SGLT2i as fourth-line therapy and risk of mortality, end-stage renal diseases and cardiovascular diseases in patients with type 2 diabetes mellitus

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Abstract

Aim

Current guideline recommends insulin as fourth-line glucose-lowering medications. However, treatment effects of sodium glucose co-transporter-2 inhibitors (SGLT2i) on the risk of complications are uncertain. This study examines risks of all-cause mortality, cardiovascular diseases (CVD) **and** end-stage renal diseases (ESRD) in type 2 diabetes mellitus (T2DM) patients on triple oral glucose-lowering medications initiating SGLT2i, insulin or other oral medications.

Methods

A population-based retrospective cohort of patients with T2DM between 2006-2017 was extracted from Hong Kong Hospital Authority database. Patients who were initiated a fourth-line therapy with SGLT2i, insulin or other oral medications were included. Hazard ratios (HRs) for all-cause mortality, CVD **and** ESRD were assessed using Cox proportional hazard models.

Results

Over a median follow-up period of 18.5 months with 63,122 person-years, SGLT2i and insulin group had the lowest and highest incidence rate of all-cause mortality, CVD and ESRD (1.06, 0.65 and 0.61 vs 4.25, 5.58 and 4.39/100 person-years), respectively. Initiating SGLT2i as fourth-line medication had more benefits on CVD, in particular coronary heart disease and stroke. Insulin users had higher risks of CVD (HR=8.04, 95%CI=3.06-21.12) than SGLT2i users. SGLT2i was associated with **insignificant** reduction in ESRD (HR=4.62, 95%CI=0.73-

29.09) and all-cause mortality (HR=3.06, 95%CI=0.75-12.45)**, and HF (HR=2.99, 95%CI=0.37-24.42) among patients without established HF.**

Conclusion

Among T2DM patients initiating fourth-line therapy, SGLT2i users had significant benefits in lowering risk of CVD**, and potential benefits in lowering risks of ESRD and all-cause mortality**. SGLT2i was the preferred fourth-line glucose-lowering medication least likely to be associated with complication risks.

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Manuscript Text

Introduction

Sodium glucose co-transporter-2 inhibitor (SGLT2i) is a relatively new type of oral glucose-lowering drug class, and has been recommended by the American Diabetes Association as one of the options as second-line and third-line therapy for type 2 diabetes mellitus (T2DM) patients with or without established atherosclerotic cardiovascular diseases (CVD), and those patients with heart failure or chronic renal disease [1, 2]. For those without established CVD, SGLT2i is recommended if there is a compelling need in minimising hypoglycaemia and weight gain. SGLT2i works by inhibiting renal glucose reabsorption in the proximal tubule, thereby increasing urinary glucose excretion which lowers plasma glucose level and improves glycaemic control in patients with T2DM [3-5].

For those who have failed to achieve adequate glycaemic control after 3 months of triple therapy, a fourth-line glucose-lowering therapy is recommended to be added. Currently, the American Diabetes Association recommends incorporating insulin therapy as fourth-line medication [1]. Insulin is known as an effective, potent glucose-lowering drug with an overall established safety record despite of an associated risk of hypoglycaemia. Insulin is therefore considered as part of a combination therapy when hyperglycaemia is severe and poorly controlled with use of oral agents alone [6].

A number of large-scale randomised controlled trials [3, 4, 7] reported statistically significant reductions in CVD events in patients with T2DM with established CVD or at high risk treated

with SGLT2i, with evidence modestly stronger for Empagliflozin compared with Canagliflozin [1]. Latest studies has shown long-term use of SGLT2i is cardio-protective by reducing myocardial infarct size following ischaemia [8] and hospitalisation for heart failure (HF) [9, 10], thus supports its use in T2DM patients with high risk of, or established CVD. Large multinational observational studies also showed consistent evidence of risk reduction of death and heart failure with SGLT2i compared with other oral glucose-lowering drugs across baseline characteristics of patients [11-13]. Similarly, a systematic review showed robust benefits of risk reduction of hospitalisation for HF and progression of renal disease, thereby lowering risk of major adverse cardiovascular events in SGLT2i users with and without established CVD [14]. An up-to-date systematic review and meta-analysis [15] has also showed similar results. Patients on SGLT2i had a significantly lower all-cause mortality, cardiovascular mortality, HF and myocardial infarction events compared with control group [15]. The overall class effect of SGLT2i were studied in recent article, which suggested that SGLT2i as a class have a positive effect on reducing all-cause mortality, end-stage renal disease (ESRD) and less estimated glomerular filtration rate (eGFR) decline [16, 17]. In addition, renal-protective effects of SGLT2i were assessed in a systematic review and meta-analysis, which showed decreasing rate of eGFR decline, albuminuria progression, improved adverse renal endpoints and reduced all-cause mortality [18].

Given prominent cardio- and renal-protective benefits of using SGLT2i among T2DM patients [1, 19], it is postulated that SGLT2i may play a potential role as fourth-line therapy. With a lack of existing evidence to support this, it becomes vital to investigate associated all-cause mortality, CVD and ESRD risks after initiating SGLT2i or insulin as fourth-line therapy among T2DM

patients with and without established CVD. Alongside, heterogeneity of patients is likely to be present in previous analyses with pooling of patients on first-line, second-line or third-line glucose-lowering drugs**, rendering it necessary to consider patients initializing fourth-line therapy**. Issues with time-related and confounding biases have been dealt with less so in literature, while such methodological limitations could potentially hinder the evidence of investigation by over exaggerating the benefits observed within a glucose-lowering drug [20]. In this respect, a large-sample population-based analysis has been conducted to critically assess the effects of SGLT2i, insulin or other oral glucose-lowering drugs on risks of all-cause mortality, ESRD **and** CVD events. The effect of SGLT2i as fourth-line therapy on weight loss, renal and metabolic outcomes were also assessed.

Methods

Data source description

We assembled the population-based retrospective cohort from the Hong Kong Hospital Authority administrative database in the Hong Kong adult population with diabetes from January 1, 2006 to December 31, 2017. The Hospital Authority database has been extensively used for conducting high-quality large population-based studies [21, 22]. Documented DM diagnosis was defined as the International Classification of Primary Care, Version 2 (ICPC-2) codes T89/T90 or International Statistical Classification of Diseases and Related Health Problems, 9th Revision, Clinical Modification (ICD-9-CM) codes 250.x. The database contains comprehensive individual patient-level information on prescription and dispensing of glucose-lowering drug, serial

readings of anthropometric and laboratory variables, presence of comorbidities as classified based on ICD-9-CM or ICPC-2 diagnosis codes.

Identification of study population

We included patients with and without established CVD who were on triple oral glucose-lowering drugs in the study period, and subsequently initiated with either 1) SGLT2i or 2) insulin. A control group was formed if patients were dispensed oral glucose-lowering drugs other than SGLT2i and insulin as fourth-line drug therapy in order to reflect the effectiveness of SGLT2i and insulin. Patients who were under 18 years old, had type 1 diabetes or gestational diabetes, occurred ESRD events before initiation of fourth-line medication, and received **SGLT2i** and/or insulin before initiation of fourth-line medication were commenced, were excluded. Baseline date of eligible patients was defined as the date of initiating fourth-line medication. Patients were observed from baseline date until occurrence of study outcome, death from any cause, and censored at last healthcare service utilisation date, whichever came first. Analyses of CVD outcomes were based on patients without established CVD at baseline. Analyses of other outcomes were based on patients with and without established CVD at baseline.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Ethics

approval of this study was granted by Institutional Review Board of the University of Hong Kong /Hospital Authority Hong Kong West Cluster (Ref No. UW 16-1018). Since this is neither a clinical trial nor a prospective study, patients' informed consent was not required for this retrospective cohort analysis utilising the de-identified and anonymised data from the Hospital Authority.

Outcome measures

Primary study outcomes were all-cause mortality, composite CVD (coronary heart disease including acute myocardial infarction **and** other ischaemic heart disease, congestive heart failure, and stroke) **and** ESRD by treatment groups. Events of CVD were identified by diagnosis codes of ICD-9-CM and ICPC-2, whereas ESRD events were identified by above diagnosis codes and recorded eGFR<15ml/min/1.73m^2. All ICD-9-CM and ICPC-2 diagnosis codes for comorbidities and event outcomes are listed in Supplementary Table S1. Secondary outcomes were changes in body mass index (BMI), eGFR, and metabolic outcomes including glycated haemoglobin (HbA1c), blood pressure, and low-density lipoprotein cholesterol (LDL-C) from baseline to one-year measurement. eGFR was estimated by serum creatinine from blood test based on the Modification of Diet in Renal Disease Study formula adjusted for Chinese population.

Baseline covariates

Patient covariates included age, sex, clinical characteristics, and history of CVD and **severe hypoglycaemia** at baseline. Clinical characteristics included BMI, fasting glucose, HbA1c, systolic and diastolic blood pressure (SBP and DBP), lipid profiles (total cholesterol [TC] to

high-density lipoprotein cholesterol [HDL-C] ratio, LDL-C and triglyceride), eGFR, Charlson comorbidity index, duration of DM, duration of DM drug dispensed before initiating fourth-line medication (i.e. dispensing time between first glucose-lowering drug and first fourth-line drug), and ever use of anti-hypertensive drugs.

Statistical analysis

To address missing baseline data, multiple imputation by chained equations [23] was adopted. Missing baseline data was imputed five times [24] by random chained equation using other known baseline data [25]. Model parameters were estimated from multiple imputed data and then used to obtain multiple imputation linear predictions by applying Rubin's combination rules observation wise to the completed-data predictions [23].

To minimise the outcome bias due to discrepancy in baseline covariates, inverse probability of treatment weights (IPTW) using propensity-score was applied to balance covariates across three groups. Duration of patient on oral glucose-lowering drug was calculated to account for person-time exposed to monotherapy, dual and triple oral drug therapy in each group. IPTW using the propensity-scores was implemented using the Stata command marginal mean weighting through stratification [26]. The lowest and highest 1% (corresponding to 1st and 99th percentiles) propensity-score weights in each group were removed to trim extreme weights [27]. In the context of IPTW, multiple imputation followed by pooling treatment effects estimates across imputed datasets is the preferred approach [28]. After propensity-score weighting, the balance of

baseline covariates between groups was assessed using univariate linear, binary logistic or multinomial logistic regression, as appropriate.

Patients were grouped into three treatment groups, 1) SGLT2i, 2) insulin or 3) other oral glucose-lowering drugs. Baseline characteristics were presented by mean ± standard error (SE) for continuous variables, N (%) for categorical variables.

Incidence rates (IR) of each outcome event for each treatment group were estimated using the total number of patients with event occurrence during follow-up period divided by person-years at risk. Cox proportional hazards regression model was used to examine the association between the fourth-line medications and incidence of events. Hazard ratio (HR) and its 95% confidence interval (CI) were reported for each treatment group in the regression model. Cox test was used to compare the equality of survival curves between the groups. Proportional hazards assumptions were confirmed through Schoenfeld residuals test. Goodness-of-fit of Cox regression model were assessed using Akaike information criterion and Bayesian information criterion.

Secondary outcomes were compared at baseline and 12-month by paired t-test within the same group, and were compared within group at the same period by one-way analysis of variance test. **To perform the paired comparison, patients with no missing clinical characteristics at both baseline and 12-month follow-up are included.**

E-values were calculated as a sensitivity analysis to quantify the potential for unmeasured confounding bias on observed treatment-outcome association [29, 30]. Competing risk for mortality was accounted for the analysis of disease outcomes, by comparing the sub-hazard ratio (SHR) by competing risk regression and the HRs estimated from primary analysis. As sensitivity analyses, six scenarios were tested to check the robustness of the treatment effects: 1) selecting basal insulin users (neutral protamine Hagedorn insulin and long-acting insulin) only within the insulin group, 2) multiple imputation of missing baseline covariates with IPTW without propensity-score trimming, 3) multiple imputation of missing baseline covariates without IPTW, 4) complete-case with IPTW and propensity-score trimming, 5) complete-case with IPTW without trimming, and 6) complete-case analysis without IPTW.

All statistical analyses were performed using Stata version 13.0 (StataCorp LP, College Station, Texas). All significance tests were two-tailed and P values <.05 were taken to indicate statistical significance. Statistical analyses were conducted by two co-authors (CKHW and EHMT) and cross-checked for quality assurance.

Results

The selection process of the cohort group is outlined in Figure 1. In total, 8,984 eligible patients were included in current analysis. A majority of patients received insulin (75.6%) as their fourth-line glucose-lowering medication, followed by other oral drugs (17.5%) and SGLT2i (7.0%). Our cohort in SGLT2i group was distributed by three types of SGLT2i (Dapagliflozin: 57.3%; Empagliflozin: 41.8%; and Canagliflozin: 0.9%), while 46.5% and **45.1%** of our cohort in other

oral glucose-lowering medication group received thiazolidinedione and dipeptidyl peptidase-4 inhibitor, respectively.

Patient characteristics

Table 1 illustrates baseline characteristics of patients according to their treatment groups after weighting. All baseline covariates achieved a balance across the three treatment groups by univariate test. 51.7% of patients were male and mean age was 64.5 years (SE: 0.5). **The majority of patients received DPP4i as the third-line therapy (85.4%, 72.3% and 51.3% for patients received SGLT2i, insulin and others oral anti-diabetics drugs as fourth-line medications respectively). Less than half patients received alpha-glucosidase inhibitor (22.8%) and thiazolidinedione (23.2%) as third-line medications for patients initiated others oral anti-diabetics drugs as fourth-line medications.** The data completion rate of baseline covariates is shown in Supplementary Table S2. Details of baseline characteristics in each group before weighting are listed in Supplementary Table S3.

Incidence rates of primary outcomes

Supplementary Table S4 depicts the cumulative incidence and IR of CVD, ESRD and all-cause mortality across the follow-up period for patients treated with SGLT2i, insulin and other oral drugs as the fourth-line medication. Over a median follow-up period of 18.5 months, SGLT2i and insulin users had the lowest and highest IR for CVD (IR: 0.65 vs 5.58, per 100 person-years), ESRD (IR: 0.61 vs 4.39, per 100 person-years) and all-cause mortality (IR: 1.06 vs 4.25, per 100 person-years), respectively.

Table 2 presents the HRs from multivariable Cox proportional regressions adjusted by baseline covariates. The HRs of CVD (8.04, p<0.001; 3.39, p=0.02) including CHD (11.75, p<0.001; 4.82, p=0.02) of insulin and other drugs group were significantly greater than one, respectively, indicated that SGLT2i had significantly lower risks of composite CVD and CHD than insulin and other drug groups. **Notably, the HRs of HF (2.99, p=0.31; 0.97, p=0.98) of insulin and other drugs group were insignificantly different from 1.** Reduced risk of stroke (HR=7.21, p=0.002) was found in SGLT2i users when compared to insulin users. **Although the HRs of ESRD (4.62, p=0.10) and HRs of all-cause mortality (3.06, p=0.12) of insulin were not significantly greater than one, which may result from the small number of events in ESRD and mortality, a strong tendency for better results among SGLT2i users was demonstrated.**

Figure 2 depicts the Kaplan Meier survival curves for all-cause mortality, CVD **and** ESRD, events by treatment groups. Patients treated with SGLT2i were observed to have higher survival rates than insulin users. The distribution of survival curves between groups of all outcomes were significantly different.

Paired comparison of clinical outcome at baseline and 12-month follow-up

Figure 3 compares the paired clinical characteristics at baseline and 12-month follow up. Patients treated with insulin had a significant increase in BMI with paired difference of 0.13 kg/m^2 (p=0.03), while SGLT2i users had significant reduction in percentage of total weight loss (4.73%, p=0.02). The fasting glucose level, HbA1c level and TC/HDL ratio of patients receiving

all types of fourth-line medication was reduced, the greatest level of reduction was present in the SGLT2i group of a paired difference -2.04mmol/L ($p<0.001$), -1.19% ($p<0.001$) and -0.21 ($p<0.001$), respectively. SGLT2i group showed an insignificant increase in eGFR level (0.17mL/min/1.73m^2, $p=0.86$), but a significant drop was shown for insulin users (-3.16, $p<0.001$). Insulin significantly increased SBP (0.94mmHg, $p=0.04$), but decreased DBP (-0.76mmHg, $p=0.002$) and triglyceride (-0.09mmol/L, $p<0.001$). SGLT2i group showed effectiveness in lowering total weight loss, HbA1c, fasting glucose level, LDL-C and TC/HDL-C ratio, as well as an insignificant increase in eGFR level after 12-month initiation. Though effective in lowering the HbA1c, fasting glucose level and lipid profile, insulin showed a significant increase in BMI and deterioration in renal function by eGFR level. Supplementary Table S5 lists the results of the comparisons between baseline and 12-month follow-up.

Sensitivity analyses

The E-values of those significant **HRs (CVD, CHD and stroke)** were greater than all HR of the measured confounders, implying that it was unlikely that an unmeasured or unknown confounder would have greater effect on the outcomes than these known risk factors by having a HR exceeding those E-values (Supplementary Table S6). When all-cause mortality was considered as the competing event (Supplementary Table S7), the risk of CVD (SHR=6.30, $p<0.001$), CHD (SHR=8.99, $p<0.001$) **and** stroke (SHR=4.69, $p=0.01$) were also significantly higher in insulin users when compared to SGLT2i users. Similar results were observed when considering different scenarios (Supplementary Table S8), except for the limited samples for HF, stroke and ESRD in complete-case analysis.

Discussion

Mounting data from randomised controlled trial and post-hoc observational analysis supported the use of SGLT2i as second-line or third-line glucose-lowering medications for T2DM patients with and without established CVD [1, 2]. Despite a number of large-scale landmark randomised controlled trials of SGLT2i had been conducted [3, 4, 7, 17], there was a lack of empirical evidence based on direct head-to-head comparisons between SGLT2i and insulin, and across fourth-line options. When initiating a fourth-line agent to achieve glycaemic goals, basal insulin was a standard option for those patients without established CVD or chronic renal disease [1]. This population-based cohort study evaluated the clinical and healthcare services impact of adding SGLT2i as fourth-line medications among T2DM patients on triple oral therapy. The SGLT2i ranked the best in the incidence of all primary outcomes. The addition of SGLT2i as fourth-line medication was found to reduce risk of CVD in patients without established CVD. When compared to insulin as fourth-line medication, SGLT2i was found to have **significant** beneficial effects on composite CVD, coronary heart disease **and** stroke events**, and potential beneficial effects on ESRD and all-cause mortality** with a median follow-up of 10.5 months after initiation. **While no significant reduce of risk of HF was found, possibly due to insufficient samples, observed** cumulative incidence rate of heart failure among SGLT2i users complemented that reported in observational studies [9-13].

Analysis of secondary outcomes elucidated improvements in BMI, fasting glucose and glycaemic control one-year after the initiation of SGLT2i, and the amelioration of CVD outcome

over the study period. Our findings aligned with our postulations that using SGLT2i as fourth-line medication could play an increasing cardio-protective role for T2DM patients. Using SGLT2i as four-line medication had the potential of playing a renal-protective role for this patient population who had T2DM but not a history of ESRD. Renal function reflected by eGFR remained unchanged at 12-month after initiation of SGLT2i, whereas initiating insulin had significant reduction in eGFR. Collectively, SGLT2i demonstrated its superiority in primary and secondary outcomes as fourth-line medication when compared to insulin and other oral medications.

Current study had important translational implications for risk reduction in mortality, complications and hospital admissions through pharmacological approaches in T2DM patients. The use of SGLT2i could be extended to a broader population of T2DM patients with CVD or at high risk of developing CVD. Another implication was to reveal the importance of decision-making for considering not only insulin but also SGLT2i in the fourth-line treatment algorithm for T2DM patients on triple oral therapy with inadequate control. **Our** findings provided evidence in clinical effectiveness to support SGLT2i as preferred fourth-line option over other oral drugs.

Several limitations of this study should be recognised. Lifestyle risk factors and issues with drug adherence were not captured in the database and could not be assessed; hence, it was not possible to include these factors in the propensity-score weighting. However, the likelihood that unmeasured confounders could affect the treatment-outcome relationship seemed unlikely, as

indicated by E-values in sensitivity analysis. In addition, time-varying factors, such as changes in HbA1c, blood pressure and lipid profile, were not included in the propensity-score weighting and subsequent multivariable analyses. These could potentially exert an influence on the risks of all-cause mortality, CVD and ESRD events from developing, thereby reducing the validity of results. Moreover, specific individual factors such as patient preferences and cost considerations were not quantifiable in this study, thus only biomedical factors, such as age and comorbidities, could be taken into account. Our study results provided an important indication of the relative risks among fourth-line diabetes medications with respect to all-cause mortality and complication events. Nevertheless, since the overall duration of this study was relatively short, additional studies with longer follow-up duration are needed to develop a full picture of the associated risks of fourth-line medication for patients with T2DM. While the effects of anti-diabetic drugs on clinical parameters should be recognised in drug prescription, patient preferences and social factors should also be acknowledged in shared decision-making.

Conclusions

For T2DM patients on oral glucose-lowering triple therapy with inadequate control, the use of SGLT2i as fourth-line medication had more benefits on CVD events, in particular coronary heart disease and stroke, when compared to insulin and other oral glucose-lowering drugs**, and had potentially more benefits on ESRD and all-cause mortality when compared to insulin**. Initiation of SGLT2i was associated with better BMI, fasting glucose, HbA1c and renal functions after 12 months when compared to insulin. SGLT2i was the preferred fourth-line glucose-lowering medication, as it was least likely to be associated with complication risks amongst three options.

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Research data

Restrictions apply to the availability of data generated or analysed during this study because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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Figure legends

Figure 1. **Flowchart** of **inclusion of** type 2 diabetes mellitus patients on third-line oral therapy and received sodium glucose co-transporter-2 inhibitors (SGLT2i), insulin or other glucose-lowering medications as fourth-line medications

Figure 2. Kaplan Meier survival curves for all-cause mortality, cardiovascular diseases (CVD), **and** end-stage renal diseases (ESRD) for type 2 diabetes mellitus patients initiating sodium glucose co-transporter-2 inhibitors (SGLT2i), insulin or other oral glucose-lowering drugs as fourth-line medications

Figure 3. Paired comparison of clinical characteristics at baseline and 12-month follow-up for type 2 diabetes mellitus patients initiating sodium glucose co-transporter-2 inhibitors (SGLT2i), insulin or other oral glucose-lowering drugs as fourth-line medications

Figure 1. Flowchart of inclusion of type 2 diabetes mellitus patients on third-line oral therapy and received sodium glucose co-transporter-2 inhibitors (SGLT2i), insulin or other glucose-lowering medications as fourth-line medications

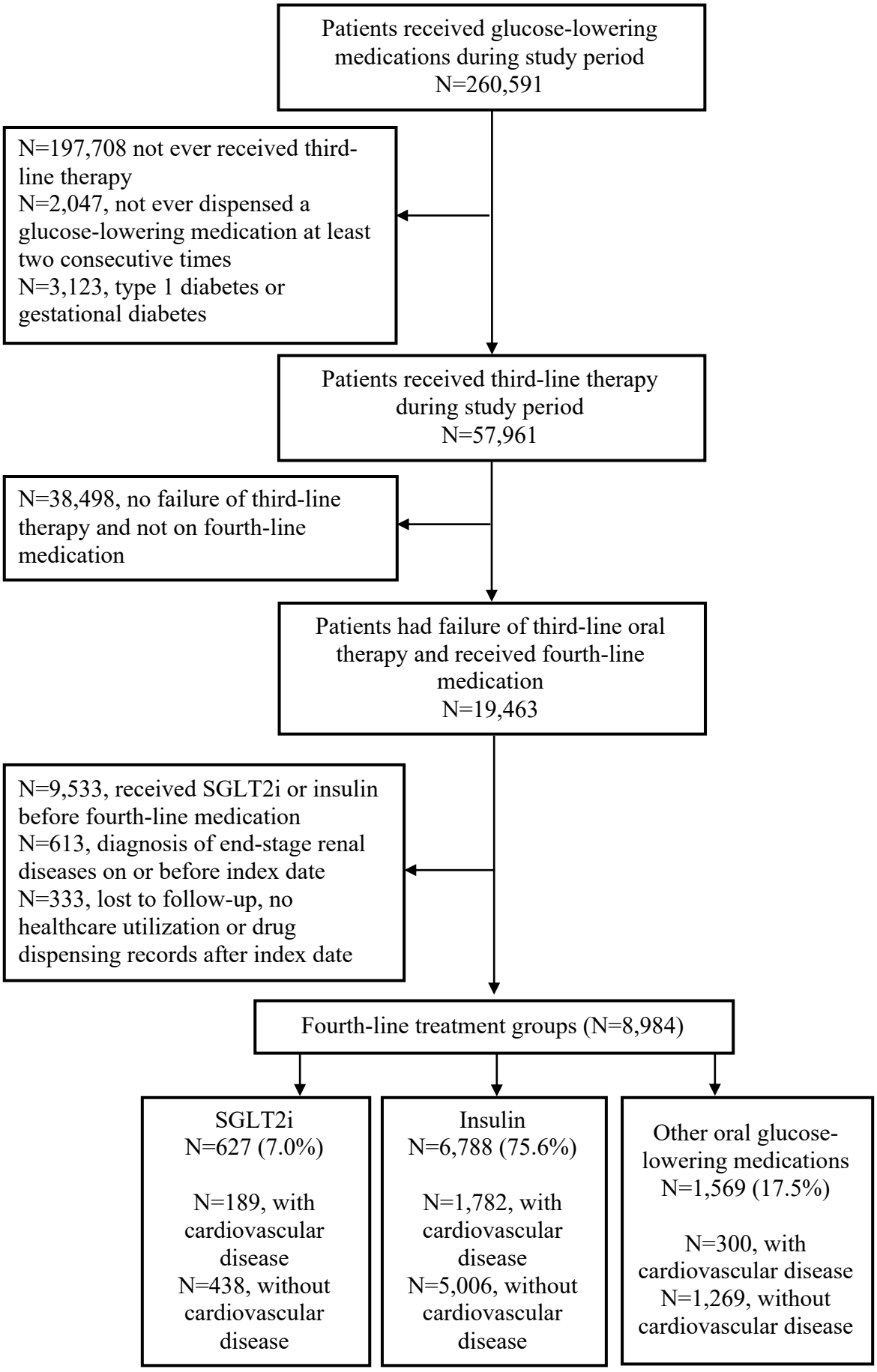


Figure 2. Kaplan Meier survival curves for all-cause mortality, cardiovascular diseases (CVD) and end-stage renal diseases (ESRD) for type 2 diabetes mellitus patients initiating sodium glucose co-transporter-2 inhibitors (SGLT2i), insulin or other oral glucose-lowering drugs as fourth-line medications

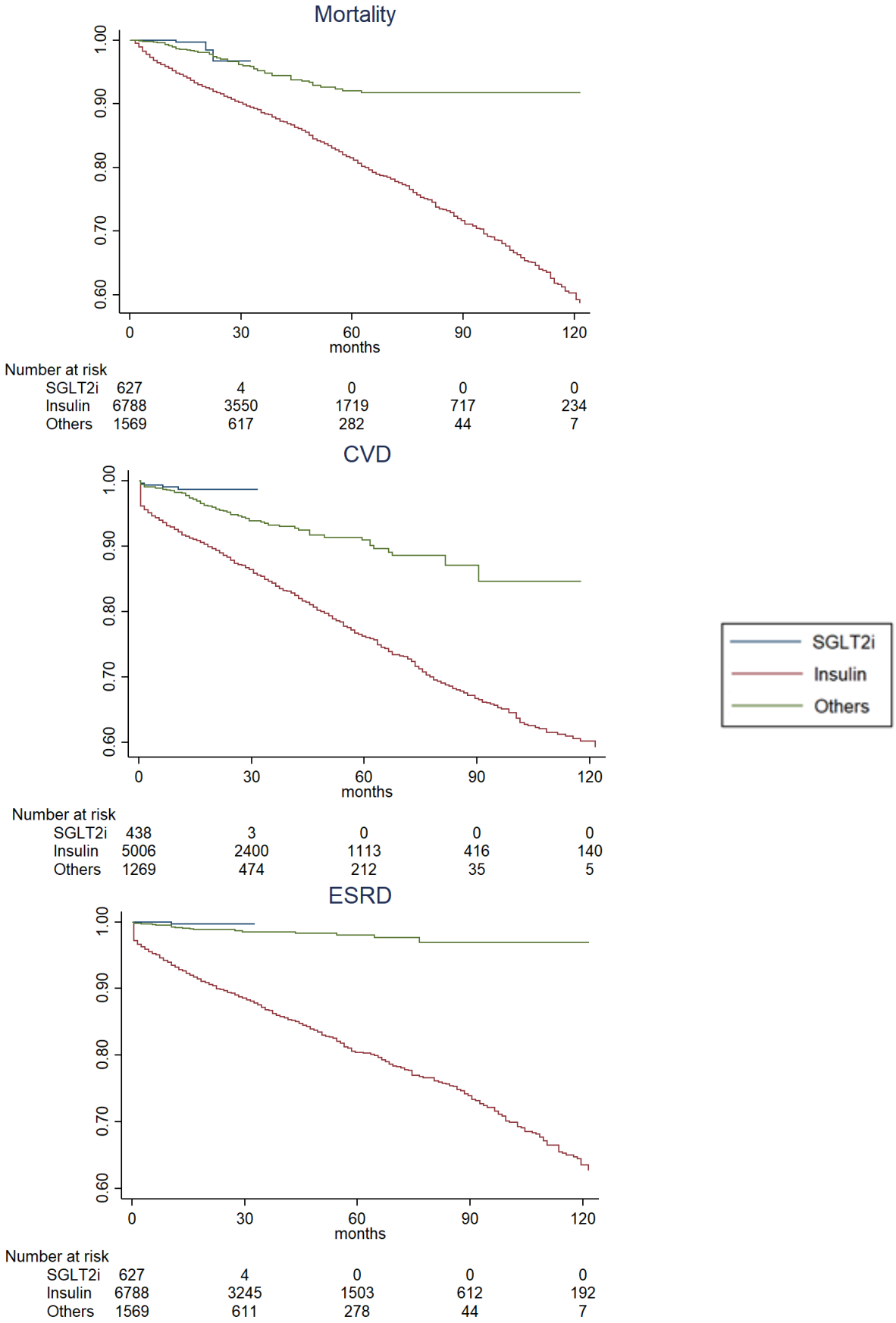
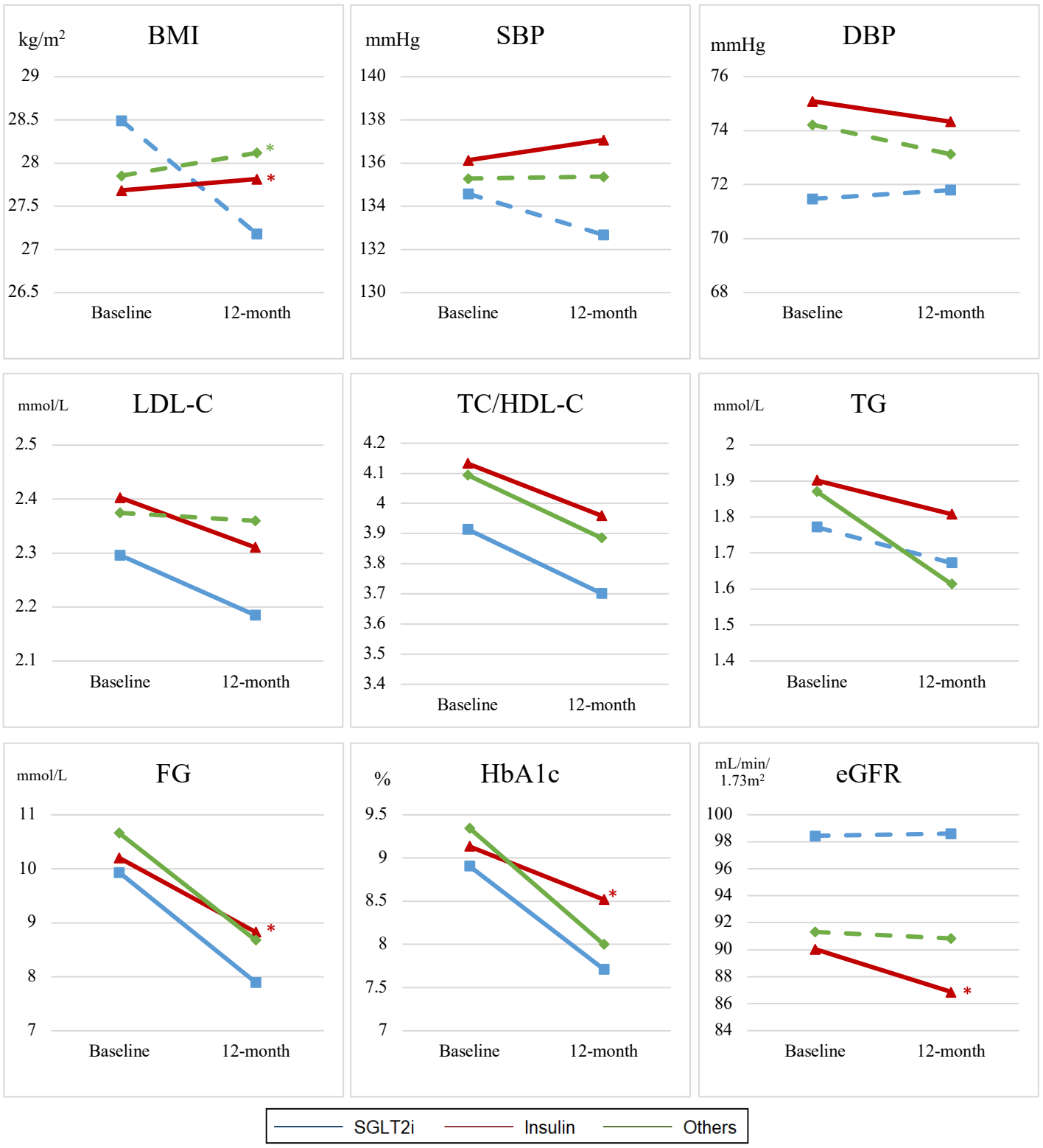


Figure 3. Paired comparison of clinical characteristics at baseline and 12-month follow-up for type 2 diabetes mellitus patients initiating sodium glucose co-transporter-2 inhibitors (SGLT2i), insulin or other oral glucose-lowering drugs as fourth-line medications



BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; LDL-C = Low-density Lipoprotein Cholestrol; TC = Total Cholestrol; HDL-C = High-density /lipoprotein Cholestrol; TG = Triglyceride; FG = Fasting Glucose; eGFR = estimated Glomerular Filtration Rate;

Solid line: Significant difference from baseline to 12-month within group.
Dash line: Not significant difference from baseline to 12-month within group.

* Significant difference in paired difference from baseline to 12-month data between SGLT2i and insulin/other groups.
Patients were included for both non-missing data at baseline and 12-month follow-up.

Supplementary Tables

Supplementary Table S1. Definition of the event outcome measures

Event	ICPC-2 codes	ICD-9-CM codes	Clinical parameters
DM	T89, T90	250	NA
CHD	K74-K76	410-414	NA
Heart Failure	K77	428	NA
Stroke	K89-K91	430-438	NA
ESRD	NA	585, 586	eGFR < 15ml/min/1.73m^2

ICPC-2 = the International Classification of Primary Care-2; ICD-9-CM = the International Classification of Diseases, Ninth Edition, Clinical Modification; DM = Diabetes Mellitus; CHD = Coronary Heart Disease; ESRD = end stage renal disease; eGFR = Estimated Glomerular Filtration Rate; NA = Not applicable

Supplementary Table S2. Data completion rate of baseline characteristics of patients initiating fourth-line glucose-lowering medications of SGLT2i, insulin, or other oral medications

Factor	Total (N = 8,984)	SGLT2i (N = 627)	Insulin (N = 6,788)	Others[b] (N = 1,569)
Socio-Demographics, n (%)				
Sex	8,984 (100%)	627 (100%)	6,788 (100%)	1,569 (100%)
Age	8,984 (100%)	627 (100%)	6,788 (100%)	1,569 (100%)
Clinical Characteristics, n (%)				
SBP	6,778 (75%)	426 (68%)	5,184 (76%)	1,168 (74%)
DBP	6,778 (75%)	426 (68%)	5,184 (76%)	1,168 (74%)
BMI	5,601 (62%)	345 (55%)	4,295 (63%)	961 (61%)
LDL-C	8,917 (99%)	627 (100%)	6,729 (99%)	1,561 (99%)
TC/HDL-C Ratio	8,930 (99%)	627 (100%)	6,741 (99%)	1,562 (100%)
Triglyceride	8,931 (99%)	627 (100%)	6,742 (99%)	1,562 (100%)
Fasting Glucose	8,896 (99%)	626 (100%)	6,710 (99%)	1,560 (99%)
Haemoglobin A1c	8,972 (100%)	627 (100%)	6,780 (100%)	1,565 (100%)
eGFR	8,973 (100%)	627 (100%)	6,780 (100%)	1,566 (100%)
Charlson's Index[a]	8,984 (100%)	627 (100%)	6,788 (100%)	1,569 (100%)
Duration of Diabetes	8,984 (100%)	627 (100%)	6,788 (100%)	1,569 (100%)
Duration of first anti-diabetic drugs to baseline	8,984 (100%)	627 (100%)	6,788 (100%)	1,569 (100%)
Use of anti-hypertensive drugs	8,984 (100%)	627 (100%)	6,788 (100%)	1,569 (100%)
Disease status, n (%)				
Established Cardiovascular Disease	8,984 (100%)	627 (100%)	6,788 (100%)	1,569 (100%)
Established Severe hypoglycaemia (1 year before baseline)	8,984 (100%)	627 (100%)	6,788 (100%)	1,569 (100%)

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; BMI = Body Mass Index; LDL-C = Low Density Lipoprotein - Cholesterol; TC = Total Cholesterol; HDL-C = High Density Lipoprotein - Cholesterol; eGFR = Estimated Glomerular Filtration Rate;

Notes:

[a] The calculation of Charlson Index does not include Acquired Immune Deficiency Syndrome (AIDS).

[b] "Others" includes metformin, sulfonylurea, alpha-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonists, thiazolidinedione and meglitinide.

Supplementary Table S3. Baseline characteristics of patients initiating fourth-line glucose-lowering medications of SGLT2i, insulin, or other oral medications without inverse probability of treatment weights

Factor	Total (N=8,984)	SGLT2i (N=627)	Insulin (N=6,788)	Others[b] (N=1,569)	P-value
Socio-Demographics					
Sex, %					<0.001*
Female	45.8%	38.0%	46.8%	44.6%	
Male	54.2%	62.0%	53.2%	55.4%	
Age, mean (SE), year	64.2 (0.1)	58.4 (0.5)	65.1 (0.1)	62.8 (0.3)	<0.001*
Clinical Characteristics, mean (SE)					
SBP, mmHg	137.2 (0.2)	135.9 (0.9)	137.8 (0.3)	135.0 (0.5)	<0.001*
DBP, mmHg	75.9 (0.1)	78.8 (0.5)	75.7 (0.2)	76.0 (0.3)	<0.001*
BMI, kg/m^2	27.7 (0.1)	29.0 (0.2)	27.5 (0.1)	28.1 (0.1)	<0.001*
LDL-C, mmol/L	2.4 (0.0)	2.2 (0.0)	2.4 (0.0)	2.3 (0.0)	<0.001*
TC/HDL-C Ratio	4.1 (0.0)	3.9 (0.0)	4.2 (0.0)	3.9 (0.0)	<0.001*
Triglyceride, mmol/L	1.9 (0.0)	1.9 (0.0)	1.9 (0.0)	1.7 (0.0)	<0.001*
Fasting Glucose, mmol/L	10.1 (0.0)	9.4 (0.1)	10.4 (0.0)	8.9 (0.1)	<0.001*
Haemoglobin A1c, %	9.1 (0.0)	8.6 (0.0)	9.3 (0.0)	8.2 (0.0)	<0.001*
eGFR, $mL/min/1.73m^2$	89.5 (0.4)	108.4 (1.2)	85.9 (0.5)	97.5 (0.8)	<0.001*
Charlson Comorbidity Index[a], %					<0.001*
1-2	9.4%	16.6%	8.6%	10.0%	
3	18.8%	24.4%	17.8%	21.0%	
4	23.3%	23.8%	22.4%	27.0%	
5	21.2%	18.0%	20.8%	24.2%	
6 or above	27.3%	17.2%	30.5%	17.8%	

Duration of Diabetes, %					<0.001*
<5 years	23.8%	16.3%	26.1%	16.4%	
5 - ≤10 years	52.5%	38.4%	53.0%	56.0%	
>10 years	23.7%	45.3%	20.8%	27.6%	
Duration of first anti-diabetic drugs to baseline, year	7.2 (0.0)	8.3 (0.1)	7.0 (0.0)	7.6 (0.1)	<0.001*
Use of anti-hypertensive drugs, %	92.0%	90.6%	92.5%	90.6%	0.02*
Disease status, %					
Established Cardiovascular Disease	25.3%	30.1%	26.3%	19.1%	<0.001*
Established Severe hypoglycaemia (1 year before baseline)	4.4%	2.1%	5.1%	2.2%	<0.001*
Third-line therapy received, %					
Metformin	0.8%	1.1%	0.8%	1.0%	NA
Sulfonylurea	0.7%	3.0%	0.3%	1.2%	NA
Alpha-glucosidase inhibitor	16.0%	1.1%	16.3%	20.7%	NA
Dipeptidyl peptidase-4 inhibitor	68.1%	85.5%	70.3%	51.4%	NA
Glucagon-like peptide-1 receptor agonists	0.2%	0.8%	0.1%	0.2%	NA
Meglitinide	0.02%	0.0%	0.03%	0.0%	NA
Thiazolidinedione	14.3%	8.5%	12.2%	25.6%	NA

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; BMI = Body Mass Index; LDL-C = Low Density Lipoprotein - Cholesterol; TC = Total Cholesterol; HDL-C = High Density Lipoprotein - Cholesterol; eGFR = Estimated Glomerular Filtration Rate; SE = Standard Error; NA = Not applicable

Notes:

* Significant difference ($p<0.05$) between groups by univariate linear regression or logistic regression, as appropriate

[a] The calculation of Charlson comorbidity Index does not include Acquired Immune Deficiency Syndrome (AIDS).

[b] "Others" includes metformin, sulfonylurea, alpha-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonists, thiazolidinedione and meglitinide.

Supplementary Table S4. The incidence of cardiovascular disease, end-stage renal disease and all-cause mortality of patients initiating fourth-line glucose-lowering medications of SGLT2i, insulin, or other oral medications

Event	Before weighting						After weighting			
	Cumulative Incidence		Incidence rate (case/100 person-years)		Person-Year	Median follow-up period (months)	Cumulative Incidence	Incidence rate (case/100 person-years)		Median follow-up period (months)
	Case with event	Rate	Estimate	95% CI[b]			Rate	Estimate	95% CI[b]	
SGLT2i										
CVD	5	1.1%	1.132	(0.471,2.719)	442	11.5	0.7%	0.654	(0.254,1.683)	10.5
CHD	3	0.6%	0.618	(0.199,1.915)	486	11.5	0.3%	0.274	(0.082,0.922)	10.5
Heart Failure	1	0.2%	0.164	(0.023,1.167)	609	11.5	0.7%	0.628	(0.089,4.415)	11.5
Stroke	3	0.5%	0.508	(0.164,1.574)	591	11.5	0.4%	0.368	(0.114,1.191)	10.5
ESRD	1	0.2%	0.158	(0.022,1.121)	633	11.5	0.6%	0.606	(0.086,4.288)	10.5
All-cause mortality	3	0.5%	0.473	(0.153,1.467)	634	11.5	1.1%	1.057	(0.265,4.221)	10.5
Insulin										
CVD	924	18.5%	5.904	(5.535,6.297)	15,651	28.5	16.8%	5.578	(5.212,5.970)	26.5
CHD	613	10.7%	3.311	(3.059,3.584)	18,513	29.5	9.7%	3.134	(2.888,3.402)	27.5
Heart Failure	512	8.0%	2.425	(2.224,2.645)	21,111	30.5	7.2%	2.264	(2.071,2.475)	28.5
Stroke	473	7.8%	2.344	(2.142,2.565)	20,176	30.5	7.1%	2.225	(2.027,2.444)	29.5
ESRD	1018	15.0%	4.766	(4.482,5.068)	21,359	28.5	13.3%	4.392	(4.118,4.683)	26.5
All-cause mortality	1055	15.5%	4.521	(4.256,4.802)	23,335	31.5	14.0%	4.249	(3.995,4.519)	29.5

Others[a]										
CVD	70	5.5%	2.183	(1.727,2.759)	3,207	20.5	6.2%	2.413	(1.782,3.268)	21.5
CHD	39	2.8%	1.098	(0.802,1.502)	3,554	21.5	3.4%	1.277	(0.856,1.905)	21.5
Heart Failure	19	1.2%	0.470	(0.300,0.737)	4,043	21.5	1.9%	0.717	(0.304,1.688)	21.5
Stroke	33	2.3%	0.880	(0.625,1.237)	3,751	21.5	2.5%	0.968	(0.634,1.479)	21.5
ESRD	21	1.3%	0.514	(0.335,0.788)	4,089	21.5	1.6%	0.625	(0.364,1.075)	21.5
All-cause mortality	59	3.8%	1.431	(1.109,1.847)	4,124	21.5	6.9%	2.603	(1.813,3.738)	22.5

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; CVD = Cardiovascular Disease; CHD = Coronary Heart Disease; ESRD = End-stage Renal disease; CI = Confidence Interval

Note:

[a] "Others" includes metformin, sulfonylurea, alpha-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonists, thiazolidinedione and meglitinide.

[b] The 95% CIs of incidence rate were constructed by Poisson distribution.

Supplementary Table S5. Paired comparisons of clinical outcome at baseline and 12-month follow-up

		Baseline	At 12-month	Paired difference
BMI, mean (SE), kg/m^2	SGLT2i	28.49 (0.95)	27.18 (0.93)	-1.31
	Insulin	27.68 (0.10)	27.82 (0.10)	0.13*
	Others[a]	27.86 (0.24)	28.12 (0.30)	0.26
	P-value	0.57	0.48	0.06
SBP, mean (SE), mmHg	SGLT2i	134.58 (3.77)	132.68 (5.26)	-1.90
	Insulin	136.13 (0.39)	137.07 (0.39)	0.94*
	Others[a]	135.28 (1.24)	135.38 (1.04)	0.10
	P-value	0.75	0.23	0.69
DBP, mean (SE), mmHg	SGLT2i	71.47 (1.70)	71.79 (2.64)	0.32
	Insulin	75.09 (0.22)	74.33 (0.23)	-0.76*
	Others[a]	74.22 (0.67)	73.13 (0.58)	-1.09
	P-value	0.05	0.10	0.82
LDL-C, mean (SE), mmol/L	SGLT2i	2.30 (0.06)	2.18 (0.05)	-0.11*
	Insulin	2.40 (0.01)	2.31 (0.01)	-0.09*
	Others[a]	2.37 (0.05)	2.36 (0.06)	-0.01
	P-value	0.21	0.04*	0.33
TC/HDL-C ratio, mean (SE)	SGLT2i	3.91 (0.10)	3.70 (0.09)	-0.21*
	Insulin	4.13 (0.02)	3.96 (0.02)	-0.17*
	Others[a]	4.09 (0.05)	3.89 (0.04)	-0.21*
	P-value	0.09	0.008*	0.60
Triglyceride, mean (SE), mmol/L	SGLT2i	1.77 (0.09)	1.67 (0.07)	-0.10
	Insulin	1.90 (0.02)	1.81 (0.02)	-0.09*
	Others[a]	1.87 (0.07)	1.61 (0.04)	-0.26*
	P-value	0.34	<0.001*	0.08

Fasting glucose, mean (SE), mmol/L	SGLT2i	9.93 (0.21)	7.89 (0.16)	-2.04*
	Insulin	10.20 (0.05)	8.83 (0.04)	-1.37*
	Others[a]	10.66 (0.34)	8.68 (0.29)	-1.98*
	P-value	0.17	<0.001*	0.002*
HbA1c, mean (SE), %	SGLT2i	8.91 (0.15)	7.71 (0.10)	-1.19*
	Insulin	9.13 (0.02)	8.52 (0.02)	-0.61*
	Others[a]	9.35 (0.18)	8.00 (0.13)	-1.34*
	P-value	0.16	<0.001*	<0.001*
eGFR, mean (SE), mL/min/1.73m^2	SGLT2i	98.44 (2.18)	98.60 (2.30)	0.17
	Insulin	90.04 (0.56)	86.88 (0.55)	-3.16*
	Others[a]	91.32 (1.87)	90.83 (1.93)	-0.48
	P-value	<0.001*	<0.001*	<0.001*

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; LDL-C = Low Density Lipoprotein - Cholesterol; TC = Total Cholesterol; HDL-C = High Density Lipoprotein - Cholesterol; HbA1c = Haemoglobin A1c; eGFR = Estimated Glomerular Filtration Rate; SE = Standard Error;

Notes:

* Significant difference at 0.05 level

[a] "Others" includes metformin, sulfonylurea, alpha-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonists, thiazolidinedione and meglitinide.

Patients were included for both non-missing data at baseline and 12-month follow-up.

Supplementary Table S6. E-value of hazard ratio of multivariable Cox proportional regressions of patients initiating fourth-line glucose-lowering medications of insulin or other oral medications compared to that of SGLT2i on the disease outcomes adjusted for baseline characteristics

	CVD			CHD			Stroke		
	HR	E-value	E-value CI	HR	E-value	E-value CI	HR	E-value	E-value CI
Fourth-line medication (vs SGLT2i)									
Insulin	8.044	15.572	5.578	11.745	22.980	6.318	7.214	13.909	3.605
Others[a]	3.390	6.237	1.794	4.820	9.112	2.035	3.063	5.577	1.000
Male (vs. Female)	1.407			1.490			1.184		
Age	0.999			0.993			1.020		
SBP	1.012			1.005			1.004		
DBP	0.991			0.990			1.015		
BMI	1.031			1.003			1.008		
LDL-C	1.013			0.988			1.087		
TC/HDL-C Ratio	1.046			1.043			1.048		
Triglyceride	0.972			1.014			1.012		
Fasting glucose	1.005			1.007			1.014		
Haemoglobin A1c	0.971			0.960			0.988		
eGFR	0.992			0.992			0.998		
Charlson Comorbidity Index[b]	1.468			1.345			1.377		
Duration of Diabetes	0.901			0.885			0.941		
Use of anti-hypertensive drugs	2.204			2.271			1.757		

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; CVD = Cardiovascular Disease; CHD = Coronary Heart Disease; ESRD = End-stage Renal disease; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; BMI = Body Mass Index; LDL-C = Low Density Lipoprotein - Cholesterol; TC = Total Cholesterol; HDL-C = High Density Lipoprotein - Cholesterol; HbA1c = Hemoglobin A1c; eGFR = Estimated Glomerular Filtration Rate; HR = Hazard Ratio; CI = Confidence Interval;

Notes:

* Significant at 0.05 level by multivariable Cox proportional hazard regression

[a] "Others" includes metformin, sulfonylurea, alpha-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonists, thiazolidinedione and meglitinide.

[b] The calculation of Charlson Index does not include Acquired Immune Deficiency Syndrome (AIDS).

Supplementary Table S7. Competing risk regressions of all-cause mortality of patients initiating fourth-line glucose-lowering medications of insulin or other oral medications compared to that of SGLT2i on the disease outcomes adjusted for baseline characteristics

	Insulin			Others[b]		
	SHR[a] (vs SGLT2i)	95% CI	P-value	SHR[a] (vs SGLT2i)	95% CI	P-value
CVD	6.303	(2.421,16.405)	<0.001*	3.073	(1.137,8.306)	0.03*
CHD	8.989	(2.664,30.336)	<0.001*	3.817	(1.069,13.626)	0.04*
Heart Failure	2.091	(0.233,18.735)	0.51	0.349	(0.040,3.084)	0.34
Stroke	4.689	(1.386,15.866)	0.01*	2.366	(0.653,8.564)	0.19
ESRD	2.815	(0.385,20.580)	0.31	0.477	(0.066,3.458)	0.46

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; CVD = Cardiovascular Disease; CHD = Coronary Heart Disease; ESRD = End-stage Renal disease; SHR = Subhazard Ratio; CI = Confidence Interval;

Notes:

* Significant at 0.05 level by competing risk regression.

[a] All subhazard ratios are adjusted by sex, age, SBP, DBP, BMI, LDL-C, TC/HDL-C ratio, triglyceride, fasting glucose, haemoglobin A1c, eGFR, Charlson comorbidity Index, duration of diabetes and the usages of insulin, oral anti-diabetic drugs and anti-hypertensive drugs at baseline.

[b] "Others" includes metformin, sulfonylurea, alpha-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonists, thiazolidinedione and meglitinide.

Supplementary Table S8. Scenarios sensitivity analyses of multivariable Cox proportional regressions of patients initiating fourth-line glucose-lowering medications of insulin or other oral medications compared to that of SGLT2i on the disease outcomes adjusted for baseline characteristics

	(1)						(2)					
	Insulin			Others[b]			Insulin			Others[b]		
	HR[a] (vs SGLT2i)	95% CI	P-value	HR[a] (vs SGLT2i)	95% CI	P-value	HR[a] (vs SGLT2i)	95% CI	P-value	HR[a] (vs SGLT2i)	95% CI	P-value
CVD	6.967	(2.715,17.877)	<0.001*	3.235	(1.206,8.681)	0.02*	8.099	(3.083,21.272)	<0.001*	3.402	(1.248,9.275)	0.02*
CHD	9.135	(2.831,29.473)	<0.001*	3.800	(1.117,12.922)	0.03*	11.778	(3.439,40.342)	<0.001*	4.825	(1.350,17.248)	0.02*
Heart Failure	2.426	(0.282,20.876)	0.42	0.851	(0.099,7.314)	0.88	2.989	(0.366,24.447)	0.31	0.968	(0.119,7.913)	0.98
Stroke	6.073	(1.829,20.166)	0.003*	3.187	(0.882,11.524)	0.08	7.253	(2.104,24.999)	0.002*	3.067	(0.837,11.229)	0.09
ESRD	4.072	(0.666,24.897)	0.13	0.769	(0.112,5.285)	0.79	4.624	(0.735,29.096)	0.10	0.803	(0.122,5.288)	0.82
All-Cause Mortality	2.198	(0.541,8.933)	0.27	1.455	(0.342,6.183)	0.61	3.094	(0.760,12.594)	0.12	1.745	(0.411,7.408)	0.45
	(3)						(4)					
	Insulin			Others[b]			Insulin			Others[b]		
	HR[a] (vs SGLT2i)	95% CI	P-value	HR[a] (vs SGLT2i)	95% CI	P-value	HR[a] (vs SGLT2i)	95% CI	P-value	HR[a] (vs SGLT2i)	95% CI	P-value
CVD	3.304	(1.362,8.015)	0.008*	1.529	(0.615,3.805)	0.36	9.258	(1.839,46.592)	0.007*	4.082	(0.770,21.635)	0.10
CHD	3.779	(1.206,11.843)	0.02*	1.621	(0.499,5.270)	0.42	6.379	(1.318,30.880)	0.02*	3.112	(0.588,16.482)	0.18
Heart Failure	7.699	(1.075,55.151)	0.04*	2.101	(0.280,15.761)	0.47	NA	NA	NA	NA	NA	NA
Stroke	3.884	(1.237,12.200)	0.02*	1.862	(0.568,6.102)	0.30	NA	NA	NA	NA	NA	NA
ESRD	10.794	(1.513,77.006)	0.02*	2.067	(0.278,15.402)	0.48	NA	NA	NA	NA	NA	NA
All-Cause Mortality	5.087	(1.629,15.886)	0.005*	2.213	(0.692,7.083)	0.18	2.392	(0.547,10.454)	0.25	1.286	(0.277,5.969)	0.75
	(5)						(6)					
	Insulin			Others[b]			Insulin			Others[b]		
	HR[a] (vs SGLT2i)	95% CI	P-value	HR[a] (vs SGLT2i)	95% CI	P-value	HR[a] (vs SGLT2i)	95% CI	P-value	HR[a] (vs SGLT2i)	95% CI	P-value

CVD	9.297	(1.846,46.810)	0.007*	4.080	(0.770,21.624)	0.10	4.054	(1.002,16.403)	0.05	1.944	(0.464,8.145)	0.36
CHD	6.404	(1.322,31.030)	0.02*	3.110	(0.587,16.474)	0.18	2.678	(0.658,10.887)	0.17	1.424	(0.332,6.107)	0.63
Heart Failure	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Stroke	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
ESRD	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
All-Cause Mortality	2.415	(0.552,10.560)	0.24	1.293	(0.279,5.999)	0.74	4.854	(1.204,19.570)	0.03*	1.984	(0.471,8.350)	0.35

(1) = Basal insulin with multiple imputation, inverse probability of treatment weighting and propensity score trimming; (2) Multiple imputation and inverse probability of treatment weighting; (3) = Multiple imputation; (4) = Complete-case with inverse probability of treatment weighting and propensity score trimming; (5) = Complete-case with inverse probability of treatment weighting; (6) = Complete-case

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; CVD = Cardiovascular Disease; CHD = Coronary Heart Disease; ESRD = End-stage Renal disease;
HR = Hazard Ratio; CI = Confidence Interval; NA = Not Applicable

Notes:

* Significant at 0.05 level by multivariable Cox proportional hazard regression

[a] All hazard ratios are adjusted by sex, age, SBP, DBP, BMI, LDL-C, TC/HDL-C ratio, triglyceride, fasting glucose, haemoglobin A1c, eGFR, Charlson comorbidity Index, duration of diabetes and the usages of insulin, oral anti-diabetic drugs and anti-hypertensive drugs
at baseline.

[b] "Others" includes metformin, sulfonylurea, alpha-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonists, thiazolidinedione and meglitinide.

Tables

Table 1. Baseline characteristics of patients initiating fourth-line glucose-lowering medications of SGLT2i, insulin, or other oral medications

Factor	Total (N=8,984)	SGLT2i (N=627)	Insulin (N=6,788)	Others[b] (N=1,569)	P-value
Socio-Demographics					
Sex, %					0.40
Female	48.3%	50.9%	46.1%	47.9%	
Male	51.7%	49.1%	53.9%	52.1%	
Age, mean (SE), year	64.5 (0.5)	64.6 (1.5)	64.3 (0.2)	64.6 (0.5)	0.75
Clinical Characteristics, mean (SE)					
SBP, mmHg	136.6 (0.6)	136.2 (1.3)	137.1 (0.3)	136.6 (0.9)	0.69
DBP, mmHg	75.1 (0.4)	74.5 (1.0)	75.9 (0.2)	74.9 (0.5)	0.08
BMI, kg/m^2	27.6 (0.1)	27.5 (0.3)	27.7 (0.1)	27.6 (0.2)	0.69
LDL-C, mmol/L	2.3 (0.0)	2.3 (0.1)	2.4 (0.0)	2.4 (0.1)	0.16
TC/HDL-C Ratio	4.0 (0.0)	3.9 (0.1)	4.1 (0.0)	4.1 (0.0)	0.08
Triglyceride, mmol/L	1.9 (0.0)	1.8 (0.1)	1.9 (0.0)	1.9 (0.1)	0.79
Fasting Glucose, mmol/L	10.2 (0.1)	9.9 (0.3)	10.1 (0.0)	10.6 (0.3)	0.17
Haemoglobin A1c, %	9.2 (0.1)	9.1 (0.2)	9.1 (0.0)	9.3 (0.2)	0.44
eGFR, $mL/min/1.73m^2$	92.0 (1.1)	95.6 (3.0)	89.7 (0.5)	90.7 (1.6)	0.13
Charlson Comorbidity Index[a], %					0.59
1-2	9.2%	9.3%	9.3%	9.0%	
3	17.9%	19.5%	18.6%	15.7%	
4	24.5%	24.3%	23.3%	25.9%	
5	18.5%	14.3%	21.2%	19.9%	
6 or above	29.9%	32.7%	27.6%	29.4%	

Duration of Diabetes, %					0.07
<5 years	20.7%	17.5%	23.6%	20.7%	
5 - ≤10 years	55.1%	57.6%	52.6%	55.1%	
>10 years	24.3%	24.8%	23.8%	24.2%	
Duration of first anti-diabetic drugs to baseline, year	7.4 (0.1)	7.5 (0.2)	7.2 (0.0)	7.4 (0.1)	0.16
Use of anti-hypertensive drugs, %	91.9%	91.6%	92.0%	92.0%	0.97
Disease status, %					
Established Cardiovascular Disease	27.0%	30.5%	25.2%	25.5%	0.52
Established Severe hypoglycaemia (1 year before baseline)	3.8%	2.3%	4.4%	4.6%	0.29
Third-line therapy received, %					
Metformin	1.1%	1.8%	0.7%	0.9%	NA
Sulfonylurea	1.4%	2.2%	0.3%	1.6%	NA
Alpha-glucosidase inhibitor	13.3%	1.9%	14.7%	22.8%	NA
Dipeptidyl peptidase-4 inhibitor	69.3%	85.4%	72.3%	51.3%	NA
Glucagon-like peptide-1 receptor agonists	0.2%	0.3%	0.1%	0.2%	NA
Meglitinide	0.01%	0.0%	0.03%	0.0%	NA
Thiazolidinedione	14.6%	8.4%	11.9%	23.2%	NA

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; BMI = Body Mass Index; LDL-C = Low Density Lipoprotein - Cholesterol; TC = Total Cholesterol; HDL-C = High Density Lipoprotein - Cholesterol; eGFR = Estimated Glomerular Filtration Rate; SE = Standard Error; NA = Not Applicable

Notes:

* Significant difference ($p<0.05$) between groups by univariate linear regression binary logistic or multinomial logistic regression, as appropriate.

[a] The calculation of Charlson comorbidity Index does not include Acquired Immune Deficiency Syndrome (AIDS).

[b] "Others" includes metformin, sulfonylurea, alpha-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonists, thiazolidinedione and meglitinide.

Table 2. Multivariable Cox proportional regressions of patients initiating fourth-line glucose-lowering medications of insulin or other oral medications compared to that of SGLT2i on the disease outcomes adjusted for baseline characteristics

	Insulin (vs SGLT2i)			Others[b] (vs SGLT2i)		
	HR[a]	95% CI	P-value	HR[a]	95% CI	P-value
CVD	8.044	(3.064,21.121)	<0.001*	3.390	(1.244,9.241)	0.02*
CHD	11.745	(3.431,40.211)	<0.001*	4.820	(1.349,17.226)	0.02*
Heart Failure	2.986	(0.365,24.422)	0.31	0.968	(0.119,7.912)	0.98
Stroke	7.214	(2.093,24.867)	0.002*	3.063	(0.836,11.223)	0.09
ESRD	4.622	(0.735,29.090)	0.10	0.803	(0.122,5.288)	0.82
All-cause mortality	3.059	(0.751,12.453)	0.12	1.732	(0.408,7.354)	0.46

SGLT2i = Sodium Glucose Co-transporter-2 Inhibitors; CVD = Cardiovascular Disease; CHD = Coronary Heart Disease; ESRD = End-stage Renal disease; HR = Hazard Ratio; CI = Confidence Interval;

Notes:

* Significant at 0.05 level by multivariable Cox proportional hazard regression

[a] All hazard ratios are adjusted by sex, age, SBP, DBP, BMI, LDL-C, TC/HDL-C ratio, triglyceride, fasting glucose, haemoglobin A1c, eGFR, Charlson comorbidity Index, duration of diabetes and the usages of insulin, oral anti-diabetic drugs and anti-hypertensive drugs at baseline.

[b] "Others" includes metformin, sulfonylurea, alpha-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonists, thiazolidinedione and meglitinide.