Received: 30 August 2024 | Revised: 29 November 2024 | Accepted: 8 December 2024

DOI: 10.1111/dom.16141

ORIGINAL ARTICLE

WILEY

Beyond glycated haemoglobin: Modelling contemporary management of type 2 diabetes with the updated Cardiff model

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Funding information
AstraZeneca

Abstract

Aims: Recommendations on the use of newer type 2 diabetes (T2D) treatments (e.g., SGLT2 inhibitors and GLP-1 receptor agonists [RA]) in contemporary clinical guidelines necessitate a change in how T2D models approach therapy selection and escalation. Dynamic, person-centric clinical decision-making considers factors beyond a patient's HbA1c and glycaemic targets, including cardiovascular (CV) risk, comorbidities and bodyweight. This study aimed to update the existing Cardiff T2D health economic model to reflect modern T2D management and to remain fit-for-purpose in supporting decision-making.

Materials and Methods: The Cardiff T2D model's therapy selection/escalation module was updated from a conventional, glucose-centric to a holistic approach. Risk factor progression equations were updated based on UKPDS90; the cardio-kidney-metabolic benefits of SGLT2i and GLP-1 RA were captured via novel risk equations derived from relevant outcomes trial data. The significance of the updates was illustrated by comparing predicted outcomes and costs for a newly diagnosed T2D population between conventional and holistic approaches to disease management, where the latter represents recent treatment guidelines.

Results: A holistic approach to therapy selection/escalation enables early introduction of SGLT2i and GLP-1 RA in modelled pathways in a manner aligned to guidelines and primarily due to elevated CV risk. Compared with a conventional approach, only considering HbA1c, patients experience fewer clinical events and gain additional health benefits.

Conclusions: Predictions based on a glucose-centric approach to therapy are likely to deviate from real-world observations. A holistic approach is more able to capture the nuances of contemporary clinical practice. T2D modelling must evolve to remain robust and relevant.

KEYWORDS
cardiovascular disease, GLP-1, health economics, pharmaco-economics, SGLT2 inhibitor

1 | INTRODUCTION

The American Heart Association[1] has applied the term 'cardiovascular-kidney-metabolic (CKM) syndrome' to describe the overlap of cardiorenal syndrome (a bidirectional association between heart and kidney disfunction)[2] and cardiometabolic disease (systemic effects including cardiovascular disease [CVD] arising from excess adipose tissue).[3] Type 2 diabetes (T2D), part of CKM syndrome, has a multidirectional pathophysiology that affects and is affected by obesity, chronic kidney disease (CKD) and CVD. Clinicians are directed to consider such comorbidities when determining antidiabetic treatment, aligning to contemporary national treatment guidelines[4] and international consensus.[5]

Historically, T2D management was governed by blood glucose levels, measured as HbA1c. When an intervention no longer facilitated a patient meeting HbA1c targets, therapy was updated by adding or substituting another antidiabetic drug, until insulin therapy became the only viable approach to maintain HbA1c within target levels. Now, with T2D viewed as part of CKM syndrome rather than a discrete metabolic disorder,[6] clinicians take a holistic, person-centred approach, where therapy choice is informed by patients' HbA1c levels, bodyweight, CV and kidney disease risk factors and comorbidities. Cardiovascular outcomes trials (CVOTs) have shown that newer antidiabetic drug classes, including sodium-glucose linked cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RA) (cardiometabolic drugs [CMDs]), offer broader health benefits to patients beyond their effect on HbA1c, such as cardio-kidney-protective effects and weight loss.[7–14] Accordingly, current treatment guidelines recommend early initiation of SGLT2i and GLP-1 RA in eligible patient subgroups to achieve treatment goals.[5]

Health economic models where HbA1c values are the sole determinant of treatment escalation (a conventional glucose-centric approach) are at odds with the multifactorial decision-making process implemented by todays' clinicians (a holistic approach). Novel modelling methods are required to reflect this treatment paradigm, maintain model relevance and inform healthcare system stakeholders of the clinical and economic benefits associated with new therapeutics and updated guidelines. Another limitation of current health economic models relates to the recognition of cardio-kidney-protective effects observed in CVOT studies of CMDs, which cannot be fully explained by changes in surrogate markers (e.g., HbA1c, systolic blood pressure [SBP], blood lipids). Equations that assess risk solely on surrogate risk factors are inadequate for modelling CVOT results, and updated risk equations that consider both surrogate risk factors and treatment-specific effects on outcomes are required. With an estimated 5 million patients with T2D in the UK alone, it is crucial to address model limitation to ensure robust evidence for decision-making.[15]

The Cardiff T2D model is an established, person-level, fixed-time increment (six-monthly) Monte Carlo microsimulation for predicting health outcomes and associated costs for T2D patients over a user-determined time horizon (Figure S1).[16,17] First developed in 2003,[18,19] the model has since been enriched by the incorporation of risk equations based on the findings from the United Kingdom Prospective Diabetes Study (UKPDS)[17,20] and other clinical trial programs as data became available.[21] The model build and risk equations incorporated have been extensively validated, both internally through predictive accuracy testing, and externally in peer-reviewed publications and through participation in the Mount Hood diabetes modelling network. However, the previous model version is limited by its glucose-centric approach, where exceeding user-defined HbA1c thresholds triggers therapy escalation to the next-line treatment.

The overall objective of this study was to modernize the Cardiff T2D model. The treatment selection/escalation module was updated to a holistic approach reflective of contemporary guidelines (e.g., American Diabetes Association [ADA], European Association of the Study of Diabetes [EASD][5] consensus and UK National Institute for Health and Care Excellence [NICE] NG28[4]). Specifically, treatment selection/escalation was updated from a static progression through pre-determined treatment lines to a dynamic, patient-centric treatment augmentation regulated by a novel 'physician decision' submodule. The cardio-kidney-metabolic benefits of SGLT2i and GLP-1 RA were then included via novel risk equations derived from relevant CVOTs.[21] These allow the model to more closely capture the interplay of diseases within CKM syndrome than is possible when considering HbA1c alone, and gives the user a choice between equations from pivotal trials, pooled CVOT data, network meta-analysis and real-world evidence. Finally, the latest evidence from UKPDS90[22] was incorporated to assess long-term risk factor progression trends.

The relevance of these updates were demonstrated in a case study. Newly diagnosed patients with T2D were modelled over a lifetime time horizon with either the conventional glucose-centric approach or the holistic approach, with a comparison of the predicted clinical and health-economic outcomes.

2 | MATERIALS AND METHODS

A flow diagram of the patient simulation process in the updated Cardiff T2D Model is depicted in Figure 1. This section will focus on specific updates within the model structure; a walkthrough of the modelled patient journey is included in Supplementary Methods.

2.1 | Updating the treatment or therapy selection/escalation module

Within the model, the treatment module (Figure 2) assesses the need to update/intensify interventions applied to manage the disease course of individual patients in the model. To reflect current practice, it was updated to consist of two components, a glucose-centric therapy algorithm (GCA), like the approach in previous Cardiff T2D versions and a comorbidity-centric algorithm (CCA). In combination, these algorithms reflect the holistic, multifactorial approach to management recommended in contemporary guidelines. The GCA consists of three consecutive treatment lines predefined by the model user.

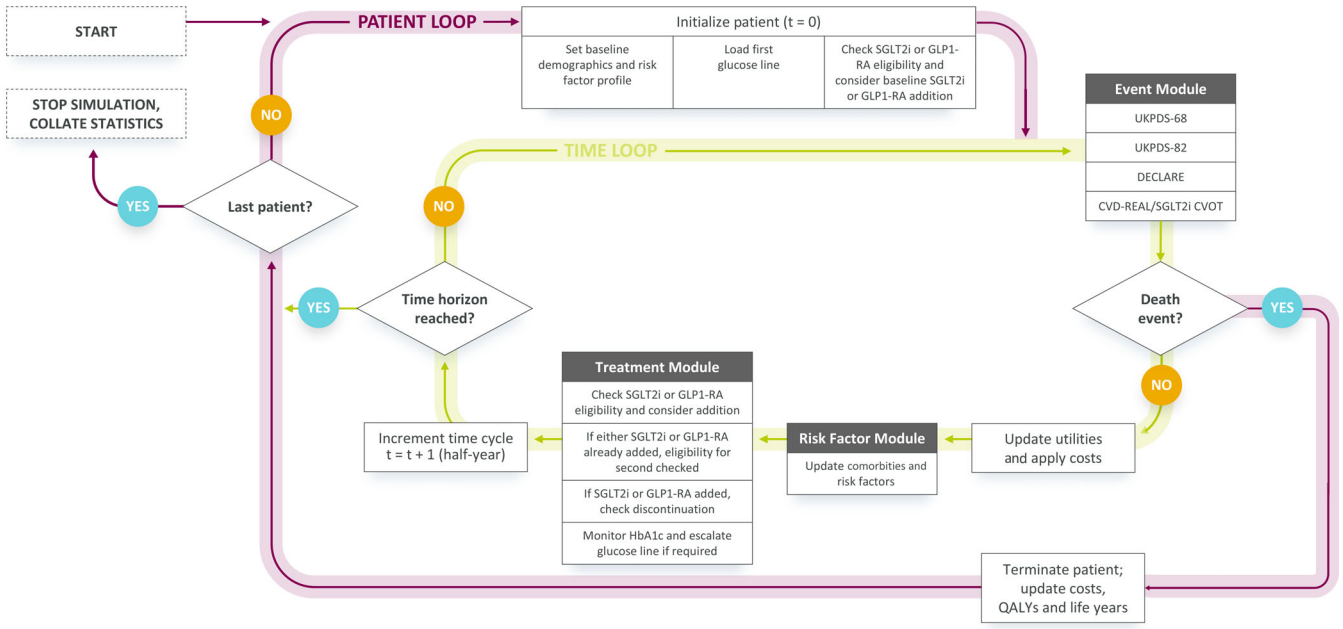

FIGURE 1 Flow diagram of patient simulation process in the Cardiff T2D model (updated version). CVD, cardiovascular disease; CVOT, Cardiovascular outcomes trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; QALYs, quality adjusted life years; SGLT2i, sodium-glucose-linked cotransporter-2 inhibitor; t, time; UKPDS, United Kingdom Prospective Diabetes Study.

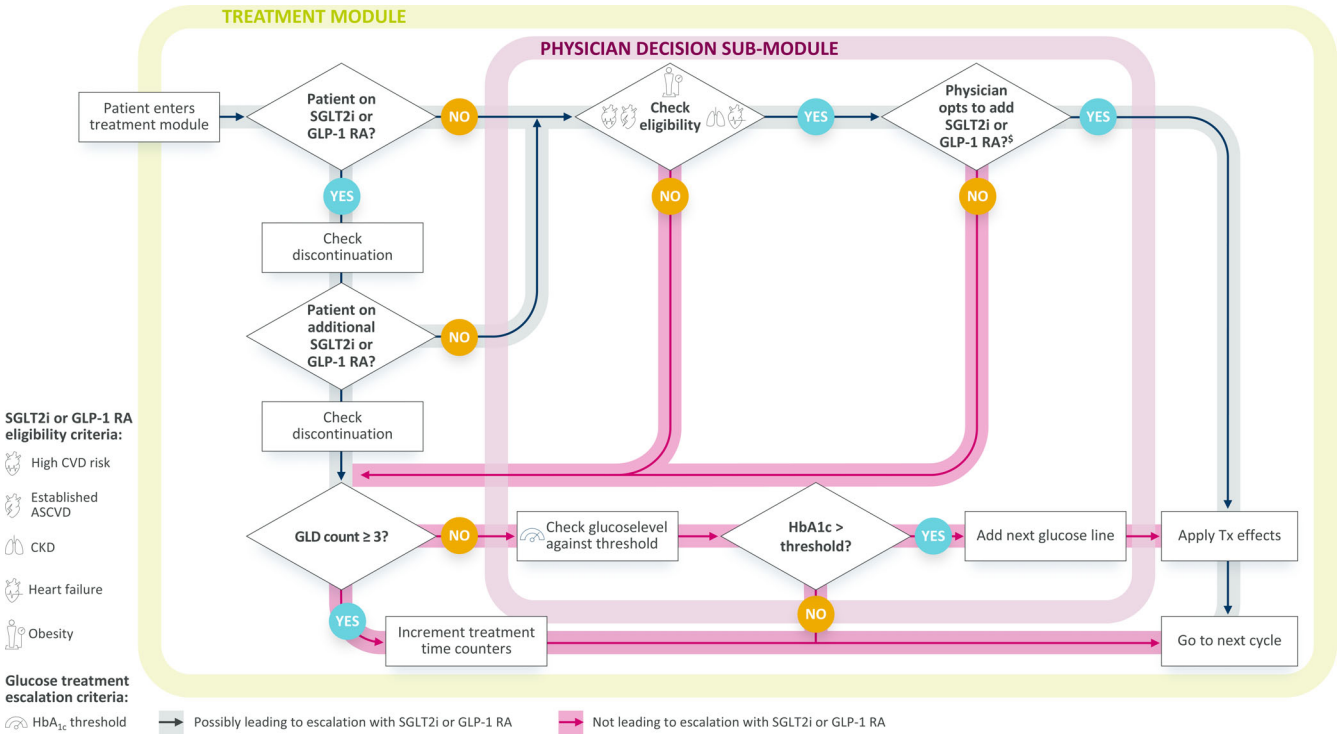

FIGURE 2 Treatment module within the Cardiff model (updated model). If a patient satisfies multiple criteria, the patient can receive both sodium-glucose-linked cotransporter-2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1 RA). ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; GLD, glucose-lowering drug; HbA1c, glycated haemoglobin; Tx, therapy.

Patients start on first glucose line and transition to second or third glucose line when their HbA1c level exceeds predefined thresholds. Conditional on the scenario of interest, first line may represent monotherapy initiation or advanced glucose management (e.g., dual or triple therapy). Patients are directed through the CCA prior to the GCA to reflect guidelines calling for the consideration of a patient's

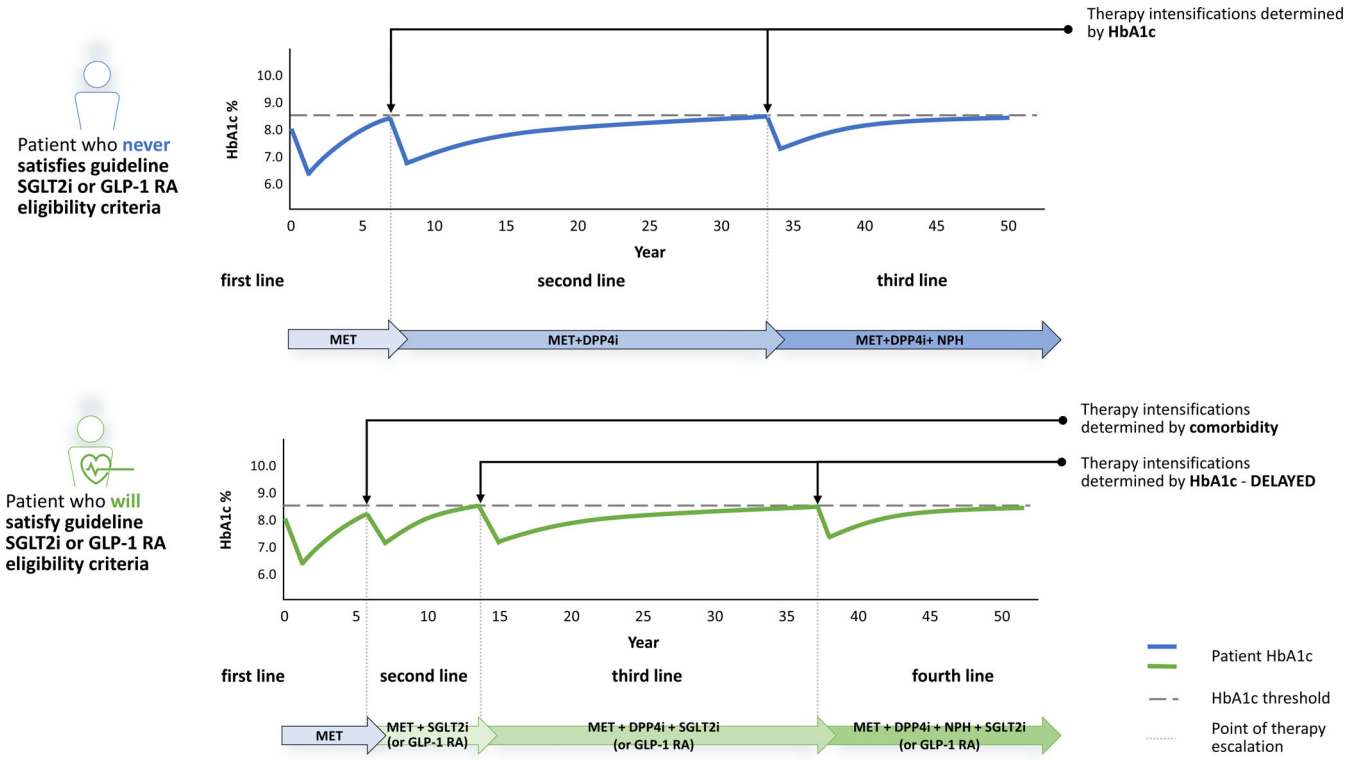

FIGURE 3 Treatment escalation in the Cardiff model when a patient never becomes eligible for a sodium-glucose-linked cotransporter-2 inhibitor (SGLT2i) or glucagon-like peptide-1 receptor agonist (GLP-1 RA), and therapy escalation is driven by glycated haemoglobin (HbA1c) alone (the conventional glucose-centric approach), and when a patient does become eligible to receive an SGLT2i or GLP-1 RA (a holistic approach considering blood glucose and comorbidities). Treatment escalation occurs in the treatment module, with SGLT2i or GLP-1 RA use being determined within the physician decision sub-module (see Figure 2). In the case study shown, metformin is used as a first-line glucose agent, with dipeptidyl peptidase inhibitors (DPP4i) as a second line and neutral protamine Hagedorn (NPH) insulin as third line. Introduction of SGLT2i or GLP-1 RA essentially presents a fourth line. Escalation to DPP4i or insulin therapy is driven by HbA1c alone. A patient may receive a SGLT2i or GLP-1 RA at any time point when they become eligible and informed by physician preferences. If a patient satisfies multiple criteria, they can receive both SGLT2i and GLP-1 RA. MET, metformin.

CV risk or medical history of established comorbidities and to allow the prioritization of therapies that address these conditions.[4,5,23] The CCA determines patient eligibility for either an SGLT2i or GLP-1 RA, which class is required, and whether it is administered. Since the latter two decisions are made by physicians, a 'physician decision sub-module' was incorporated to mimic physician preferences towards either drug class or omission, conditional on the individual patient's constitution and the comorbidity (CM) that triggered eligibility (see Figure 2, Table S1).

The sub-module replicates the ability of a physician to use discretion when interpreting guidelines (i.e., prioritization of particular drugs or recognizing that for some patients guideline-compliance may be inappropriate [omission]). The sub-module consists of user-definable proportions (Table S1) representing preferences towards either therapy or omission based on the eligibility criteria satisfied and patient-specific criteria, for example, BMI, HbA1c. Eligibility criteria (high CVD risk [QRISK3[24] score ≥10%], established atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), CKD or BMI ≥35) are aligned to T2D management guidelines.[4,5] To minimise complexity, physician preferences (as reflected in the proportion between therapy and omission) are defined separately for three eligibility criteria (or CM) types: 'high CVD risk or established ASCVD' (CM1); 'HF or CKD' (CM2); and 'BMI > threshold'. Physician preferences may differ within each group based on the patient's HbA1c or BMI levels to align to guidelines or clinical practice; the proportions may be user-defined to reflect physicians' personal interpretation of guidelines/patients' conditions. For each individual simulated, proportions representing physician preferences are compared with uniformly distributed random numbers between 0 and 1 to determine the decision (SGLT2i addition, GLP-1 RA addition, omission of both). If neither drug is added, the patient progresses to the GCA; if a CMD is added, the GCA is bypassed for that cycle, as addition of an SGLT2i or GLP-1 RA lowers HbA1c, modifies risk factors for CM development, and delays the requirement for glucose-determined intensification (Figure 3). Once a CMD (SGLT2i or GLP-1 RA) is added, discontinuation is checked in each subsequent cycle.

Patients receiving one of these drug classes may go on to receive the other in subsequent cycles, conditional on eligibility for a second CMD and physician preferences. In line with ADA guideline recommendations for patients receiving either an SGLT2i or GLP-1 RA,

HbA1c exceedance represents an additional criterion for initiation of the alternative therapy.

2.2 | Considering cardio-kidney-metabolic benefit within the event module

Within the event module, an individual's risk of an event is assessed using risk equations that consider risk factors, including patient demographics, biochemical surrogate markers and medical/event history, amongst others. The user selects which risk equations are used. The order in which event risk equations are evaluated is random per model cycle. Predicted event risk is compared with a uniformly distributed random number ranging from 0 to 1 to determine whether an event occurs.

Earlier versions of the Cardiff model utilised UKPDS68 and UKPDS82 risk equations.[20,25] As reported previously, novel risk equations have since been added to the model, including equations derived from the DECLARE-TIMI-58 CVOT,[21] parametric survival equations derived from pooled CVOT data,[26] and separately equations from real-world evidence considering SGLT2i at class-level.[26] UKPDS-based risk equations represent surrogate risk models with limited capability to capture cardio-kidney-metabolic effects not explained by surrogate changes; the DECLARE risk equations and parametric survival equations were derived using a hybrid approach that allows consideration of both surrogate-dependant and -independent treatment effects on cardio-kidney outcomes by supplementing changes in surrogate risk markers with observed and extrapolated event-rate reductions. To address the limitations of UKPDS-based risk equations and enable their continued use in evaluations using CVOT and kidney outcomes data, a calibration feature was added that allows consideration of risk adjustments (hazard ratios [HR]) to capture surrogate-independent effects. Required risk adjustments can be evaluated empirically (Supplementary Methods).[27] The calibration approach involves exploration of the component part of the trial-reported HR that is captured via the surrogate risk model, and the uncaptured component part requiring amendment via external risk adjustment.

To the author's knowledge, no published risk equations capture the cardio-kidney-protective effects of GLP-1 RA. To enable the recognition of GLP-1 RA-specific effects, the DECLARE and SLGT2i-specific parametric survival risk equations were modified: the risk modifier representing the surrogate-independent treatment effects on CV outcomes was adjusted based on odds ratios reported in a systematic literature review evaluating the comparative effectiveness of SGLT2i and GLP-1 RA,[28] while patients follow different estimated glomerular filtration rate (eGFR) decline patterns depending on their therapy. Further details on the consideration of cardio-kidney-protective effects of SGLT2i and GLP-1 RA inside DECLARE risk equations are in the Supplementary Methods.

2.3 | Incorporating latest evidence for progression within the risk factor module

Equations from UKPDS68 were previously used to describe the progression over time of three risk factors (HbA1c, SBP and total cholesterol:HDL cholesterol ratio) in patients with T2D, based on data from UKPDS participants in the study's 10-year interventional phase. More recently, updated trajectory equations for a wider set of risk factors were published in the UKPDS90 study,[22] based on the extended 20-year follow up. The Cardiff T2D model was updated to incorporate novel trajectory equations for HbA1c, SBP, LDL-cholesterol, HDL-cholesterol, body mass index (BMI), heart rate, white blood cell count and haemoglobin. These equations may be chosen by the user as an alternative to UKPDS68-derived equations to predict natural risk factor progression over time. Treatment effects on these trajectories were captured via first-year parameter change, followed by an effect waning pattern back to natural progression. Treatment effects on eGFR and urine albumin–creatinine ratio (uACR) are applied annually as linear decline and increase patterns as long as the patient remains on-treatment, and impacts how patients develop CKD. As patients progress through the model, declining eGFR and increasing uACR are mapped to CKD stages, which incur annual, stage-specific costs and disutilities.

2.4 | Case study—The impact of holistic management on key events and outcomes

To illustrate the impact of the updates described above, a conventional glucose-centric modelling approach was compared against a holistic treatment approach, with the model using DECLARE-derived risk equations to best capture treatment effects on cardio-kidney outcomes. In the base case, patients were treated via the conventional glucose-centric approach consisting of metformin (MET) at first line, dipeptidyl petidase-4 inhibitors (DPP4i) addition at second line and neutral protamine Hagedorn (NPH) insulin addition at third line, that is, the GCA, with the CCA 'switched off'. Patients treated holistically were subject to the same GCA in combination with CM-driven CMD addition as patients became eligible (the CCA 'switched on'), aligned either to ADA-EASD guidelines[5] (base case) or to NICE NG28[4] (scenario, broader SGLT2i use with limited GLP-1 RA use).

The model was initiated with patient profiles reflective of newly diagnosed patients with T2D in the UK (Table S2).[4]

Treatment effects considered include HbA1c change, weight change and rates of hypoglycaemia; values for treatment effects (Table S3) were sourced from network meta-analyses for all therapy options.[28–34] Cardioprotective effects of SGLT2i were captured using DECLARE risk equations. For GLP-1 RA, CV-protective effects in the DECLARE equations were adjusted to reflect reduced risk of hospitalization for heart failure (HHF) and myocardial infarction (MI) in patients treated with SGLT2i versus GLP-1 RA (odds ratio [OR] HHF 0.74 [0.65–0.85]; OR MI 0.95 [0.84–1.08]).[28] Kidney-protective effects were captured by modifying a patient's eGFR decline, with an annual change of −0.66 mL/min/1.73 m^2 associated with SGLT2i therapy,[26] and −1.05 mL/min/1.73 m^2 associated with GLP-1 RA therapy.[35]

Published costs associated with T2DM complications, CKD stages and therapy costs were adjusted to 2022 prices (Table S4).

Using the model in a probabilistic sensitivity analysis mode, health economic projections were assessed over a lifetime horizon for patients drawn probabilistically from a cohort of 1000, with 1000 bootstrap iterations. Lifetime costs, quality adjusted life years (QALYs), life years (LYs), event rates and time-to-escalation were recorded. Costs and health benefits were applied from the perspective of the UK healthcare payer and discounted at 3.5% annually.

3 | RESULTS

Results are presented in Table 1 for the base case (alignment to ADA-EASD guidelines) and scenario analysis (alignment to NG28). The patient population had a mean QRISK3 score of 15.9% at baseline.[24]

In the base case, dynamic introduction of CMDs over time by the updated model in response to eligibility criteria resulted in an additional 1.03 QALYs at an additional cost of £3685 per-patient (an additional £3.7 M in costs per 1000 patients). Total clinical lifetime events decreased from 2186 to 2006 per 1000 patients between glucose-centric and holistic approaches. QALY gains derived from reduced CM (~32% reduction in HHF and 94% reduction of end-stage kidney disease [ESKD]) and an improved BMI profile. Total per-patient lifetime costs were £48 098 for the holistic approach compared with £44 413 predicted by the conventional approach. Per-patient treatment costs increased by £16 006; retained kidney function resulted in a cost-offset of £11 213, with avoided HHF resulting in a cost-offset of £526.

The model predicted most patients would receive a CMD within 1.3 years of diagnosis, predominantly (84.3%) due to CV risk status (Figure 4A,B), with patients equally likely to receive an SGLT2i or GLP-1 RA (Table S1). After 4.0 years, nearly all patients receive at least one CMD: 52.9% SGLT2i, 46.9% GLP-1 RA, the difference being driven by preference for SGLT2i for patients with CKD. After 6.7 years, 95.3% of patients were predicted to receive both SGLT2i and GLP-1 RAs (Figure 4C,D). The use of CMDs delayed time until first and second glucose-control escalations by 3.1 and 3.4 years, respectively (7.2 vs. 4.1 years [first escalation], and 9.91 vs. 6.5 years [second escalation]).

When the model is aligned to NG28 guidelines, holistic management was associated with an additional 0.80 QALYs, and a reduction in total costs of £3254 per-patient (Table 1). In this scenario, total per-patient lifetime costs were £41 159 for the holistic approach compared to £44 413 predicted by the conventional approach. Per-patient treatment costs increased by £8953 but was offset by £11 238, principally driven by avoided costs attributable to CKD progression (£6797) and ESKD (£4441). Patients eligible for a first CMD all received SGLT2i therapy. By year 2, 91.8% of patients had escalated to SGLT2i therapy due mainly to high CV risk (84.3%) (Figure S2, Table 1). In line with NG28, GLP-1 RA was exclusively triggered by BMI exceeding 35 kg/m^2; accordingly, only 29.3% of the modelled cohort receive GLP-1 RAs on average at 4.2 years post-initiation. The use of CMDs delayed time until first and second glucose-control escalations by 1.4 and 1.6 years, respectively (Table 1). Per 1000 patients, the holistic approach directed by NICE predicted cost savings of £3.3 M that were missed by the conventional management approach and decreased the total clinical lifetime events from 2186 to 2017 per 1000 patients.

4 | DISCUSSION

The updated, multifactorial, holistic approach to treatment selection/escalation predicted significantly different outcomes when compared with the conventional glucose-centric approach. The holistic approach is more able to capture the nuances of contemporary clinical practice, whereas the glucose-centric approach is unable to look beyond HbA1c or recognize that clinicians would likely escalate therapy within a few years of diagnosis due to CV risk or incident comorbidities. Predictions from the case study suggested that elevated CV risk represents the predominant reason for the initial introduction of a CMD and occurs prior to therapy intensification triggered by elevated HbA1c (Figure 4, Table 1). There was greater heterogeneity in the reasons for the additional of a second CMD. The early introduction of a CMD delayed the need for first and second glucose intensification by 1.4–3.1 years (Table 1), and was associated with improvements in kidney outcomes (slowed CKD progression, prevented ESKD), reduced HHF burden and additional QALY gains; cost offsets related to the reduced CM burden partially (ADA/EASD guideline approach) or fully (NG28 approach) compensated for the additional treatment costs incurred. Although the most common reason to receive a CMD was CV-related, the major economic return was mediated through improved kidney clinical outcomes, speaking of the complex interrelationships within CKM syndrome. BMI also plays an important role within the model. Lower BMI is associated with lower QRISK, a longer time spent in non-obesity states, avoided clinical events and costs, and a utility benefit. When BMI-related utility cost/benefits are omitted, QALYs gained in a model focused on glucose-centric management are overestimated and the value of holistic management is underestimated.

Our scenario analysis investigated the impact of UK guidelines where GLP-1 RA are less likely to be prescribed. Due to greater use of SGLT2i in this setting, the holistic approach was associated with lower therapy costs than in the base case; however, clinical outcomes were broadly comparable between the two guidelines. The ability to predict outcomes based on different guidelines and usage patterns is likely to be of interest to stakeholders.

Beyond the uncertainty with respect to generalizability to which all models are subject, our case study has several limitations. First, the GCA considers management of treatment naïve patients across three therapy lines, while it is likely more escalations are applied in clinical practice. However, as this is assumed in both conventional and holistic approaches, this is unlikely to have impacted on the overall outcomes. Particularly, we are aware that more patients treated with SGLT2i in the UK may receive GLP-1 RAs as a second CMD than would be expected from guidelines, introducing uncertainty as to the real-world validity of our modelling in this case; this is explored in a scenario analysis shown in Supplementary Scenario S1. Briefly, additional GLP-1 RA use increases total incremental costs (due to treatment costs) and QALYs (due to lower weight), with the latter being primarily

TABLE 1 Results of base case analysis (following American Diabetes Association [ADA]-European Association of the Study of Diabetes [EASD] guidelines) and scenario analysis (NG28) guidelines.

	Glycaemic-centric approach	Base case holistic approach (ADA-EASD)	Incremental difference	Scenario holistic approach (NG28)	Incremental difference
Clinical events predicted per 1000 patients					
Total clinical events	2186.3	2005.5	−180.8	2017.3	−169.0
Macrovascular					
Hospitalization for angina	28.3	27.4	−0.9	28.1	−0.2
Myocardial infarction	174.3	167.1	−7.2	168.0	−6.3
Hospitalization for heart failure	132.4	90.4	−42.0	92.0	−40.3
Stroke	242.3	234.3	−8.0	235.2	−7.5
PCI	108.1	109.9	1.9	110.6	2.5
CABG	82.3	81.5	−0.7	82.4	0.1
Noncoronary revascularization	74.8	78.3	3.5	79.0	4.2
Microvascular					
Blindness	80.5	74.1	−6.3	76.1	−4.3
ESKD	100.1	5.9	−94.2	5.7	−94.4
Amputation	120.4	121.7	1.3	123.1	2.7
Ulcer	50.8	43.3	−7.6	45.5	−5.3
Mortality					
CV related	277.3	258.9	−18.4	259.0	−18.3
Non-CV related	714.7	712.5	−2.2	712.5	−2.2
Per patient health economic outcomes					
Discounted cost (£ total)	£44 413	£48 098	£3685	£41 159	−£3254
Discounted cost (pharmacy)	£8036	£24 042	£16 006	£16 989	−£8953
Discounted QALYs	8.97	10.00	1.03	9.77	0.80
Discounted life years	14.42	14.39	−0.03	14.45	0.03
Therapy modifications over time					
First glucose intensification (average time added [year]/% population)	4.1/94.1%	7.2/86.1%	−3.1	5.5/90.7%	−1.4
Second glucose intensification (average time added [year]/% population)	6.5/88.5%	9.9/78.7%	−3.6	8.1/84.0%	−1.6
First CMD addition (average time added [year]/% population)					
SGLT2i due to high CV risk	0.0/0.0%	1.1/42.2%		1.1/84.3%	
SGLT2i due to ASCVD	0.0/0.0%	1.5/0.5%		1.5/1.0%	
SGLT2i due to HF	0.0/0.0%	1.2/0.3%		1.2/0.3%	
SGLT2i due to CKD	0.0/0.0%	4.0/8.0%		4.0/8.0%	
SGLT2i due to BMI	0.0/0.0%	1.2/1.8%		1.2/6.1%	
GLP-1 RA due to high CV risk	0.0/0.0%	1.1/42.1%		0.0/0.0%	
GLP-1 RA due to ASCVD	0.0/0.0%	1.5/0.5%		0.0/0.0%	
GLP-1 RA due to HF	0.0/0.0%	0.0/0.0%		0.0/0.0%	
GLP-1 RA due to CKD	0.0/0.0%	0.0/0.0%		0.0/0.0%	
GLP-1 RA due to BMI	0.0/0.0%	1.2/4.3%		0.0/0.0%	
Average time to addition / total %	0.0/0.0%	1.60/99.8%		1.80/99.8%	
Second CMD addition (average time added [year]/% population)					
SGLT2i due to HbA1c	0.0/0.0%	1.9/13.2%		0.0/0.0%	
SGLT2i due to high CV risk	0.0/0.0%	2.5/1.4%		0.0/0.0%	
SGLT2i due to ASCVD	0.0/0.0%	2.3/1.3%		0.0/0.0%	
SGLT2i due to HF	0.0/0.0%	2.1/0.3%		0.0/0.0%	

TABLE 1 (Continued)

	Glycaemic-centric approach	Base case holistic approach (ADA-EASD)	Incremental difference	Scenario holistic approach (NG28)	Incremental difference
SGLT2i due to CKD	0.0/0.0%	4.0/20.4%		0.0/0.0%	
SGLT2i due to BMI	0.0/0.0%	1.0/8.8%		0.0/0.0%	
GLP-1 RA due to HbA1c	0.0/0.0%	5.4/32.6%		0.0/0.0%	
GLP-1 RA due to high CV risk	0.0/0.0%	6.7/4.9%		0.0/0.0%	
GLP-1 RA due to ASCVD	0.0/0.0%	4.4/2.3%		0.0/0.0%	
GLP-1 RA due to HF	0.0/0.0%	0.0/0.0%		0.0/0.0%	
GLP-1 RA due to CKD	0.0/0.0%	0.0/0.0%		0.0/0.0%	
GLP-1 RA due to BMI	0.0/0.0%	1.2/10.0%		4.2/29.3%	
Average time to addition/total %	0.0/0.0%	3.20/95.3%		4.2/29.3%	

Abbreviations: ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CMD, cardiometabolic drugs; CV, cardiovascular; CABG, coronary artery bypass graft; EASD, European Association for the Study of Diabetes; ESKD, end-stage kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; PCI, percutaneous coronary intervention; QALY, quality-adjusted life years; SGLT2i, sodium-glucose co-linked transporter-2 inhibitor.

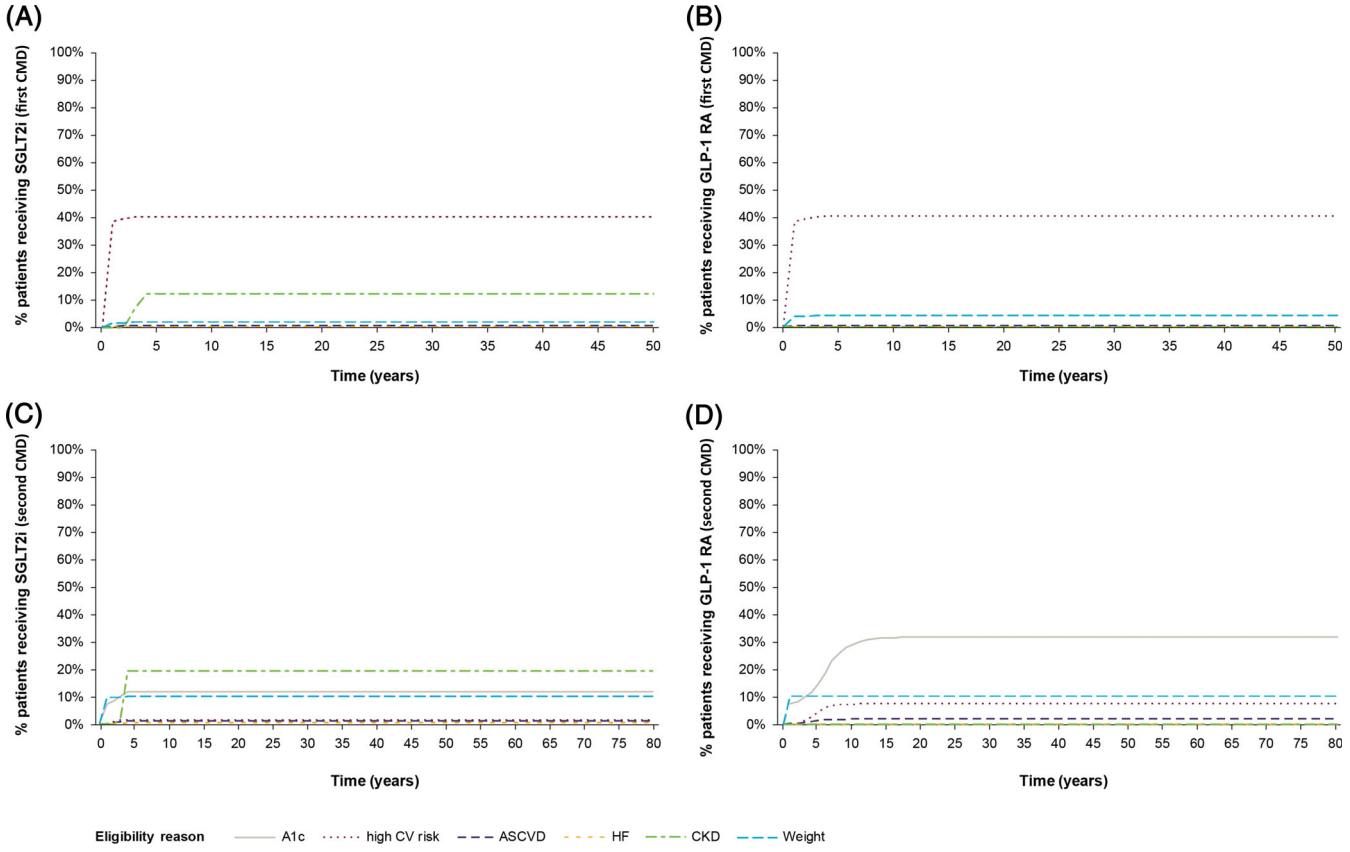

FIGURE 4 Timing and eligibility reasons for cardiometabolic drug (CMD) addition under holistic approach to management: (A) sodium glucose linked cotransporter-1 inhibitor (SGLT2i) use as first CMD; (B) glucagon-like peptide 1 receptor agonist (GLP-1 RA) use as first CMD; (C) SGLT2i use as second CMD; (D) GLP-1 RA use as second CMD (Base case, aligned to American Diabetes Association-European Association of the Study of Diabetes guidelines). ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure.

mediated through higher health utility associated with lower BMI. Second, we did not explore variation in physician preferences as a sensitivity analyses. Third, CV and kidney protective effects for SGLT2i were applied based on data from DECLARE-TIMI 58. While it is debatable if observations from DECLARE-TIMI 58 can be generalised to SGLT2i as a class, the DECLARE-TIMI 58 study included a comparatively lower risk population compared with other SGLT2i-based CVOT trials (CANVAS, EMPAREG)[36] which appears more

comparable to the population applied in this analysis. Due to a lack of patient level data from which to derive GLP-1 RA specific risk equations, additional CV-protective effects of GLP-1 RA (MI and stroke) were approximated via the application of an odds ratio to the DECLARE risk equations. The full benefit of weight loss may not be fully captured, given the limitations of the risk equations derived from an SGLT2i study, although this was mitigated by the application of risk adjustments. The benefits of BMI reduction are most prominent reflected in HF reduction across the analyses presented. In the DECLARE-TIMI 58 trial, the hazard for incident HHF increased progressively across the studied BMI range, and incident HHF was reduced more with dapagliflozin in patients with obesity than without obesity,[37] a trend reflected in the risk equations used in the present study. For drugs with greater BMI reductions, the DECLARE observed trends are extrapolated within the risk equations.

To remain relevant, T2D models need to incorporate additional complexity to reflect the current clinical evidence and therapeutic landscape for robust medical decision-making. We report key updates to the Cardiff T2D model designed to capture the nuances of current clinical diabetes management. By modernizing the underlying logic and incorporating therapy selection/escalation trigger points beyond the classical glucose-centric approach, the updated model enabled early introduction of a CMD in a manner reflective of contemporary clinical practice.

AUTHOR CONTRIBUTIONS

PM, VF, ME and JC conceptualised and designed the study. VF and GR were responsible for data collection and analysis. All authors contributed to interpretation of the results, preparation and review of the manuscript and approval of the final manuscript for publication.

ACKNOWLEDGEMENTS

The authors thank Andrew Gibson and Health Economics and Outcomes Research Ltd. for providing modelling, medical writing and editorial support, funded by AstraZeneca in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). The Cardiff T2D model is not open-access; however, all requests addressed to the corresponding author for access to the model within the context of novel, collaborative research will be considered.

FUNDING INFORMATION

This work was supported by AstraZeneca, who provided support for model development and medical writing for this study.

CONFLICT OF INTEREST STATEMENT

JC is an employee of AstraZeneca. PM, VF, GR and RJ are employees of Health Economics and Outcomes Research Ltd., who received fees from AstraZeneca in relation to this study. ME has received consulting fees or honoraria from AstraZeneca, Novo Nordisk, Napp, MSD, Sunovion and Novartis, and lecture/speaker bureau fees from AstraZeneca, Novo Nordisk, Napp, Mundipharma, Sunovion and Novartis. DCW has received consulting fees or honoraria from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Eledon, Galderma, GlaxoSmithKline, Janssen, Menarini, Merck, Pharmacosmos, ProKidney, Tricida and Vifor.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16141.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: McEwan P, Foos V, Roberts G, et al. Beyond glycated haemoglobin: Modelling contemporary management of type 2 diabetes with the updated Cardiff model. *Diabetes Obes Metab*. 2025;27(4):1752-1761. doi:10.1111/dom.16141