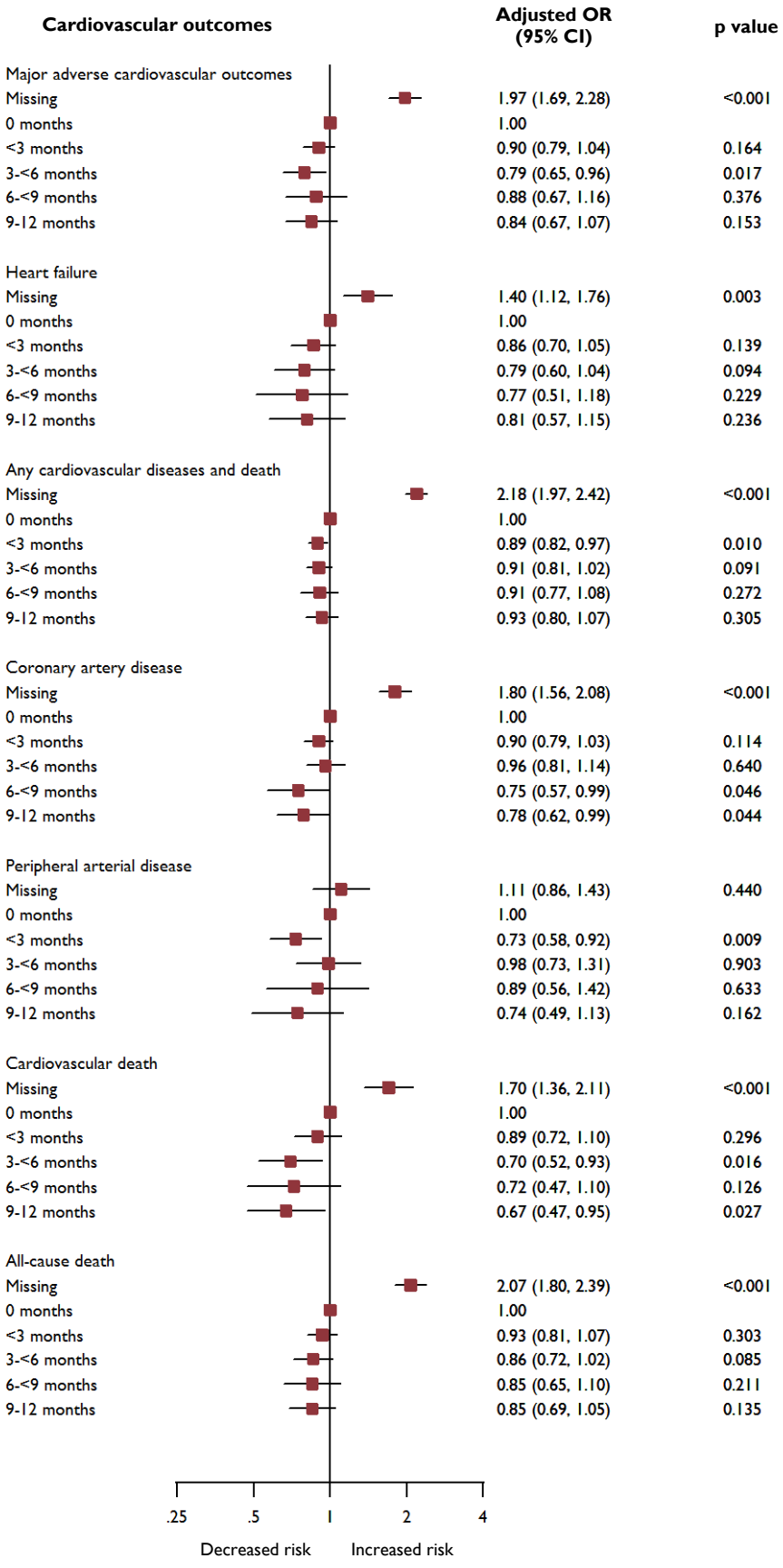
Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure F8.10
Adjusted odds ratios for the association between TITRE categories and cardiovascular outcomes by adding adjusted standard deviation of HbA1c into the multivariate analysis (N=31,126)



Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure F8.11
Adjusted odds ratios for the association between TITRE categories and cardiovascular outcomes by changing the reference group to 0 months (N=34,660)



Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Chapter 10

Figure F10.1 Distribution of TITRE values in CALIBER's cohort free from microvascular disease

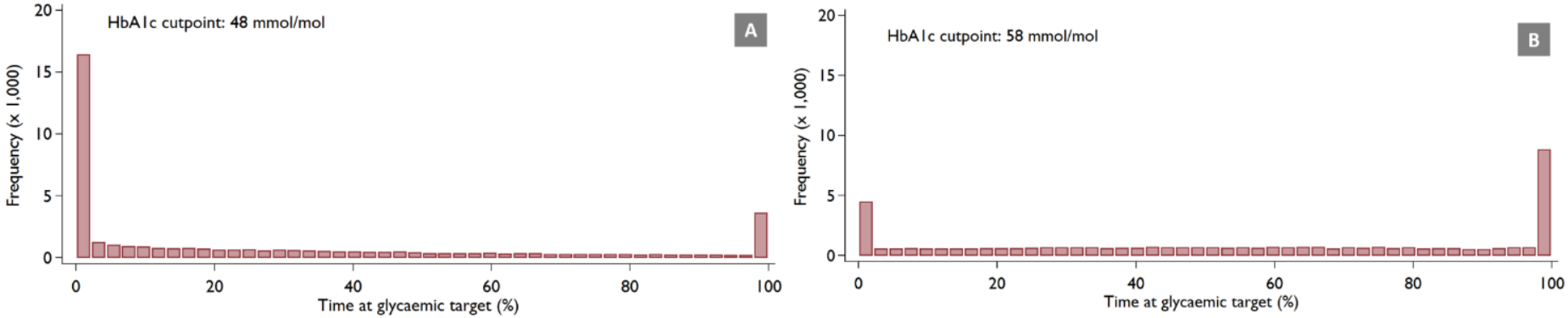


Figure F10.2 Distribution of microvascular disease-free patients by TITRE category (N=47,432)

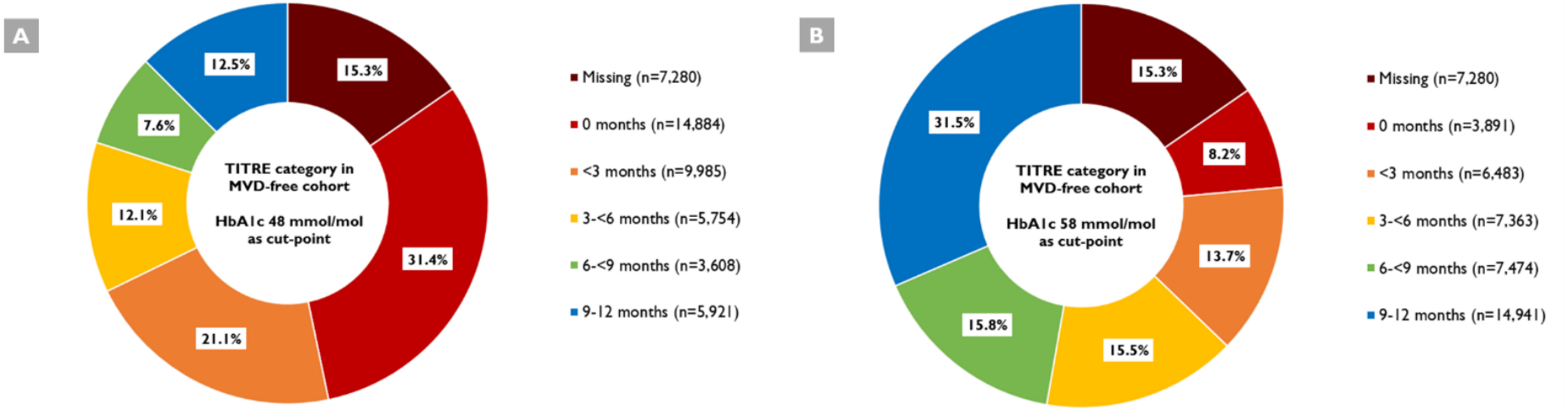


Table F10.1 Median time to microvascular events by TITRE category

Microvascular event	Median time to event (years)	Median time to event (years) by TITRE categories					
		Missing	0 months	<3 months	3-<6 months	6-<9 months	9-12 months
Overall		2.8	4.1	5.5	5.0	4.5	2.9
Diabetic nephropathy	3.8	2.3	3.8	4.7	4.5	3.8	2.8
Diabetic retinopathy	3.8	2.8	4.0	5.0	4.4	3.9	2.5
Diabetic neuropathy	3.7	2.6	3.9	4.6	4.3	4.0	2.4
Microvascular triopathy	3.8	2.6	3.9	4.8	4.4	3.9	2.5
All microvascular outcomes	3.7	2.6	3.9	4.8	4.4	3.8	2.5
CKD progression to G3a	4.0	2.3	3.9	5.0	4.6	3.5	2.8
CKD progression to G3b	3.8	2.4	3.8	4.3	4.2	4.1	2.9
CKD progression to G4/G5	3.5	2.1	3.8	4.7	4.4	3.8	2.9
NPDR	4.0	3.1	4.0	5.2	4.5	4.0	2.5
Maculopathy	3.4	2.6	3.7	4.9	4.1	2.9	2.5
Glaucoma	3.2	2.7	3.4	4.6	4.4	3.3	2.5

Figure F10.3 Distribution of TITRE categories for microvascular outcomes

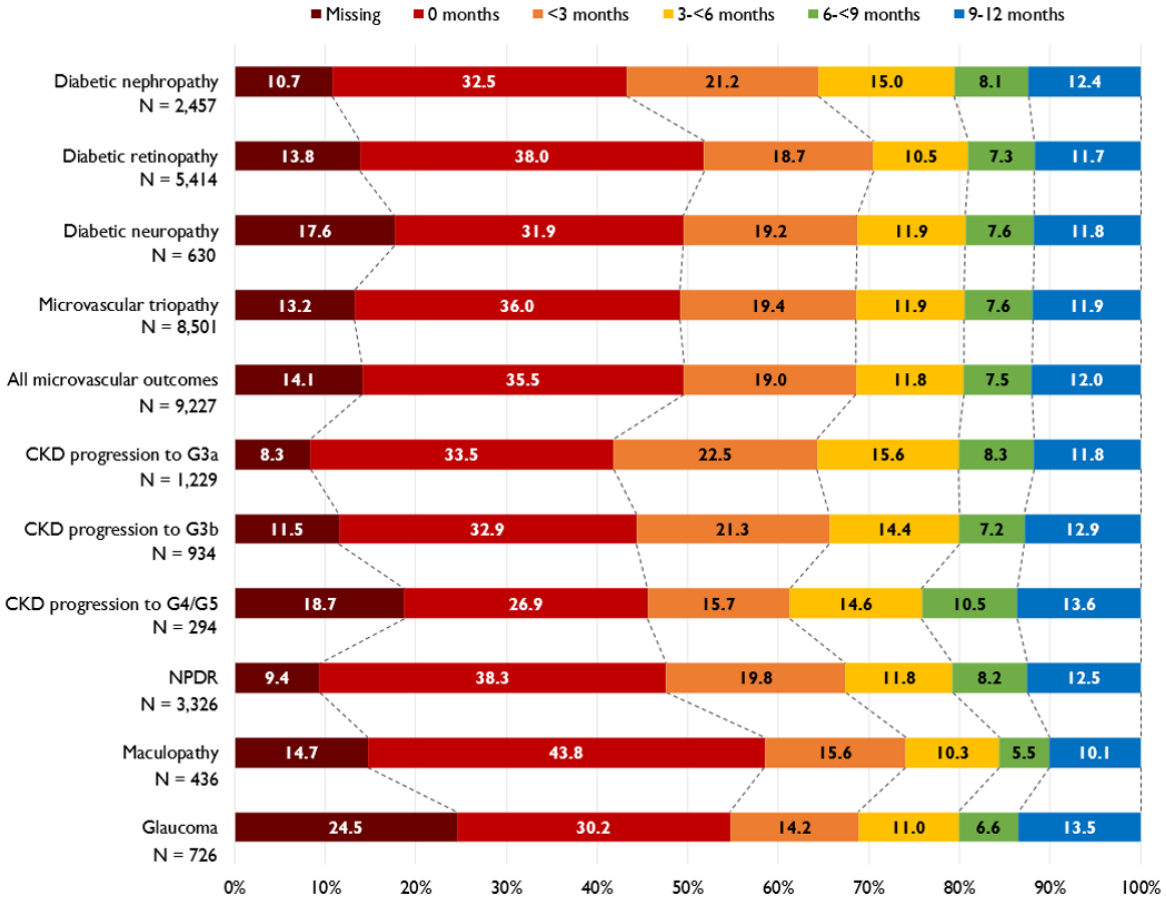


Figure F10.4 Cumulative incidence curves for secondary microvascular endpoints by TITRE category

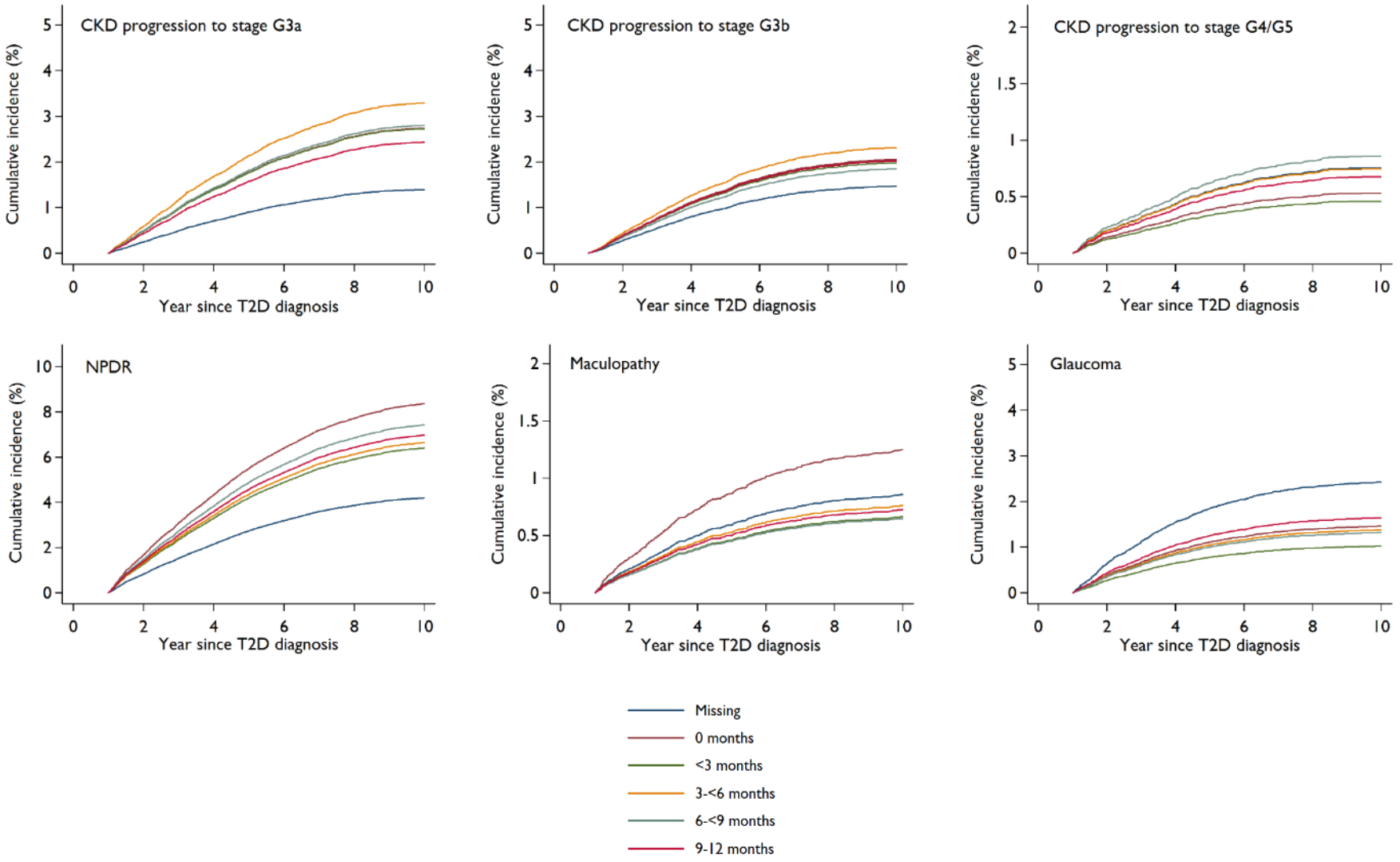


Figure F10. 5
Distribution of HbA1c levels measured using different glycaemic control metrics in CALIBER's T2D cohort without prior microvascular disease

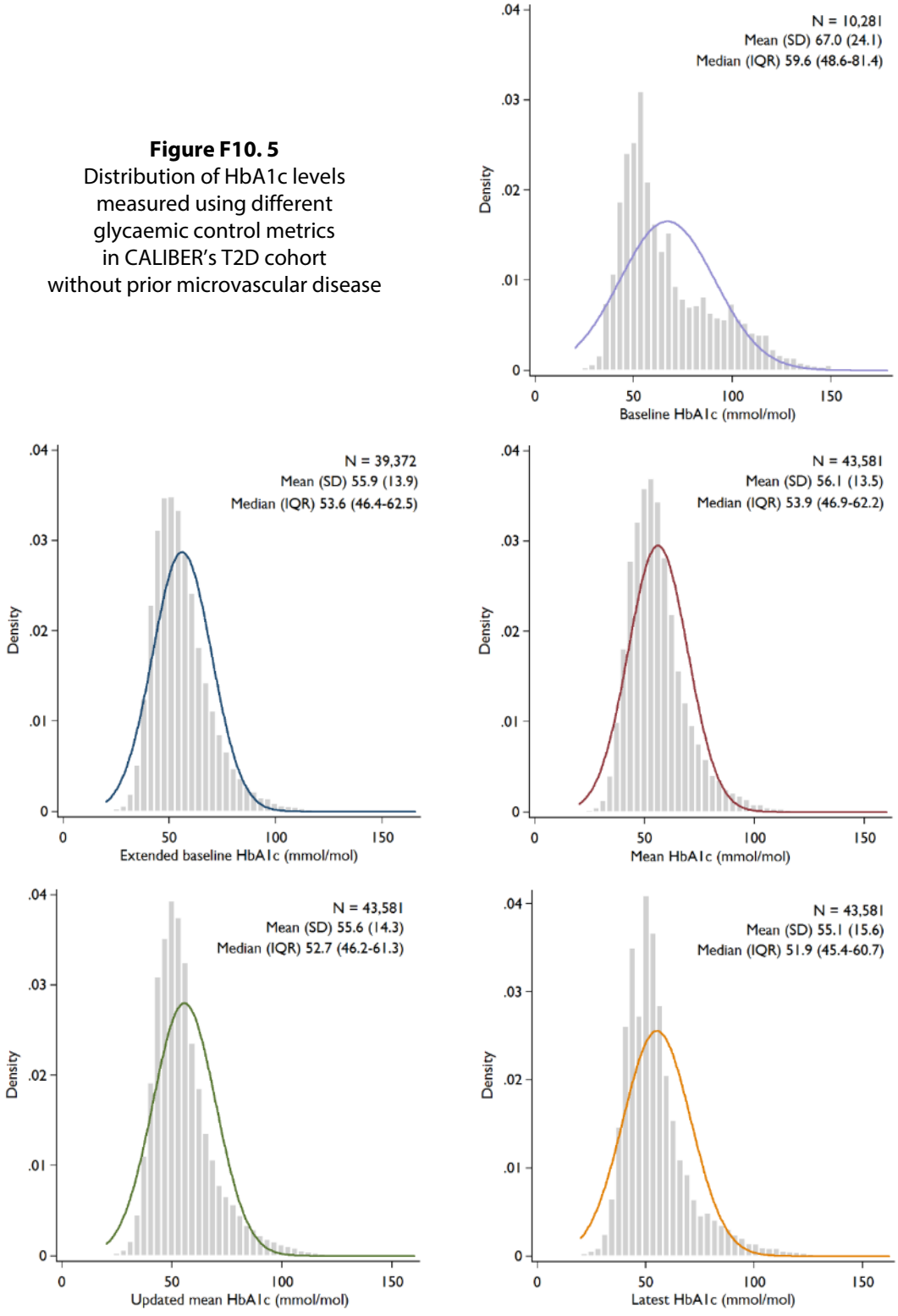
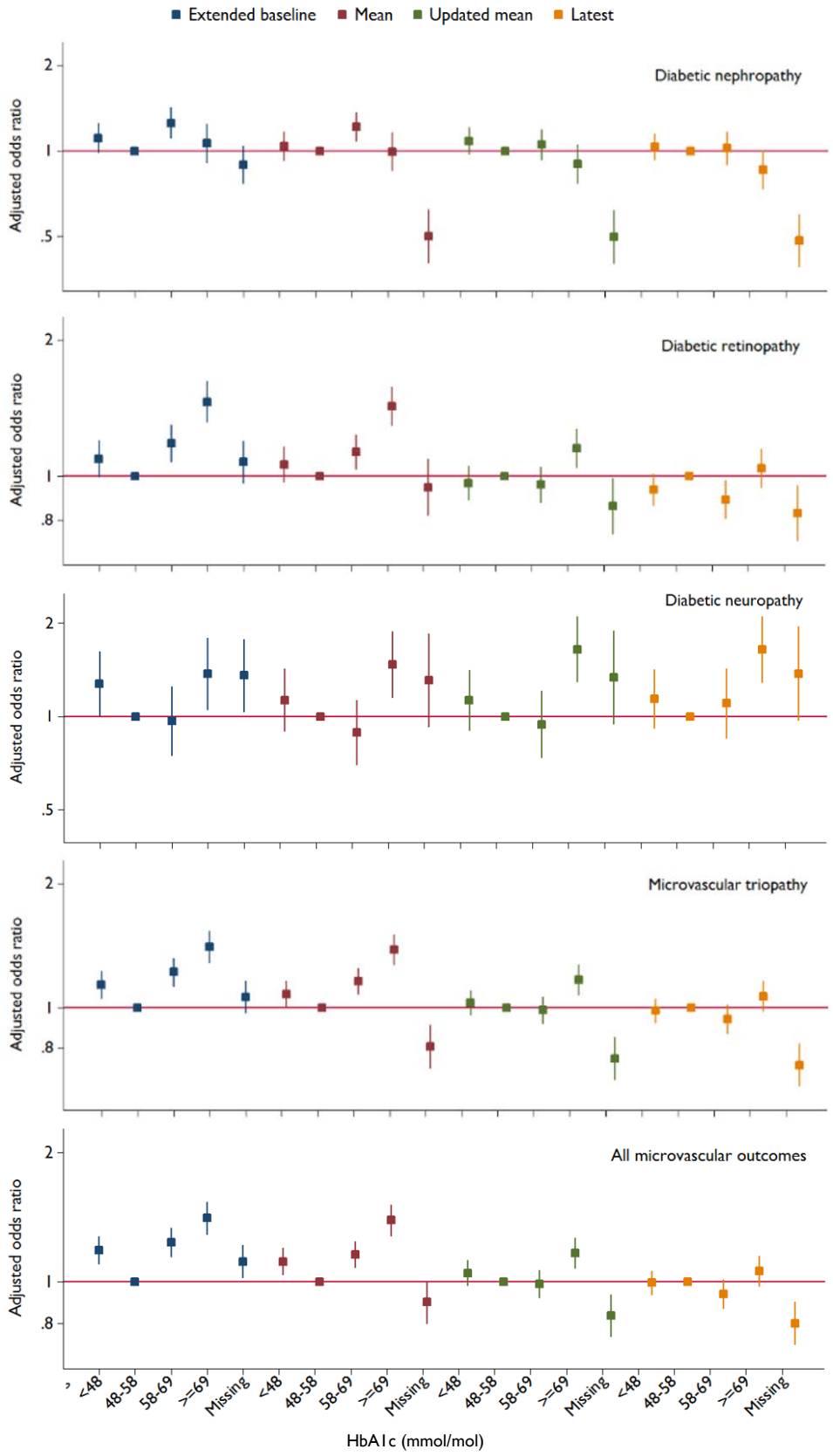
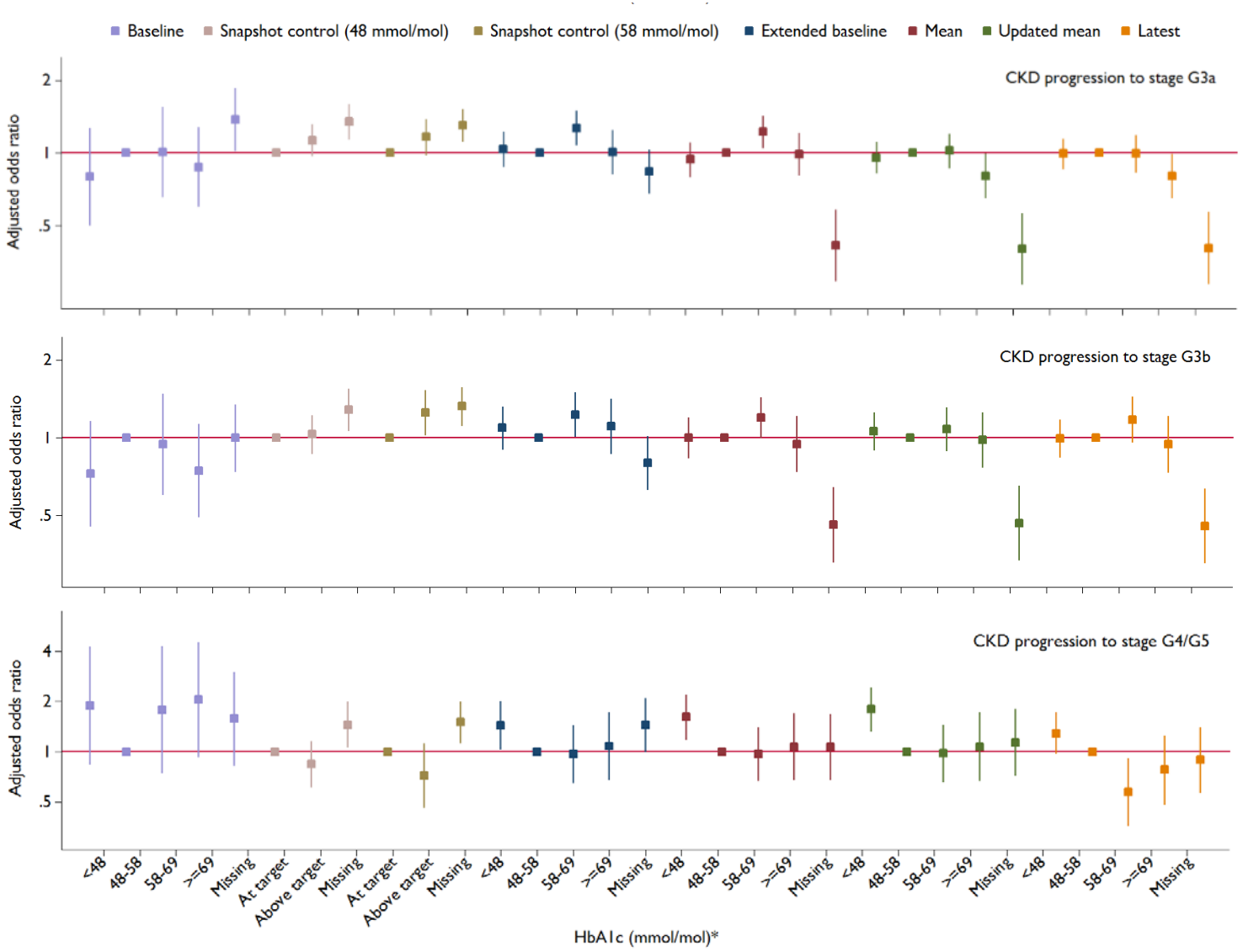
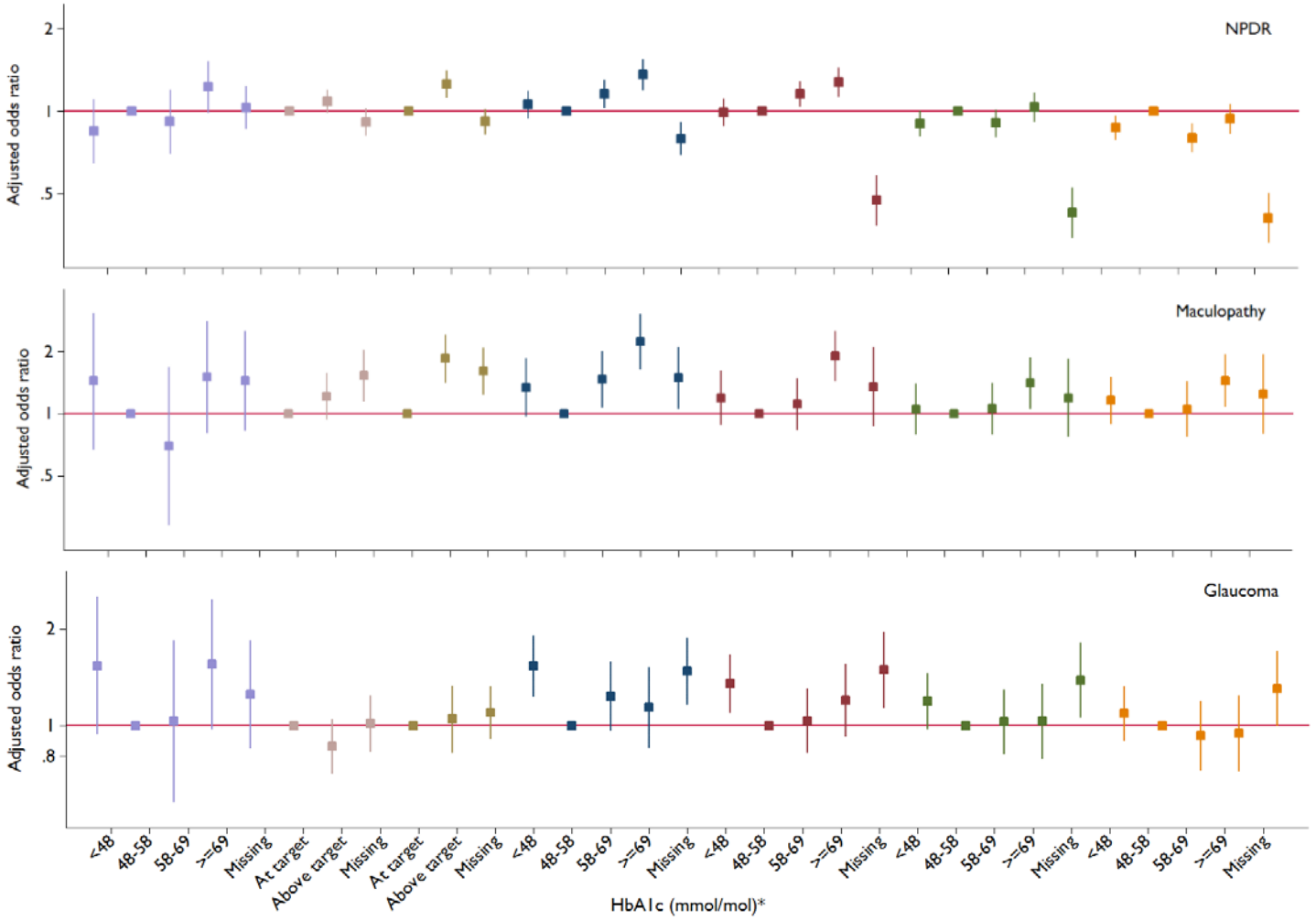


Figure F10.6 Association of HbA1c levels measured using different glycaemic control metrics and microvascular outcomes in CALIBER's T2D cohort without prior microvascular disease



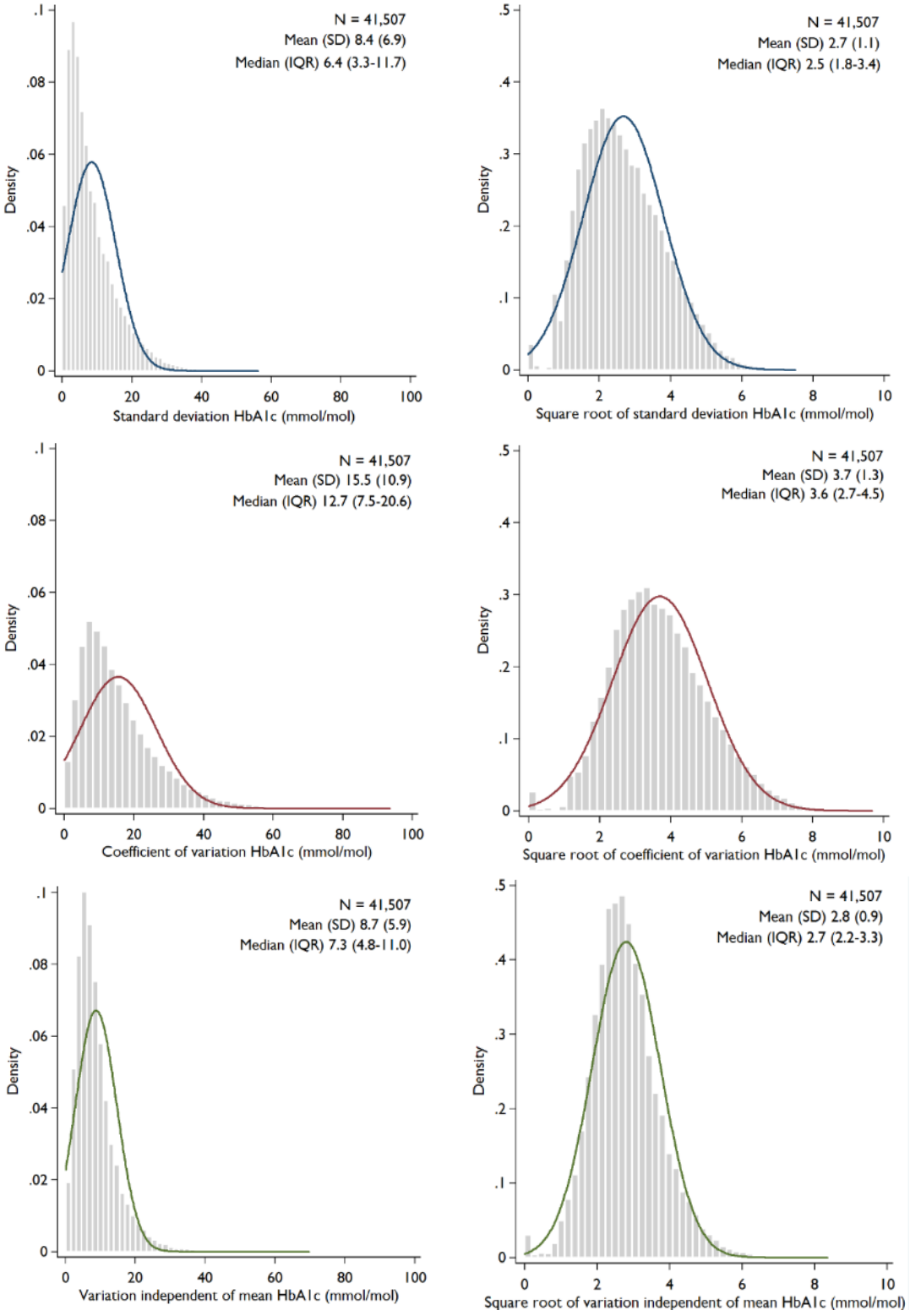

Baseline
Snapshot control (48 mmol/mol)
Snapshot control (58 mmol/mol)
Extended baseline
Mean
Updated mean
Latest
CKD progression to stage G3a
CKD progression to stage G3b
CKD progression to stage G4/G5
Adjusted odds ratio
2
1
.5
4
<48
48-58
58-69
>=69
Missing
At target
Above target
HbA1c (mmol/mol)*



Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, baseline cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

CKD, chronic kidney disease; NPDR, non-proliferative diabetic retinopathy.

Figure F10.7 Distribution of HbA1c variation values measured using different glycaemic variability metrics in CALIBER's T2D cohort without prior microvascular disease



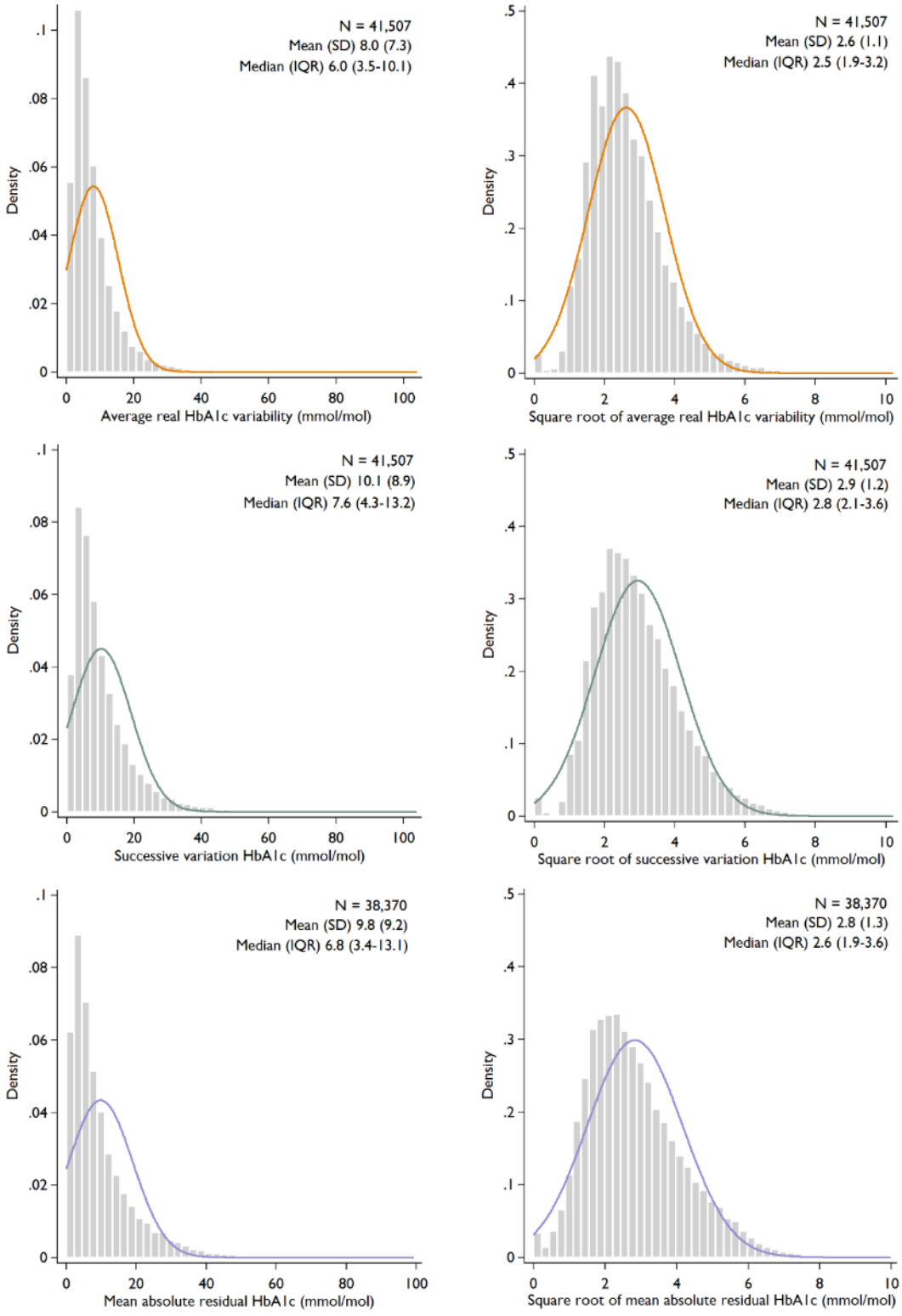
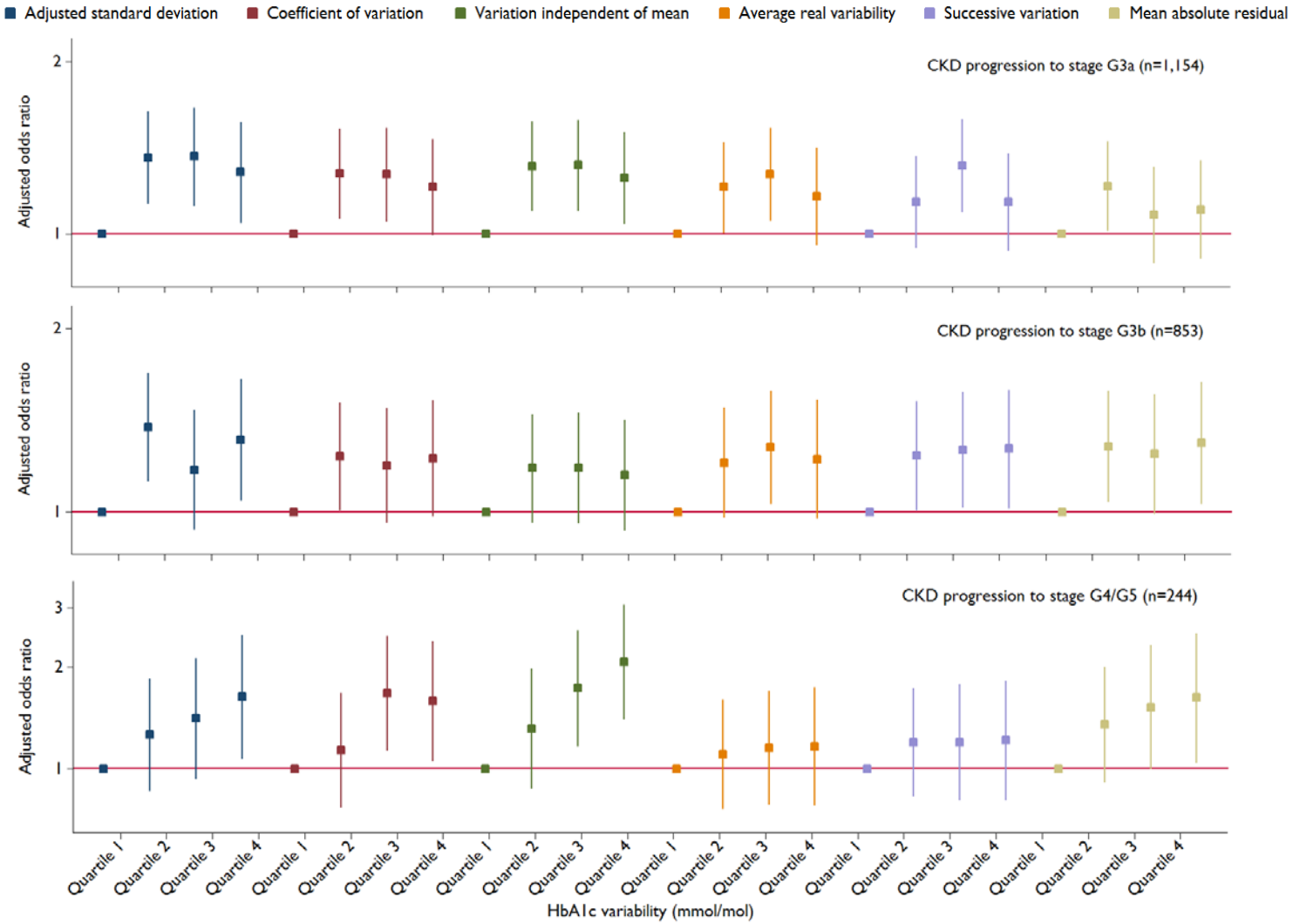
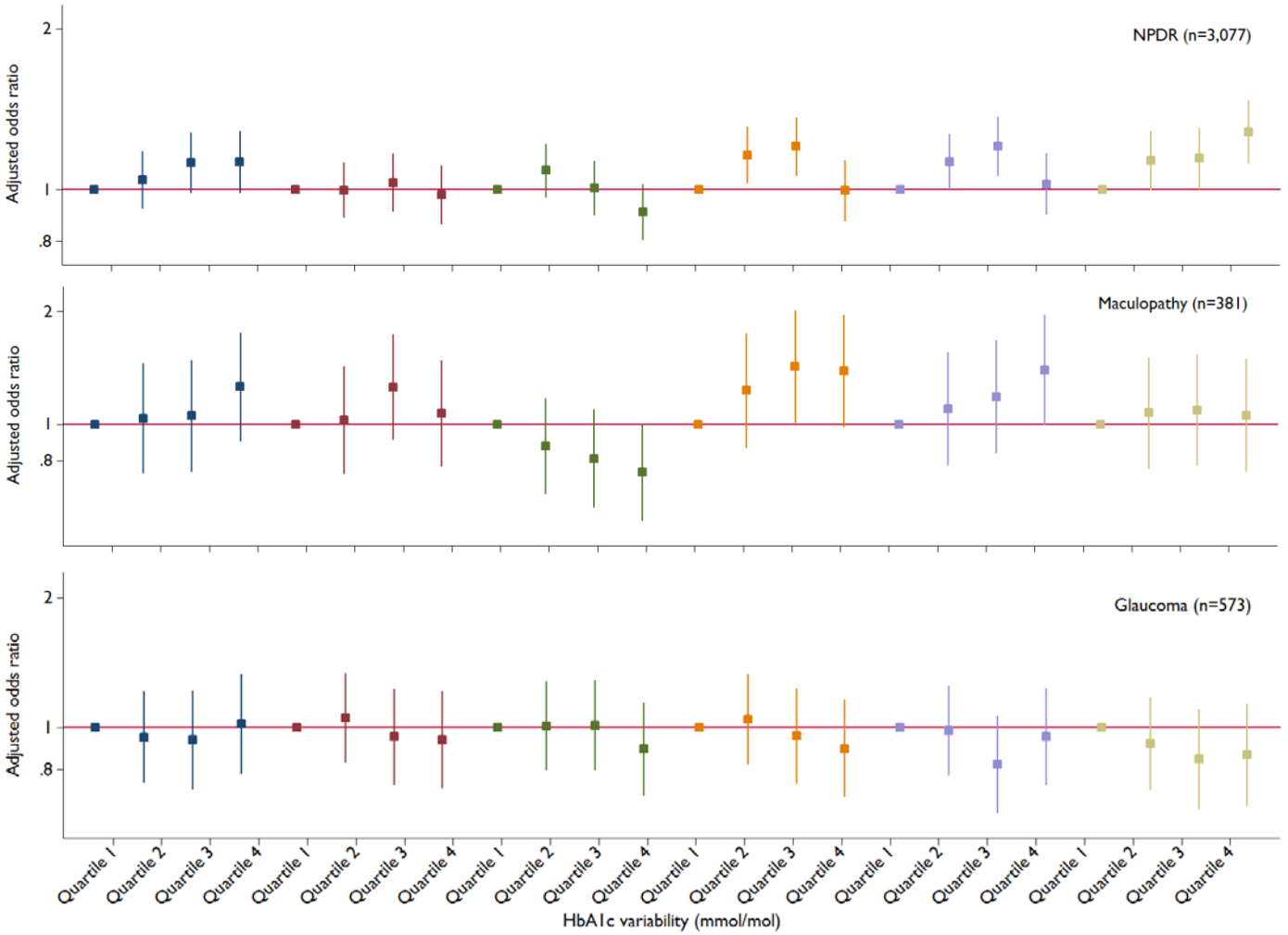

N = 41,507
Mean (SD) 8.0 (7.3)
Median (IQR) 6.0 (3.5-10.1)
Density
Average real HbA1c variability (mmol/mol)
N = 41,507
Mean (SD) 2.6 (1.1)
Median (IQR) 2.5 (1.9-3.2)
Density
Square root of average real HbA1c variability (mmol/mol)
N = 41,507
Mean (SD) 10.1 (8.9)
Median (IQR) 7.6 (4.3-13.2)
Density
Successive variation HbA1c (mmol/mol)
N = 41,507
Mean (SD) 2.9 (1.2)
Median (IQR) 2.8 (2.1-3.6)
Density
Square root of successive variation HbA1c (mmol/mol)
N = 38,370
Mean (SD) 9.8 (9.2)
Median (IQR) 6.8 (3.4-13.1)
Density
Mean absolute residual HbA1c (mmol/mol)
N = 38,370
Mean (SD) 2.8 (1.3)
Median (IQR) 2.6 (1.9-3.6)
Density
Square root of mean absolute residual HbA1c (mmol/mol)

Figure F10.8 Association of glycaemic variability measured using different metrics and secondary microvascular endpoints in CALIBER's T2D cohort without prior microvascular disease

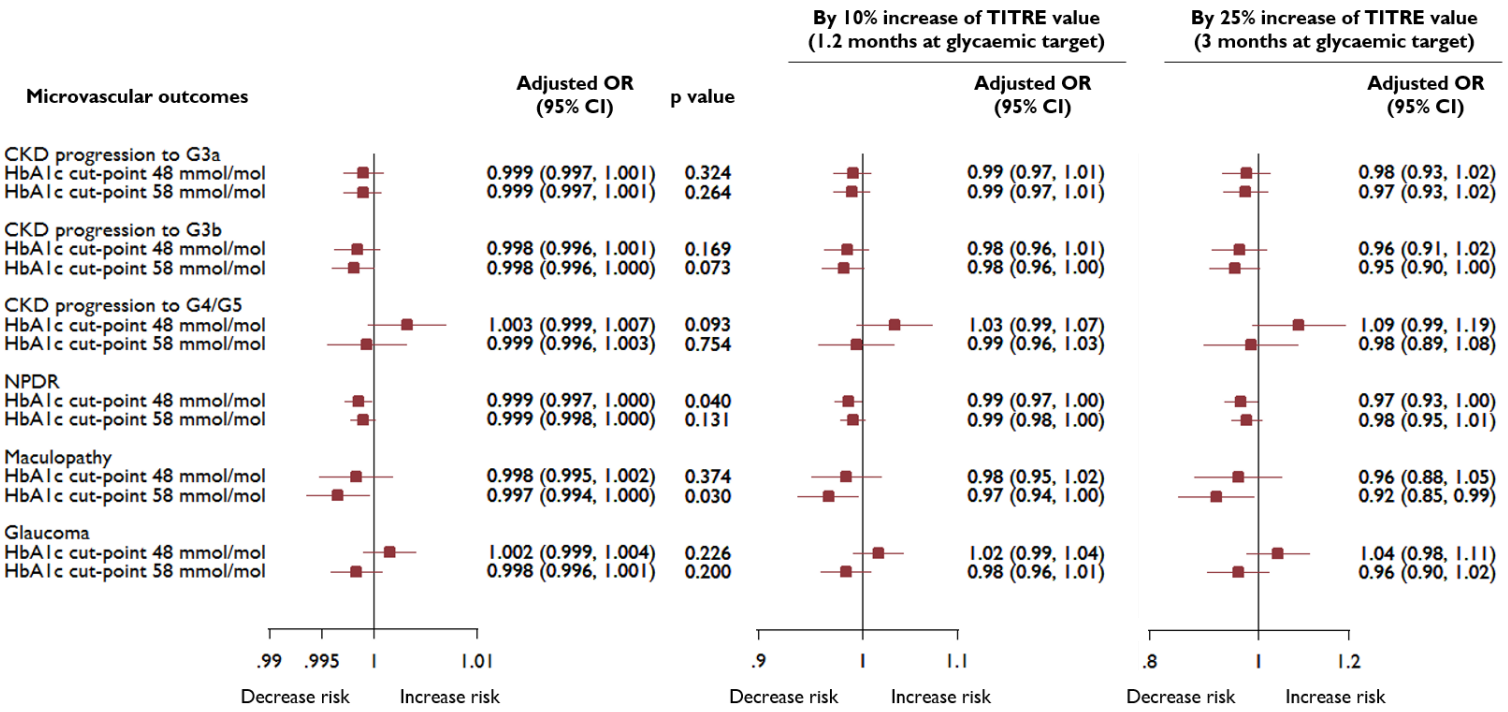




Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, renal disease, cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

CKD, chronic kidney disease; NPDR, non-proliferative diabetic retinopathy.

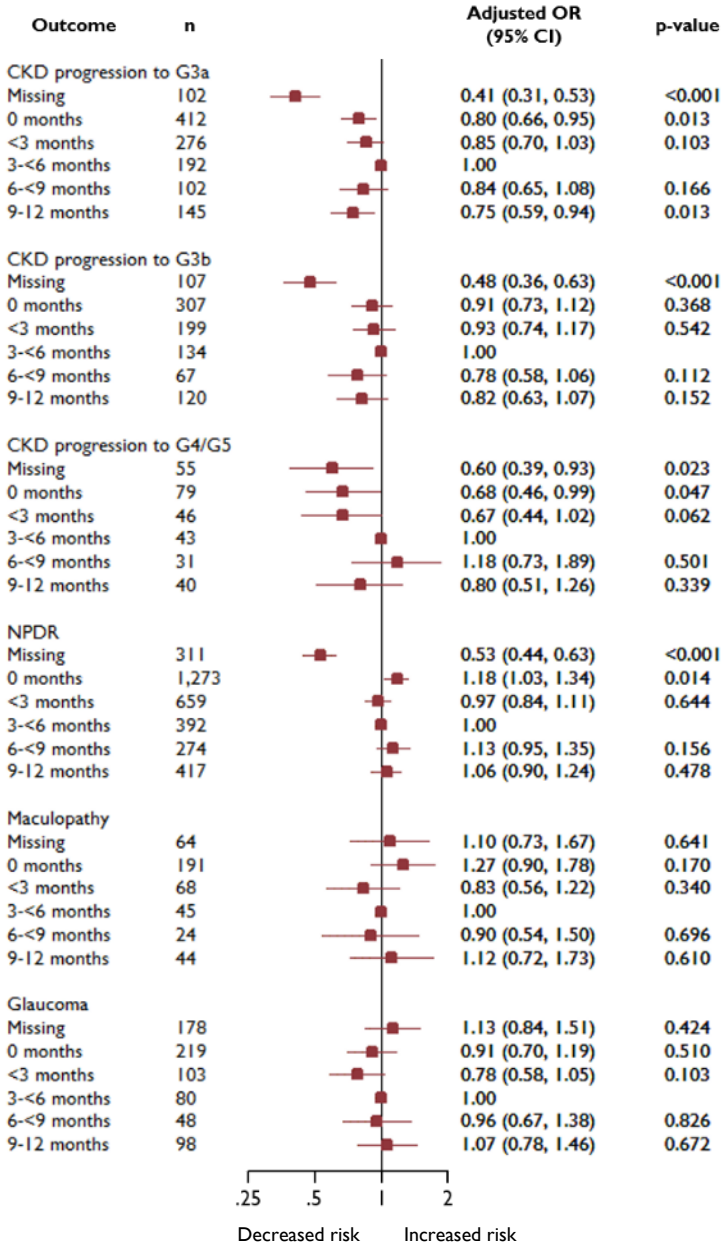
Figure F10.9 Association between non-missing TITRE values (%) and secondary microvascular endpoints using two different cut-points (N=40,152)



Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, baseline cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

CKD, chronic kidney disease; NPDR, non-proliferative diabetic retinopathy.

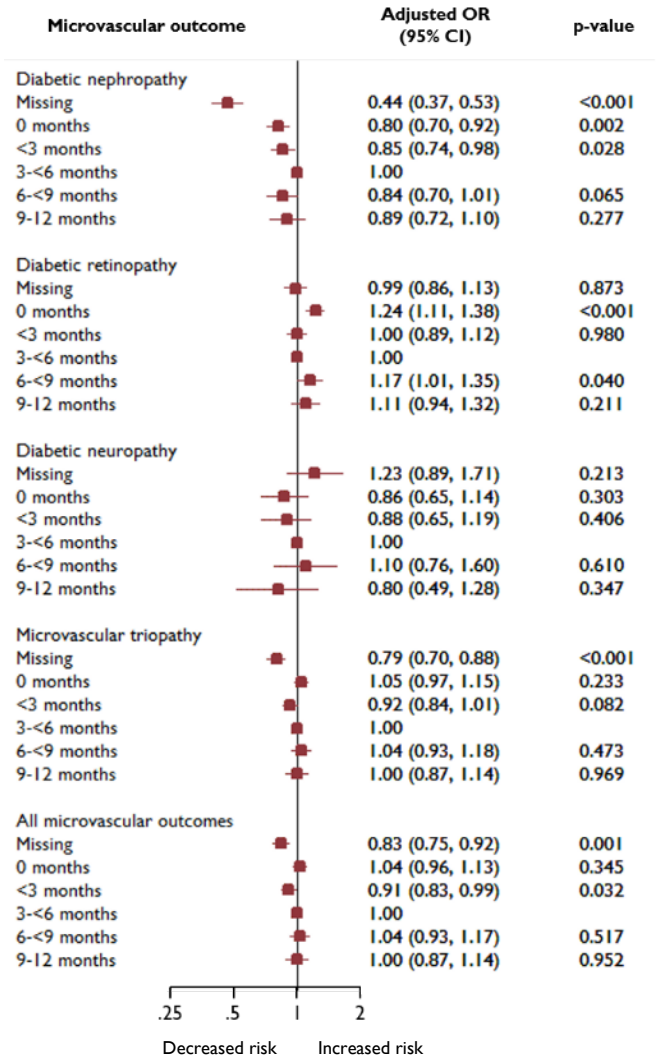
Figure F10.10 Association between TITRE category and secondary microvascular endpoints (N=47,432)



Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, baseline cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

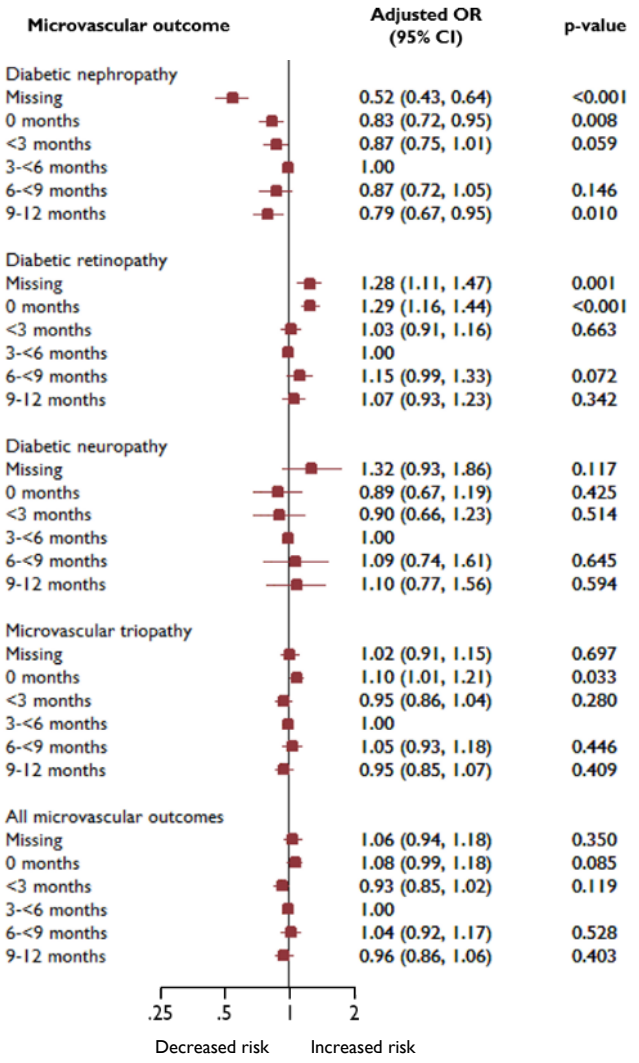
CKD, chronic kidney disease; NPDR, non-proliferative diabetic retinopathy.

Figure F10.11 Adjusted odds ratios for the association between TITRE categories and primary microvascular endpoints by excluding patients with 100% TITRE (N=43,959)



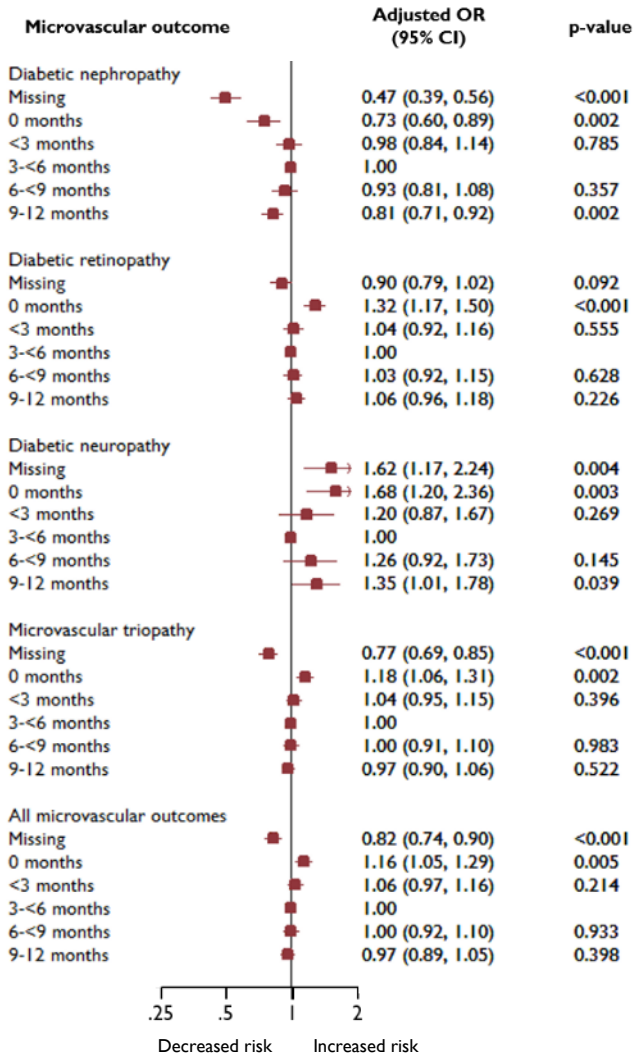
Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, baseline cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure F10.12 Adjusted odds ratios for the association between TITRE category and primary microvascular endpoints in patients whose T2D was first diagnosed in primary care (N=42,492)



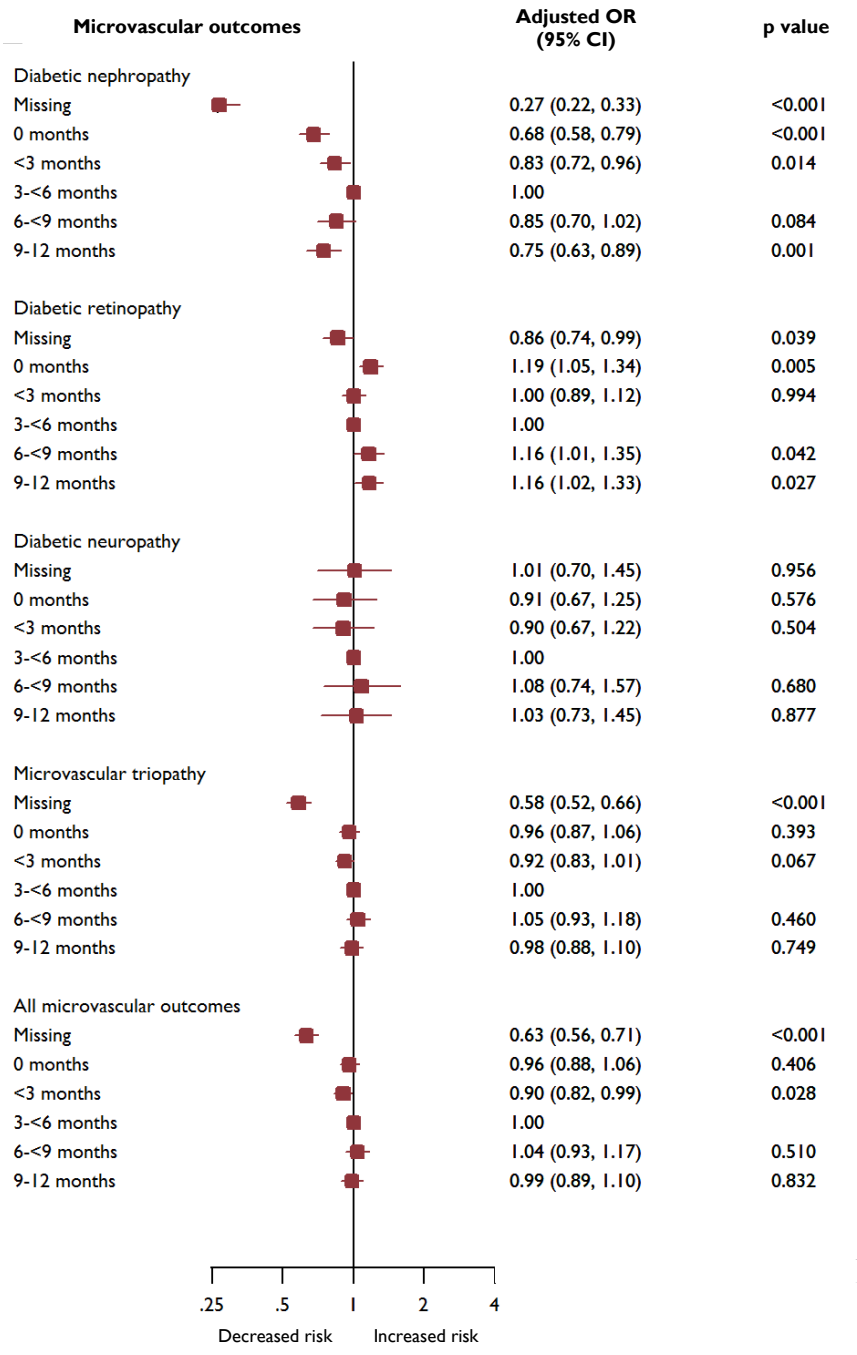
Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, baseline cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure F10.13 Adjusted odds ratios for the association between TITRE category and primary microvascular endpoints using higher HbA1c cut-point (58 mmol/mol) (N=46,367)



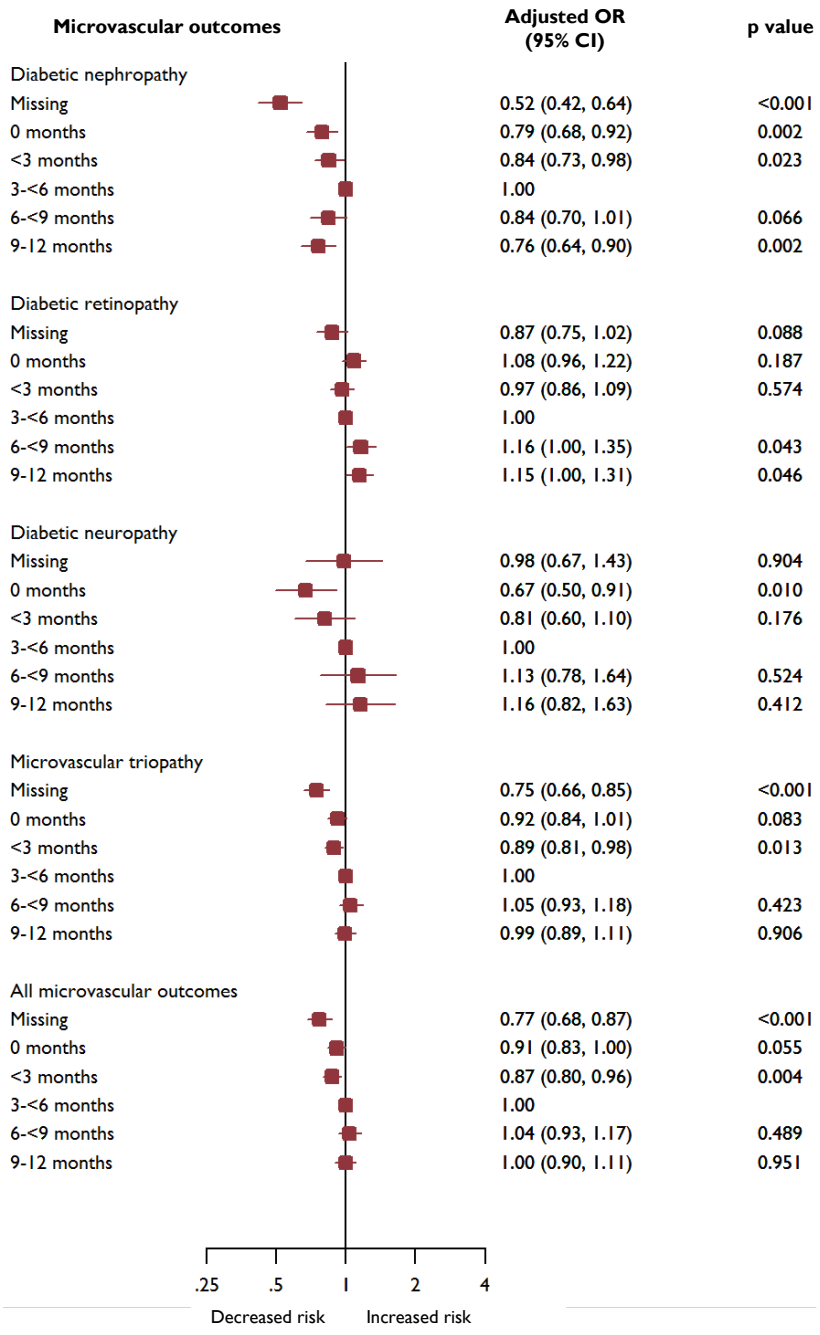
Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, baseline cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure F10.14 Adjusted odds ratios for the association between TITRE category and primary microvascular endpoints by adding snapshot glycaemic control within the first year into the multivariate analysis (N=47,432)



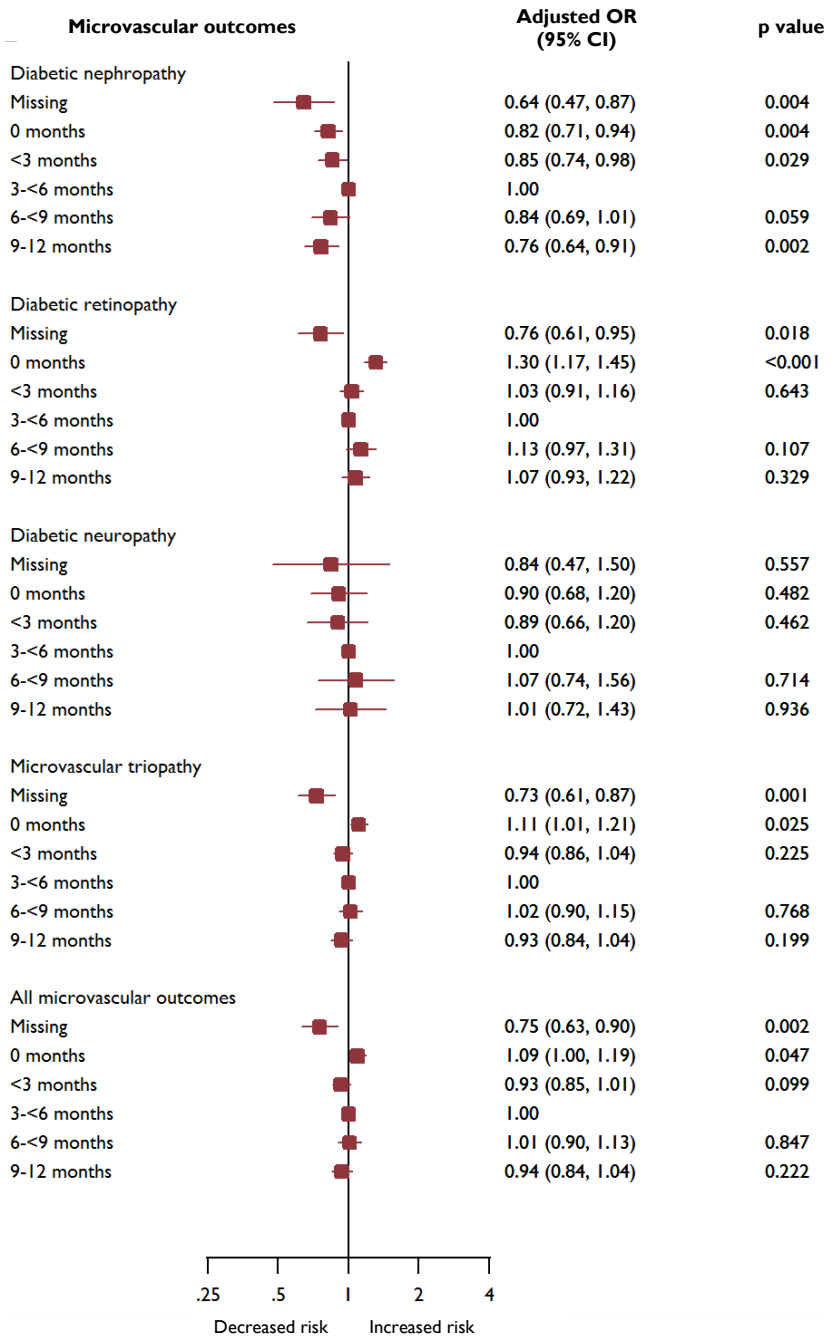
Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, baseline cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure F10.15 Adjusted odds ratios for the association between TITRE category and primary microvascular endpoints by adding mean HbA1c into the multivariate analysis (N=43,581)



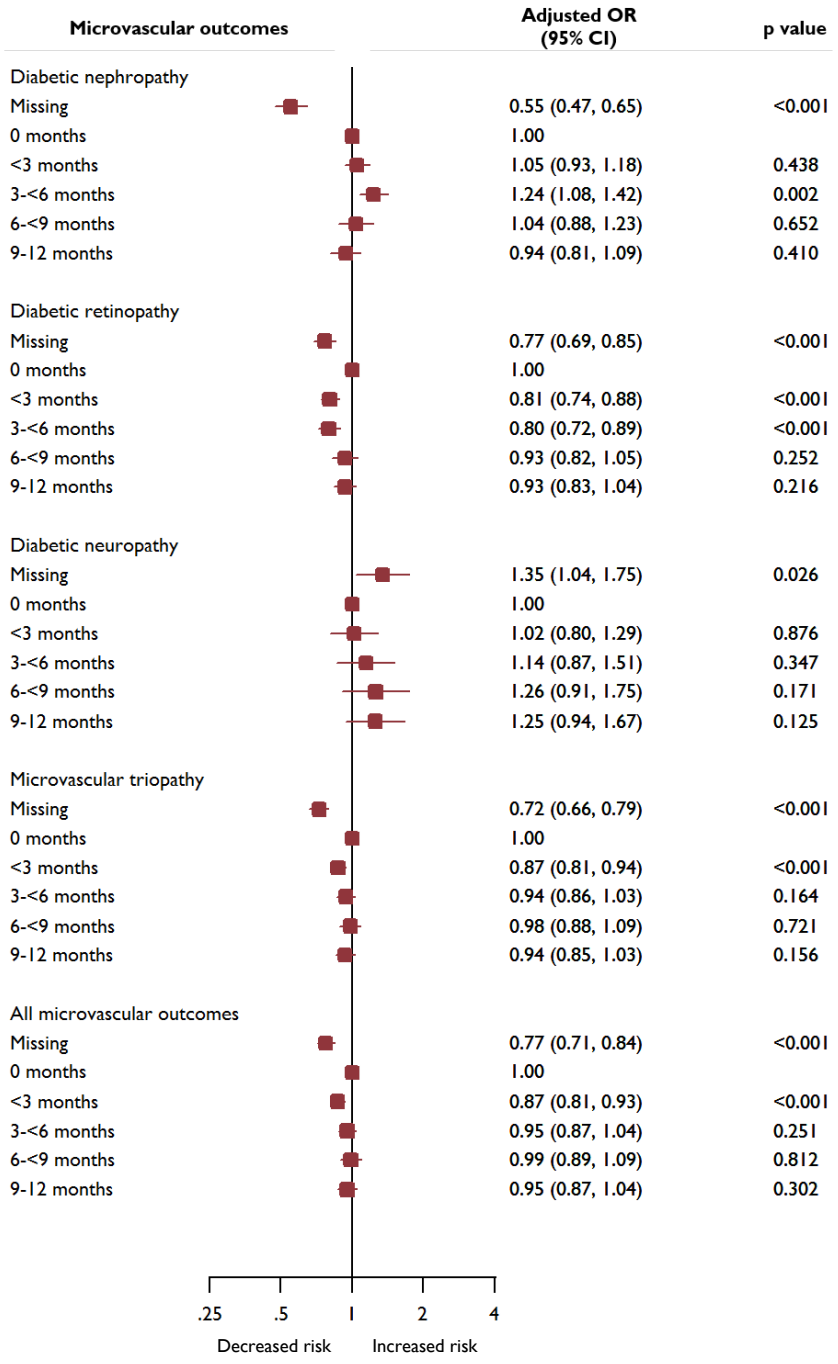
Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, baseline cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure F10.16 Adjusted odds ratios for the association between TITRE category and primary microvascular endpoints by adding adjusted standard deviation of HbA1c into the multivariate analysis (N=41,507)



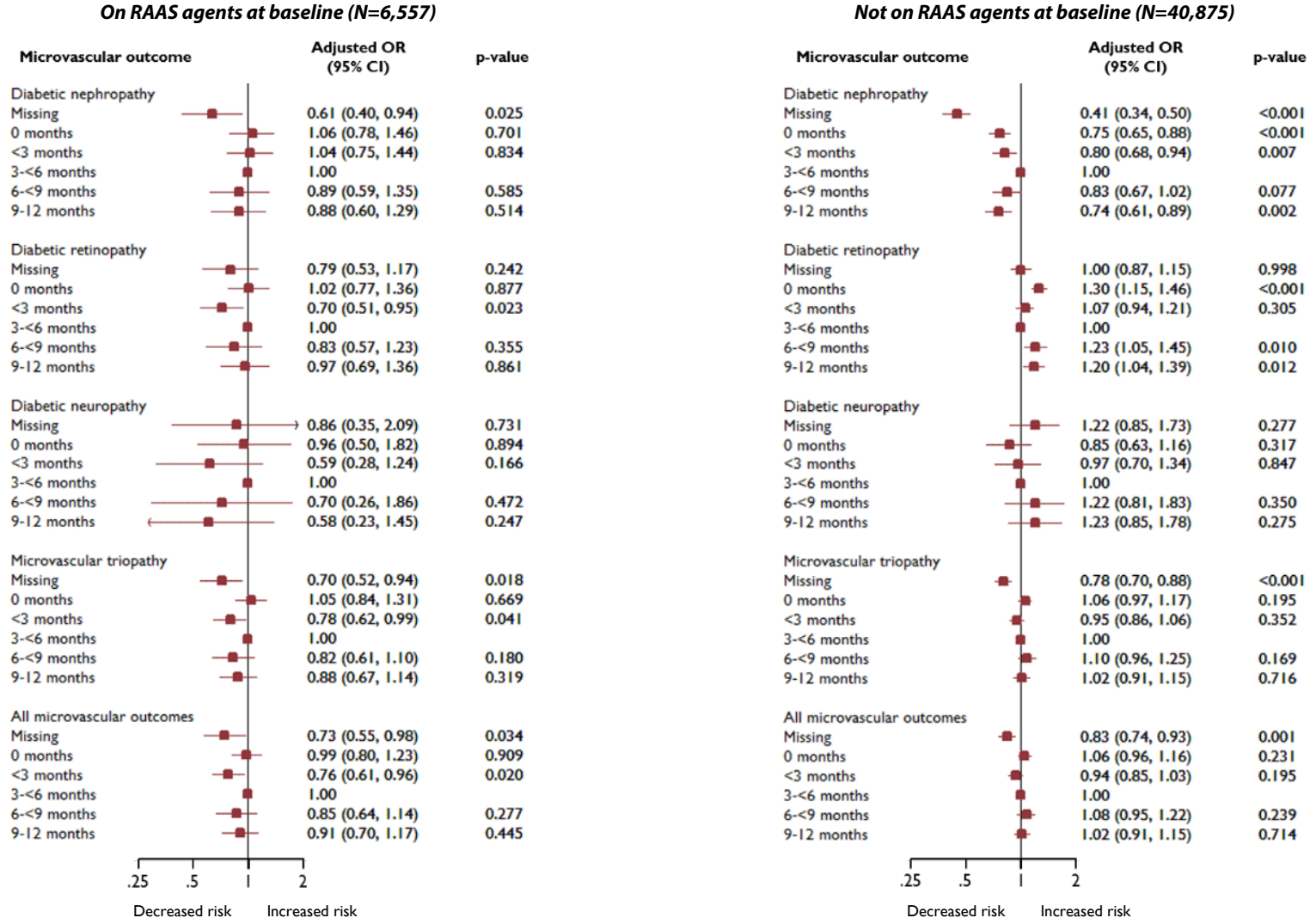
Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, baseline cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure F10.17 Adjusted odds ratios for the association between TITRE category and primary microvascular endpoints by changing the reference group to 0 months (N=47,432)



Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, baseline cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

Figure F10.18 Adjusted odds ratios for the association between TITRE category and primary microvascular endpoints by baseline prescription of RAAS agents



Odds ratios were adjusted for age, gender, ethnicity, deprivation, smoking status, body mass index, blood pressure, total cholesterol, HDL cholesterol, baseline cardiovascular medications, frequency of hypoglycaemic events, class of initial diabetes medication and time to initial diabetes medication.

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