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Cardiovascular safety in type 2 diabetes with sulphonylureas as second-line drugs: a nation-wide population based comparative safety study

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Twitter Summary (254 Characters)

Scottish study of 31,640 people living with type 2 diabetes shows that sulphonylureas as second-line glucose lowering therapy are unlikely to increase cardiovascular risk or all-cause mortality though application of the instrumental variable approach as robust methodology for causal inference

ABSTRACT (250 Words)

Objective

To assess the real-world cardiovascular (CV) safety for SU, in comparison with dipeptidylpeptidase-4 inhibitors (DPP4i) and thiazolidinediones (TZD) through development of robust methodology for causal inference in a whole nation study.

Research Design and Methods

A cohort study was performed including people with type 2 diabetes diagnosed in Scotland before 31 December 2017, who failed to reach HbA1c 48 mmol/mol despite metformin monotherapy and initiated second-line pharmacotherapy (SU/DPP4i/TZD) on or after 1 January 2010.

The primary outcome was the composite major adverse cardiovascular events (MACE), including hospitalization for myocardial infarction (MI), ischemic stroke, heart failure, and CV death. Secondary outcomes were each individual endpoint and all-cause death. Multivariable Cox proportional hazards regression and an instrumental variable (IV) approach were used to control confounding in a similar way to the randomization process in a randomized control trial.

Results

Comparing SU to non-SU (DPP4i/TZD), the hazard ratio (HR) for MACE was 1.00 (95% CI: 0.91 - 1.09) from the multivariable Cox regression and 1.02 (0.91 - 1.13) and 1.03 (0.91 - 1.16) using two different IVs. For all-cause death, the HR from Cox regression and the two IV analyses was 1.03 (0.94 - 1.13), 1.04 (0.93 - 1.17), and 1.03 (0.90 - 1.17).

Conclusion

Our findings contribute to the understanding that second-line SU for glucose lowering are unlikely to increase CV risk or all-cause mortality. Given their potent efficacy, microvascular benefits, cost effectiveness and widespread use, this study supports that SU should remain a part of the global diabetes treatment portfolio.

Article Highlights (Word Count 100)

- This whole nation study assessed the real-world cardiovascular safety for sulphonylureas, in comparison with DPP4-inhibitors and thiazolidinediones through development of robust methodology for causal inference.
- Multivariable Cox proportional hazards regression and an instrumental variable (IV) approach were used to control confounding in a similar way to the randomization process in a randomized control trial
- This study demonstrates that sulphonylureas used as second-line glucose lowering therapy are unlikely to increase cardiovascular risk or all-cause mortality in an unselected population with or without high cardiovascular risk of pre-existing major cardiovascular events
- These robust observational data extend recent trial data addressing this question

Introduction

Type 2 diabetes is associated with increased risk of micro- and macrovascular disease, with the risk of cardiovascular (CV) mortality more than double in people with type 2 diabetes compared to those without (1). In the last decade, large dedicated CV outcome trials in people with type 2 diabetes and at high risk or with established CV disease have shown that dipeptidylpeptidase-4 inhibitors (DPP4i) do not increase CV risk (2), while sodium-glucose co-transporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor analogists (GLP-1RA) reduce CV risk (3-5). As a result, national and international guidelines have favored newer, more expensive glucose-lowering medicines over older, cheaper options such as sulphonylureas (SU) and thiazolidinediones (TZD).

There are huge regional disparities around the world in terms of cost and access to medications, as notably 80% of people living with diabetes reside in developing countries, yet these regions account for only 1% of the global diabetes expenditure (6). Therefore, generic medications remain relevant as part of the global diabetes treatment strategy to control cost and effective, accessible care.

SU are inexpensive, potent glucose lowering agents that have been widely used in the management of type 2 diabetes for over 60 years. There has been a long-standing controversy over the CV safety of SU, originating from the early clinical trials evaluating SU for diabetes management, which were either underpowered, or poorly designed to evaluate risks of CV outcomes or mortality (7, 8). Although these early trials were designed before current standards were in place, the controversy surrounding SU has been backed up by repeated observational studies which tend to report increased CV risk for SU versus comparators (often metformin) (9-11). Given

the putative CV risk and other side effects of SU such as hypoglycemia, body weight gain and limited durability (8, 12), there has been a debate whether SU should remain as routine second-line pharmacotherapy in type 2 diabetes (7, 13, 14). However, the compound annual growth rate of the global SU market continues to rise at a rate of 2.69%, with the fastest growth occurring in developing countries. The United States accounts for the 44% of the market share of SU, with patients receiving SU having significantly lower total healthcare costs than those receiving over diabetes medications (15), therefore market for cost-effective SU clearly remains strong worldwide .

Few randomized control trials (RCTs) have been conducted that make head-to-head comparisons between SU and other active comparators, in particular with SGLT2i or GLP1-RA. The TOSCA.IT study (16), a randomized multicenter trial, compared the long-term CV outcomes of pioglitazone, a TZD, versus SU (2% glibenclamide, 48% glimepiride, 50% gliclazide). The trial was stopped early based on a futility analysis but provided some evidence that SU (mostly glimepiride and gliclazide) and pioglitazone as add-on drugs to metformin were similar in terms of CV safety. More recently, the CAROLINA CV outcome trial (n = 6042) has demonstrated noninferiority of linagliptin, a DPP-4 inhibitor, versus glimepiride, a SU, in time to first occurrence of CV death, non-fatal myocardial infarction (MI) or non-fatal stroke (adjusted HR: 1.02; 95% CI: 0.88 to 1.19) (17).

Observational studies have attempted to investigate the CV safety of SU in a real-world setting, but many lacked robust designs or appropriate methodologies for data analysis and were therefore criticized for suffering major biases. A meta-analysis of 44 observational studies assessing the CV safety of SU reported several likely sources

of bias such as: using selected populations with CV complications, performing within-class comparisons, or utilizing a normal glucose tolerance cohort as comparator (10). In general, the biases in observational studies could be classified into one of the two main categories: selection bias and confounding bias. They are different in principle, but both induce incomparability of the exposure groups, which may subsequently lead to biased results for comparison. Therefore, considerable effort is required for the study design and the subsequent analysis to eliminate or at least minimize the potential biases.

In this study, we analyzed a large cohort derived from the entire Scottish population with type 2 diabetes to provide real-world evidence about the CV safety of SU, in comparison with other active comparators, namely DPP4i and TZD, each being used in combination with metformin for treatment intensification. A robust new-user design of second line therapies used for treatment intensification was adopted to minimize potential selection bias. Confounding control was achieved by: (i) multivariable analysis adjusted for an appropriate set of covariates/confounders; and (ii) applying an instrumental variable approach based upon prescribing preference to emulate the randomization process in RCTs and infer causal treatment effects. The instrumental variable approach was originally developed for analyses in economics, however it has been increasingly applied in medical research, as it explores how a variable influences treatment and has no confounding with the outcome, i.e. it accounts for natural randomization (18). Treatment effect is evaluated on the valid instrument (which determines the exposure) rather than the allocated treatment, akin to an intention-to-treat analysis, which is advantageous as it does not assume the absence of unmeasured confounders to the treatment-outcome relationship. This allows an unconfounded treatment effect to be estimated as in RCT. In this way we can provide

reliable results from analyzing large, routinely collected, real-world healthcare records, and provide guidance for comparative effectiveness and studying drug safety using observational data.

Methods

Data sources

We conducted a retrospective population-based cohort study using data from a 2018 extract of the Scottish Care Information (SCI) – Diabetes national register, a clinical database which contains data on all healthcare encounters in relation to diabetes. SCI-Diabetes was rolled out across Scotland from 2000 and captures key diabetes-related data items from all hospitals and around 1,100 general practices in Scotland. The data was also linked by the Information Services Division (ISD) of National Health Services (NHS) Scotland to national mortality, cancer registry, and hospital admission records.

Study cohort

People with an incident diagnosis of type 2 diabetes in Scotland were included in the study cohort if they: (i) were aged 18 years or over at diagnosis of T2DM ; and (ii) failed to reach target HbA1c level (48 mmol/mol) through first-line metformin monotherapy, and subsequently initiated second-line treatment on or after 1 January 2010 with one of the following classes of drugs: SU, DPP4i and TZD. Cohort entry (i.e., index date) was defined by the date of the first prescription of the above second-line drugs. To make sure these drugs were prescribed as add-ons to metformin, we required that either metformin was co-prescribed on the index date or at least one prescription for metformin was issued within 60 days after the index date and prior to adding other third-line drugs. This was to exclude people who switched from metformin to one of the study drugs (potentially due to intolerance or contra-indication) but

remained on monotherapy. The study cohort was then further restricted by excluding: (i) people aged under 40, or above 85 years of age at index date; and (ii) people prescribed more than one class of second-line drugs at index date.

Study outcomes

The primary outcome was the composite major adverse cardiovascular events (MACE), including hospitalization for MI, hospitalization for ischemic stroke, hospitalization for heart failure (HF), and CV death. Each individual component of the composite endpoint as well as all-cause death were analyzed as secondary outcomes. Hospital admission for MI (ICD-9 codes 410.x, ICD-10 codes I21.x), stroke (ICD-9 codes 433.x, 434.x, or 436.x; ICD-10 codes I63.x or I64.x), and HF (ICD-9 codes 428.x; ICD-10 codes I50.x, I11.0, I13.0, or I13.2) were identified using The General/Acute and Inpatient Day Case dataset (SMR01). Cardiovascular death (ICD-9 codes 390.x-398.x, 401.x-405.x, 410.x-417.x, 420.x-429.x [except 427.5], 430.x-438.x, or 440.x-447.x; ICD-10 codes I00.x-I77.x [except I46.9]) was identified from all causes recorded in the death certificates from the General Register Office (GRO), National Records of Scotland (NRS), and Scottish Cancer Registry (SMR06). All-cause death was identified from all three databases, with the date of death defined by the earliest recording of death in any datasets.

Exposures

For the primary analysis, we assembled DPP4i and TZD to be one 'non-SU' group and considered a binary exposure, i.e., SU versus non-SU. Further subgroup analyses included: (i) head-to-head comparisons including SU versus DPP4i and SU versus TZD; (ii) study cohort stratified respectively by prior history of MACE, age at index date (< or >= 70 years old), and body mass index (BMI) (< or >= 30 kg/m^2); and (iii) SU

exposure stratified by individual SU (gliclazide, glipizide, glimepiride). The treatment effects were evaluated in an intention-to-treat (ITT) framework (19), i.e., based on the initiation of second-line treatment irrespective of their discontinuation or subsequent switches to, or additions of, third-line drug classes. This was to (i) avoid the informative (i.e., non-random) censoring and the potential time-varying confounding due to the differences in drug response, and (ii) make the estimates of treatment effects consistent with analyzing RCT data. Participants included in the study cohort were followed until the occurrence of one of the study outcomes or were censored at the end of the study period, i.e., 31 December 2017 (Supplementary Figure 1).

Covariates

We adjusted our analyses for the following covariates, selected based on the 'disjunctive cause criterion' to achieve better confounding control (20).

1. Demographics: age at cohort entry, sex, ethnicity, quintiles of Scottish Index of Multiple Deprivation (SIMD), duration of diabetes, smoking status, year of cohort entry.
2. Most recent clinical measurements (on or prior to cohort entry): body mass index (BMI), estimated Glomerular Filtration Rate (eGFR) by the CKD-EPI Creatinine Equation, HbA1c, systolic blood pressure, and total cholesterol/high density lipoproteins (HDL) cholesterol ratio.
3. Existing (ICD-coded) comorbidities: atrial fibrillation of flutter, coronary artery disease, cancer, COPD, diabetic retinopathy, and history of MI, stroke, or HF.
4. Currently used drugs: angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), beta-blockers, calcium channel

blockers, diuretics, cardiac glycosides, nitrates, oral anticoagulants, antiplatelets, and lipid lowering drugs.

Statistical analyses

Descriptive statistics

Characteristics of the study participants were summarized using descriptive statistics. Incidence of the study outcomes were reported as number of events per 1000 person years. The temporal prescribing pattern of the three classes of drugs were described graphically. SGLT2i were also incorporated when deriving the annual prescribing proportions, as they started being prescribed in Scotland from 2013 and were officially recommended as one of the second-line options by The National Institute for Health and Care Excellence (NICE) in December 2015.

Cox proportional hazards regression

Cox proportional hazard regression models were used firstly to evaluate the associations between exposures and the study outcomes. Unadjusted and adjusted hazard ratios were reported. The 95% confidence intervals were established using robust standard errors to address the potential 'clustering effect' between practices. In the absence of unmeasured confounding, conventional multivariable analysis adjusting for a reasonable selection of covariates can provide unbiased estimates for treatment effects. Residual confounding, however, may still exist when there are key unmeasured confounding factor(s). Validity of the proportional hazard assumption was assessed by checking the Schoenfeld residuals.

Instrumental variable analyses

To account for potential residual confounding, we conducted instrumental variable (IV) analyses (21), with practice-level prescribing preference as an instrument to act as a

proxy for the exposure. The rationale for the IV analysis of observational data was attempting to re-establish the balance or exchangeability brought by the randomization process in a RCT. Prescribing preference cannot be directly measured therefore we used the prescriptions issued to previous patients in the practice as a proxy for the preference. Two different IVs were defined: (i) proportion of SU prescriptions among the ten most recent prescriptions; and (ii) proportion of SU prescriptions among all the prescriptions during the last 365 days. Both IVs were evaluated at each patient's index date to allow the practice-level preference to be time-varying. This was important because the utilization of the three classes of drugs varied substantially over the study period.

Instrumental variable estimates for the exposure effects were then derived using two techniques, namely, two-stage estimation and *G*-estimation, respectively. For the two-stage estimation, the exposure was regressed on the IV and year of cohort entry in the first stage model. In the second stage, a Cox model including the exposure, the adjusted covariates, and the 'control function' was used to estimate the exposure effect. For the *G*-estimation, a structural model was formed of one linear model for the IV, regressed on year of cohort entry, and one Cox model for the outcome, regressed on the IV, the exposure, and the adjusted covariates. As noted previously, the two-stage estimation for binary or time-to-event outcome is asymptotically biased,(22)

but the bias can sometimes be reduced by using the control function approach.(23, 24) *G*-estimation is an alternative approach in causal inference which can give an unbiased estimate. Here we used a special case of *G*-estimator and its analytic standard errors, which were recently proposed to allow the *G*-estimation technique to

be implemented in IV analysis.(22, 24) Assessment of essential IV conditions were described in Supplementary Method 3.

Sensitivity analyses

For sensitivity analyses, we added additional censoring criteria, i.e., adding or switching to another class of glucose lowering drug (different from metformin and the current second-line drug), to evaluate the treatment effects in an on-treatment framework. Again, the outcome event rates were compared between: (i) SU and non-SU agents (DPP4i or TZD); (ii) SU and DPP4i; and (iii) SU and TZD.

All analyses were conducted in R version 3.6 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 31,460 people in Scotland with type 2 diabetes met the study inclusion criteria, where 19,854 initiated second-line treatment by adding SU, 9,591 were prescribed DPP4i, and another 2,015 were prescribed TZD. Baseline characteristics are summarized in Table 1, a flowchart describing the study cohort is shown in Supplementary Figure 2. People who received SU prescriptions were slightly older, with higher baseline HbA1c but lower BMI, and had more comorbidities compared with those who received non-SU agents. The percentages of missing data were extremely low, therefore the individuals with incomplete information of baseline covariates were excluded from further analyses. This also guaranteed that our study outcomes would be analyzed on the same cohort of people. The final cohort for analysis included 29,518 people, where 18,531 were SU initiators (gliclazide [n = 16,152, 87.2%],

glimepiride [n = 1,540, 8.3%], glipizide [n = 818, 4.4%], and glibenclamide [n = 21, 0.1%]), and 10,987 were non-SU initiators (9,114 DPP4i and 1,873 TZD).

Incidence rate of outcomes

Supplementary Table 1 summarizes the number of outcome events, median follow-up time and the incidence rate, stratified by exposure groups. The median follow-up of the SU group was 3.9 years for composite MACE and was 4.1 years for all-cause death, respectively, longer than those of the non-SU group (3.0 years for MACE and 3.1 years for all-cause death). Higher incidence rates per 1000 person years were observed for all study outcomes in the SU versus the non-SU group (MACE: 23.4 vs 18.7; Hospitalization for MI: 7.1 vs 5.5; Hospitalization for stroke: 5.1 vs 4.8; Hospitalization for HF: 3.4 vs 2.1; cardiovascular death: 12.2 vs 9.2; and all-cause death: 21.2 vs 16.1).

Relative effect of SU vs non-SU agents

Figure 1 shows the results of the comparison between second-line SU and non-SU (DPP4i/TZD) agents. For MACE, the multivariable Cox regression and the IV analyses provided consistent estimates showing that prescribing SU as the second-line addition to metformin was not associated with increased overall CV risk. The estimated hazard ratio (HR) was 1.00 (95% CI: 0.91 to 1.09) from the multivariable Cox regression, was 1.02 (0.91 to 1.13) from the *G*-estimation using IV-10, was 1.03 (0.91 to 1.16) from the *G*-estimation using IV-365, was 0.95 (0.77 to 1.16) from the two-stage estimation using IV-10, and was 0.96 (0.77 to 1.20) from the two-stage estimation using IV-365, respectively. The upper limits of the 95% CIs were all below 1.3, the noninferiority upper limit suggested by the FDA for CV safety trials.

For all-cause death, the estimated HR was 1.03 (95% CI: 0.94 to 1.13) from the multivariable Cox regression, was 1.04 (0.93 to 1.17) from the *G*-estimation using IV-10, was 1.03 (0.90 to 1.17) from the *G*-estimation using IV-365, was 1.02 (0.83 to 1.25) from the two-stage estimation using IV-10, and was 1.01 (0.81 to 1.25) from the two-stage estimation using IV-365, respectively. All these indicated that prescribing SU for initiation of treatment intensification was unlikely to increase the risk of all-cause death.

Similar results were obtained for the individual MACE endpoints. For hospitalizations for MI, stroke and HF, the variation of the estimates from the IV analyses were slightly larger, which could be due to the small numbers of observed events, i.e., high censoring percentages. In general, the 95% CIs of the IV estimates were slightly wider comparing to those of the conventional multivariable Cox regression. This is a typical characteristic of the IV approach.(25)

Subgroup analyses

The results of the head-to-head comparison between second line SU and DPP4i are shown in Figure 2. In our analyses, the estimated HR for 4P-MACE was 0.98 (0.88 to 1.08) from the multivariable Cox regression, was 0.91 (0.72 to 1.17) and 0.97 (0.86 to 1.10) from the two-stage estimation and *G*-estimation using IV-10, and was 0.97 (0.75 to 1.27) and 1.00 (0.88 to 1.14) from the two-stage estimation and *G*-estimation using IV-365, respectively. For all-cause death, our estimate was 1.01 (0.92 to 1.12) from the multivariable Cox regression, was 1.02 (0.80 to 1.29) and 0.99 (0.87 to 1.13) from the estimations using IV-10, and was 1.03 (0.80 to 1.33) and 0.98 (0.85 to 1.12) from the estimations using IV-365, respectively.

Figure 3 shows the results of the comparison between SU and TZD. No significantly higher risks were observed in the SU group The TZD group was of a small size (n =

1,873) with fewer outcome events observed (Table 2). Therefore, relatively wider 95% CIs were obtained for the point estimates.

The results of other subgroup analyses were shown in Supplementary Tables 2 to 4. The CV safety of SU was consistently supported across all predefined subgroups. In the subgroup analysis of individual SU, hazard ratios for glibenclamide were not evaluated due to the small sample size (n = 21). However, this is reflective of the decline in prescribing of less tissue-specific SU within the Scottish population. Our results showed little difference in outcome rates among different types of SU.

Instrument variable assessment

The IV condition (i) was satisfied for the two proposed IVs, indicated by the large difference in the deviance (analogous to the *F* statistic) and the significance results from the likelihood ratio tests (Supplementary Table 6). The point-biserial correlation was 0.497 for IV-10 and 0.516 for IV-365, respectively. The crude and adjusted odds ratios shown in the Supplementary Table 7 were similarly large with and without year of cohort entry. All these assured strong association between the exposure and the proposed IVs. As shown in the Supplementary Table 8, most covariates were balanced across the binary exposure groups (SU vs non-SU), except for age (SDif = 0.105 > 0.1) and baseline HbA1c level (SDif = 0.220 > 0.1). For the two proposed IVs, all the covariates were well balanced across the quartiles, indicating that the IV condition (iii), i.e., exchangeability, was unlikely to be violated.

Sensitivity analyses

The design of sensitivity analyses was shown in Supplementary Figure 5. Censoring additionally at adding or switching to another class of glucose lowering drug reduced the follow-up time. For MACE, the median follow-up time in the SU group was reduced

from 3.9 years to 1.8 years, while in the non-SU group this was reduced from 3.0 years to 1.4 years (Supplementary Table 5). The outcome rates in the SU group were similar with those obtained in the primary analyses, while lower outcome rates were observed in people received non-SU agents. These were also reflected by slightly higher hazard ratios shown in Supplementary Figures 6, 7 and 8. However, none of the estimates indicated significantly higher CV risk of SU comparing to DPP4i or TZD.

Discussion

This study analyzed data for the entire Scottish T2DM population to systematically assess the CV safety of SU, in comparison to DPP4i and TZD, all being prescribed as second-line add-ons to the first-line metformin. Our findings demonstrate that prescribing of SU, compared to the other two non-SU agents, is not significantly associated with higher risks of MACE or all-cause death. Furthermore, the hazard ratios presented in Figures 2 and 3 show that our approach has produced nearly identical results when compared with those of major RCT involving second-line SU as comparator to DPP4 or TZD: CAROLINA (HR for 3P-MACE: 1.02 [0.88 to 1.19]; HR for all-cause death: 1.10 [0.94 to 1.28]) and TOSCA.IT (HR for 3P-MACE: 1.04 [0.79 to 1.35]; HR for all-cause death: 0.91 [0.62 to 1.33]). Given that DPP4i have been established to be neutral for MACE risk (2, 17, 26, 27) and pioglitazone has been found to have cardioprotective effects (28, 29), our findings provide real-world evidence to support the conclusion that SUs prescribed as second-line pharmacotherapy are unlikely to increase CV risk or all-cause death.

Substantial changes in the prescribing pattern were found from our drug utilization analysis (Supplementary Figure 3). SU used to be the most prescribed second-line add-on to metformin. DPP4i was approved in 2007 and was recommended as a

second-line option in May 2009 (NICE guideline CG87), together with SU and pioglitazone. Since then, prescribing of DPP4i has increased rapidly and in 2017 it had become the most prescribed second-line drug class in Scotland (38% DPP4i, 37% SU, 22% SGLT2i and 3% TZD). Rosiglitazone was indicated to increase risk of MI in a systematic review in 2009 and was subsequently suspended from use in the EU from 2010. Based on the facts described above, we therefore restricted our study cohort to include only eligible individuals on or after 2010 to improve the comparability between exposure groups and minimize potential selection bias.

Over the study period from 2010 to 2017, higher incidence rates of CV outcomes and all-cause death were observed in the SU cohort, comparing to those prescribed non-SU agents. The incidence rate ratio (IRR) was 1.25 for MACE and was 1.32 for all-cause death, consistent with the unadjusted hazard ratios reported in Figure 1 (1.25 (1.14 to 1.36) for MACE, and 1.30 (1.18 to 1.42) for all-cause death). Higher crude incidence rates would be expected from the systematic differences in baseline characteristics. As demonstrated in Table 1, the SU cohort was slightly older, has a higher proportion of current smokers, poorer glycemic control, and more existing comorbidities, in comparison to those prescribed DPP4i or TZD. To address these systematic baseline differences, multivariable Cox regression with adjustment and IV approach were applied in further analyses.

The primary analyses of this study addressed the CV outcomes of SU as second-line agents versus DPP4i/TZD, however, within-class differences in SU K_{ATP} channel tissue-specificities have suggested that second-generation SU are preferable to first-generation, particularly in terms of safety (30-32). Novel findings of a recent study also suggest SU with high-affinity binding with cardiac mitochondrial K_{ATP} channels are

associated with increased MACE risk compared to those with low affinity (33). Our subgroup analyses showed little difference between second-generation SU. The difference in CV outcome observed in this study compared to older observational studies could be explained by gliclazide being the SU of choice within Scotland (87.2% of second-line SU users), while other studies included high use of SU with high cardiac K_{ATP} and mitochondrial $_{KATP}$ affinity such as glibenclamide (34, 35). Furthermore, some existing observational studies reporting higher CV risk of SU included a high proportion of people who switch from metformin to SU; including SU users who switched from metformin but remained on first-line monotherapy may contaminate the treatment effect estimates. In our study we excluded patients who switched treatment, ensuring the second-line drug was used for treatment intensification as add-on to metformin.

Our analyses demonstrate that observational studies can generate reliable and robust evidence, consistent with RCT findings. When unmeasured confounding is not a major concern, conventional multivariable regression together with a careful study design can minimize or at least reduce the potential biases. If residual confounding is suspected, IV approaches provide a potential way to address this so that covariate balance can be achieved. In particular, preference-based IVs defined at the level of the geographic region, hospital or individual physician have been employed in comparative effectiveness and safety studies in the past two decades (36). However, IV estimates are usually characterized by larger variance (25, 37). As a result, null effect of an exposure is often concluded when the IV-exposure association is weak; however, this was not the case for our study where the IV was strong (see supplementary Tables 6 and 7 for the evaluation of IV strength). Therefore, for comparative effectiveness or drug safety studies aiming for causal treatment effect, we recommend performing both conventional multivariable regression and IV analysis.

To date, this is the first and the only large-scale population study applying IV approach with *G*-estimation in a survival context to estimate causal treatment effects. Unlike *G*-estimation, two-stage methods generally give a biased estimate when a Cox model is used at the second stage. Existing studies usually ignore this problem or circumvent it by considering the outcome as binary or even continuous and evaluate the causal treatment effect through structural mean models. In our analyses, the two-stage estimates were obtained by using the 'control function' approach, instead of substituting the exposure in the second-stage model by its predicted value from the first-stage model. This reduced the bias and provided the point estimates close to those obtained from the *G*-estimation (24). Aalen's additive hazard model is another option under the two-stage setting. However, it may be less attractive for clinical or epidemiological studies as the interpretation of results is not as intuitive as those from a Cox proportional hazard model. The performance of the two proposed IVs were similar, although the instrument defined using the prescriptions in the previous year (IV-365) is slightly stronger than the one defined by a fixed number of historical prescriptions (IV-10), often over a longer period than a year. We did not consider longer prescribing history as older prescriptions may be less relevant to the current prescribing preference, especially when the prescribing pattern varies significantly over time.

A limitation of this study is that the potential impact of competing risk was not considered for non-fatal study outcomes. However, the results obtained for these outcomes were in keeping with the findings for all-cause death, which may suggest a negligible impact of competing endpoints. The power of subgroup analyses by SU type was limited by sample size, which reflects the shift in prescribing preference towards more tissue selective SU which were associated with lower risk of all-cause CV-related

death in a large meta-analysis (30). In this study given the data governance for large anonymized electronic health record data, outcomes were not adjudicated, however this is a limitation of all observational studies. This work utilized ICD codes to establish MACE events which is widely accepted in epidemiological research. Finally, the focus of this work was to assess real-world cardiovascular safety of SU through development of robust methodology for casual inference, whilst it is acknowledged that these models do not address other clinical risk associated with SU such as durability and the risk and associated costs of severe hypoglycemia, this work does provide support that CV risk is not increased when considering SU against the other second-line agents studied.

Conclusions

In conclusion, our study has provided the most robust real-world evidence for the CV safety of SU, being prescribed as in addition to metformin, in an unselected population with T2DM and with or without high CV risk or established major CV events. Furthermore, we have developed robust methodology for estimating causal treatment effects. We acknowledge that newer non-insulin agents such as SGLT2i and GLP-1RA may carry long-term benefits from reducing risks of CV and renal events. In particular, SGLT2i were suggested to be cost-effective even at current price (38), and would be prescribed more in the foreseeable future. However, when these newer agents are not accessible or contra-indicated, the concern of CV safety should not be the barrier of prescribing SU. Although other clinical factors such as hypoglycemia risk and durability regarding SU need to be considered, our findings from this study support the most recent international guidelines (39, 40), which recommend SU as one of the second-line options after metformin if resources are limited. Therefore, SU should remain as part of the global diabetes treatment portfolio, given the strong efficacy in

glycemic control, established microvascular benefits, and the real-world evidence added to trial evidence for CV safety.

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Author Contributions

HW, RLMC, ERP, DM, YH and LD were involved in the design of the study. HW lead the statistical analysis. HW and RLMC wrote the first draft. All authors contributed to further drafts and approved the manuscript. ERP is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data Availability

This individual patient level real-world data is only available for analysis on a Trusted Research Environment and therefore cannot be made available.

Conflict of Interest

RLMC has received honoraria from Sanofi, JMcK has received speaker fees from NAPP pharmaceuticals and has been involved in cardiovascular outcome trials funded

by Novo Nordisk, Eli Lilly, Boehringer, GlaxoSmith Kline and Medimmune Ltd. HC has received grants or Institutional Fees from Eli Lilly and Company, AstraZeneca LP, Pfizer Inc and Novo Nordisk. NS has consulted for Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi; and received grant support paid to his University from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics outside the submitted work. RMcC has received royalties or licenses from Elsevier and honoraria from Sanofi Aventis and Novo Nordisk, and institutional fees from NHS Tayside and MRC. ERP has received honoraria from Sanofi and Lilly. There are no other relationships or activities that could appear to have influenced the submitted work.

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Table 1. Baseline characteristics of the study cohort (people with type 2 diabetes in Scotland treated with sulphonylureas (SU), DPP-4 inhibitors (DPP4i) or thiazolidinediones (TZD) as second-line treatment in addition to metformin between 2010 and 2017).

Characteristics	Main exposure groups		Exposure subgroups		Overall (N = 31,460)
	SU (N = 19,854)	Non-SU agents (DPP4i & TZD) (N = 11,606)	DPP4i (N = 9,591)	TZD (N = 2,015)	
Mean Age (SD)	61.7 (10.3)	60.6 (10.2)	60.8 (10.3)	59.9 (10.0)	61.3 (10.3)
Male Sex (%)	12081 (60.8%)	7170 (61.8%)	5857 (61.0%)	1313 (65.2%)	19251 (61.2%)
Ethnicity					
White	15489 (78.0%)	9314 (80.3%)	7678 (80.1%)	1636 (81.2%)	24803 (78.8%)
Other or missing	4365 (22.0%)	2292 (19.7%)	1913 (19.9%)	379 (18.8%)	6657 (21.2%)
Duration of diabetes (years)					
Median (IQR)	3.8 (1.8 to 6.6)	3.9 (2.0 to 6.5)	4.0 (2.0 to 6.6)	3.6 (1.8 to 6.0)	3.9 (1.9 to 6.6)
Duration of Metformin (years)					
Median (IQR)	2.2 (1.0 to 4.2)	2.4 (1.1 to 4.4)	2.5 (1.1 to 4.5)	2.1 (1.0 to 4.0)	2.3 (1.0 to 4.3)
HbA1c (mmol/mol)					
Median (IQR)	73 (64 to 87)	70 (64 to 81)	70 (64 to 81)	70 (63 to 82)	72 (64 to 85)
Total cholesterol/HDL ratio					
Median (IQR)	4.0 (3.2 to 4.9)	3.9 (3.2 to 4.8)	3.9 (3.2 to 4.8)	3.9 (3.2 to 4.8)	3.9 (3.2 to 4.9)
Unknown (%)	1010 (5.1%)	417 (3.6%)	311 (3.2%)	106 (5.3%)	1427 (4.5%)
Systolic blood pressure					
Mean (SD)	134 (15)	134 (15)	134 (15)	134 (15)	134 (15)
Unknown (%)	8 (< 0.1%)	9 (< 0.1%)	9 (< 0.1%)	0 (0%)	17 (< 0.1%)
Body mass index (kg/m^2)					
<25	1504 (7.6%)	496 (4.3%)	413 (4.3%)	83 (4.1%)	2000 (6.4%)
25-29	5742 (28.9%)	2717 (23.4%)	2197 (22.9%)	520 (25.8%)	8459 (26.9%)

30-34	6623 (33.4%)	3933 (33.9%)	3208 (33.4%)	725 (36.0%)	10556 (33.6%)
35-40	3569 (18.0%)	2454 (21.1%)	2058 (21.5%)	396 (19.7%)	6023 (19.1%)
>=40	2345 (11.8%)	1954 (16.8%)	1672 (17.4%)	282 (14.0%)	4299 (13.7%)
Unknown	71 (0.4%)	52 (0.4%)	43 (0.4%)	9 (0.4%)	123 (0.4%)
Baseline eGFR (CKD-EPI)					
≥90	8856 (44.6%)	5320 (45.8%)	4429 (46.2%)	891 (44.2%)	14176 (45.1%)
60-89	8875 (44.7%)	5114 (44.1%)	4203 (43.8%)	911 (45.2%)	13989 (44.5%)
45-59	1530 (7.7%)	839 (7.2%)	686 (7.2%)	153 (7.6%)	2369 (7.5%)
<45	525 (2.6%)	294 (2.5%)	244 (2.5%)	50 (2.5%)	819 (2.6%)
Unknown	68 (0.3%)	39 (0.3%)	29 (0.3%)	10 (0.5%)	107 (0.3%)
Smoking status					
Never	8563 (43.1%)	5293 (45.6%)	4357 (45.4%)	936 (46.5%)	13856 (44.0%)
Ever	7106 (35.8%)	4187 (36.1%)	3501 (36.5%)	686 (34.0%)	11293 (35.9%)
Current	4177 (21.0%)	2119 (18.3%)	1727 (18.0%)	392 (19.5%)	6296 (20.0%)
Unknown	8 (< 0.1%)	7 (0.1%)	6 (< 0.1%)	1 (< 0.1%)	15 (< 0.1%)
SIMD quintile					
1 (most deprived)	5217 (26.3%)	3195 (27.5%)	2702 (28.2%)	493 (24.5%)	8412 (26.7%)
2	4570 (23.0%)	2798 (24.1%)	2305 (24.0%)	493 (24.5%)	7368 (23.4%)
3	3982 (20.1%)	2248 (19.4%)	1835 (19.1%)	413 (20.5%)	6230 (19.8%)
4	3344 (16.8%)	1862 (16.0%)	1541 (16.1%)	321 (15.9%)	5206 (16.5%)
5 (least deprived)	2534 (12.8%)	1381 (11.9%)	1109 (11.6%)	272 (13.5%)	3915 (12.4%)
Unknown	207 (1.0%)	122 (1.1%)	99 (1.0%)	23 (1.1%)	329 (1.0%)
History of conditions:					
Atrial fibrillation	1083 (5.5%)	530 (4.6%)	463 (4.8%)	67 (3.3%)	1613 (5.1%)
Coronary artery disease	2800 (14.1%)	1349 (11.6%)	1182 (12.3%)	167 (8.3%)	4149 (13.2%)
Cancer	2394 (12.1%)	1190 (10.3%)	1015 (10.6%)	175 (8.7%)	3584 (11.4%)
COPD	1996 (10.1%)	1020 (8.8%)	887 (9.2%)	133 (6.6%)	3016 (9.6%)
Diabetic retinopathy	5816 (29.3%)	3280 (28.3%)	2719 (28.3%)	561 (27.8%)	9096 (28.9%)
Heart failure	848 (4.3%)	380 (3.3%)	344 (3.6%)	36 (1.8%)	1228 (3.9%)

Hypertension (ICD-coded)	4550 (22.9%)	2430 (20.9%)	2053 (21.4%)	377 (18.7%)	6980 (22.2%)
Myocardial infarction	1694 (8.5%)	842 (7.3%)	753 (7.9%)	89 (4.4%)	2536 (8.0%)
Stroke	557 (2.8%)	272 (2.3%)	233 (2.4%)	39 (1.9%)	829 (2.6%)
Currently used drugs:					
ACEis/ARBs	10667 (53.7%)	6509 (56.1%)	5423 (56.5%)	1086 (53.9%)	17176 (54.6%)
Beta blockers	5201 (26.2%)	2788 (24.0%)	2390 (24.9%)	398 (19.8%)	7989 (25.4%)
Calcium channel blockers	4943 (24.9%)	2944 (25.4%)	2468 (25.7%)	476 (23.6%)	7887 (25.1%)
Diuretics	5310 (26.7%)	2947 (25.4%)	2453 (25.6%)	494 (24.5%)	8257 (26.2%)
Cardiac glycosides	544 (2.7%)	239 (2.1%)	214 (2.2%)	25 (1.2%)	783 (2.5%)
Nitrates	1263 (6.4%)	620 (5.3%)	553 (5.8%)	67 (3.3%)	1883 (6.0%)
Oral anticoagulants	941 (4.7%)	492 (4.2%)	440 (4.6%)	52 (2.6%)	1433 (4.6%)
Antiplatelets	6243 (31.4%)	3178 (27.4%)	2619 (27.3%)	559 (27.7%)	9421 (29.9%)
Lipid lowering drugs	14970 (75.4%)	8872 (76.4%)	7364 (76.8%)	1508 (74.8%)	23842 (75.8%)
Total number with complete covariates information	18,531 (93.3%)	10,987 (94.7%)	9,114 (95.0%)	1,873 (93.0%)	29,518 (94%)

Figure Legends

Figure 1. Forest plot summarising the comparison of outcome rates between sulphonylureas (SU) and non-SU agents (DPP-4 inhibitors (DPP4i) or thiazolidinediones (TZD)) as second-line treatment in addition to metformin between 2010 and 2017.

Figure 2. Forest plot summarising the comparison of outcome rates between sulphonylureas (SU) and DPP-4 inhibitors (DPP4i) as second-line treatment in addition to metformin between 2010 and 2017.

Figure 3. Forest plot summarising the comparison of outcome rates between sulphonylureas (SU) and thiazolidinediones (TZD) as second-line treatment in addition to metformin between 2010 and 2017

Figure 1. Forest plot summarising the comparison of outcome rates between sulphonylureas (SU) and non-SU agents (DPP-4 inhibitors (DPP4i) or thiazolidinediones (TZD)) as second-line treatment in addition to metformin between 2010 and 2017.

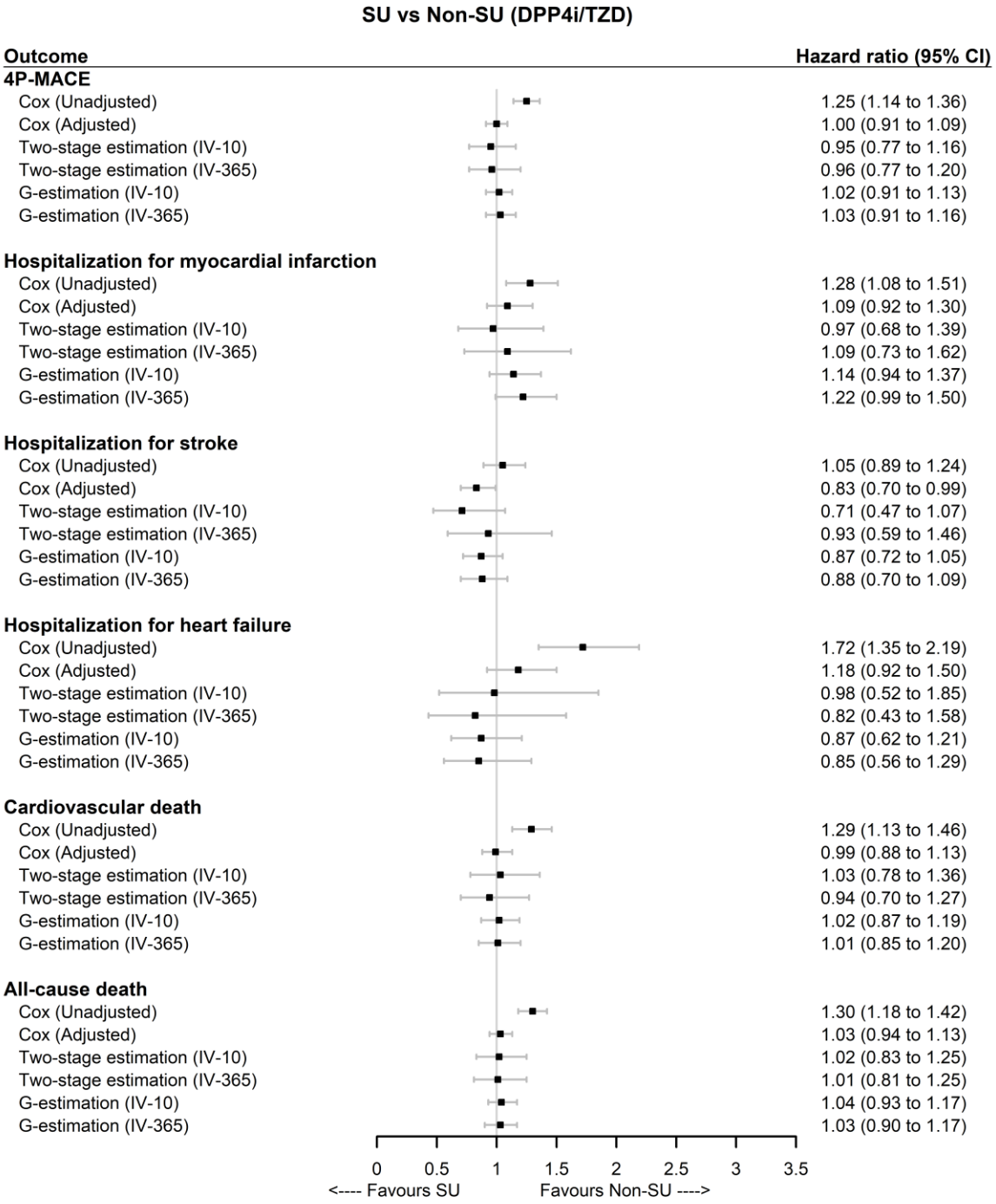
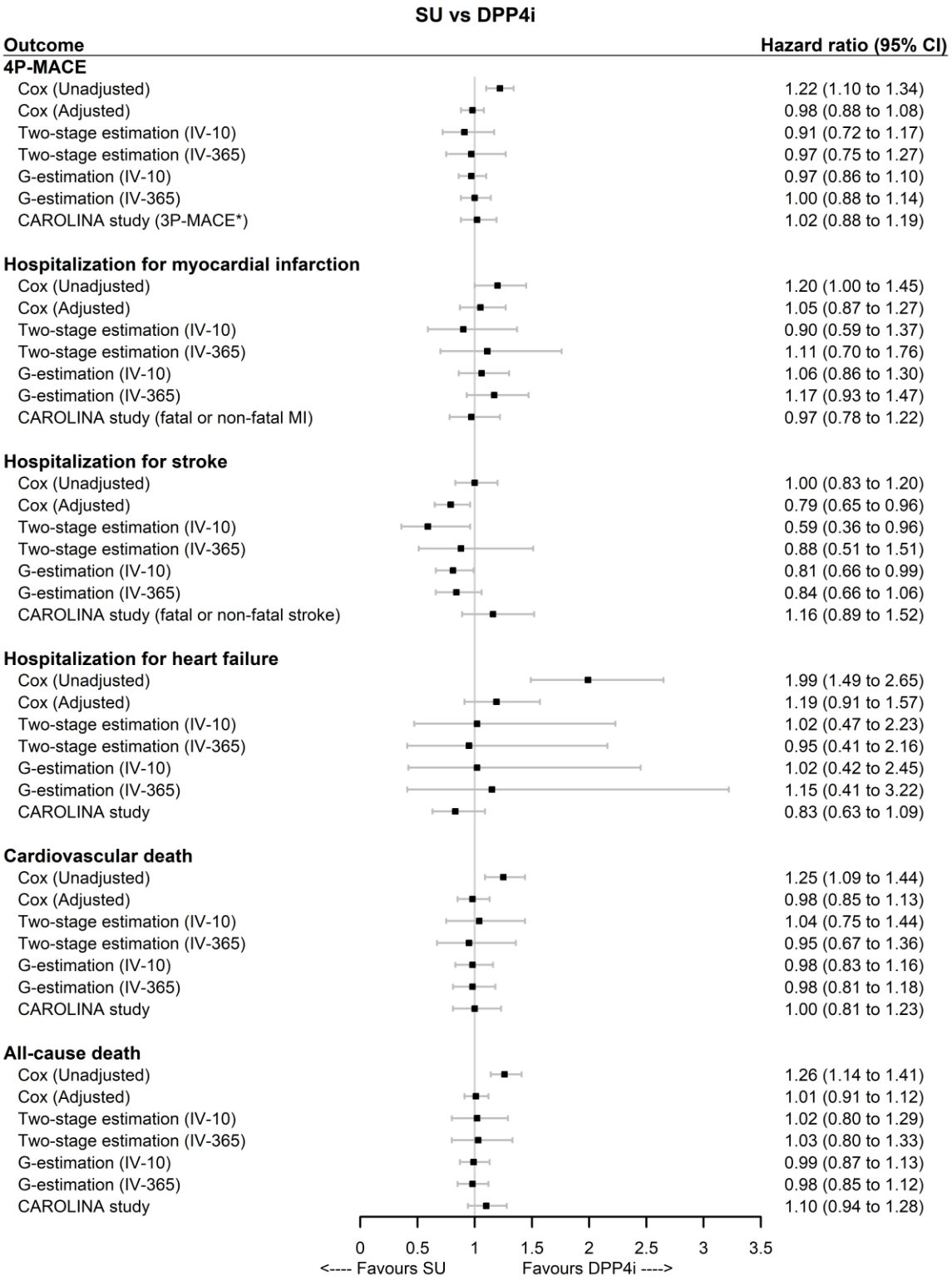
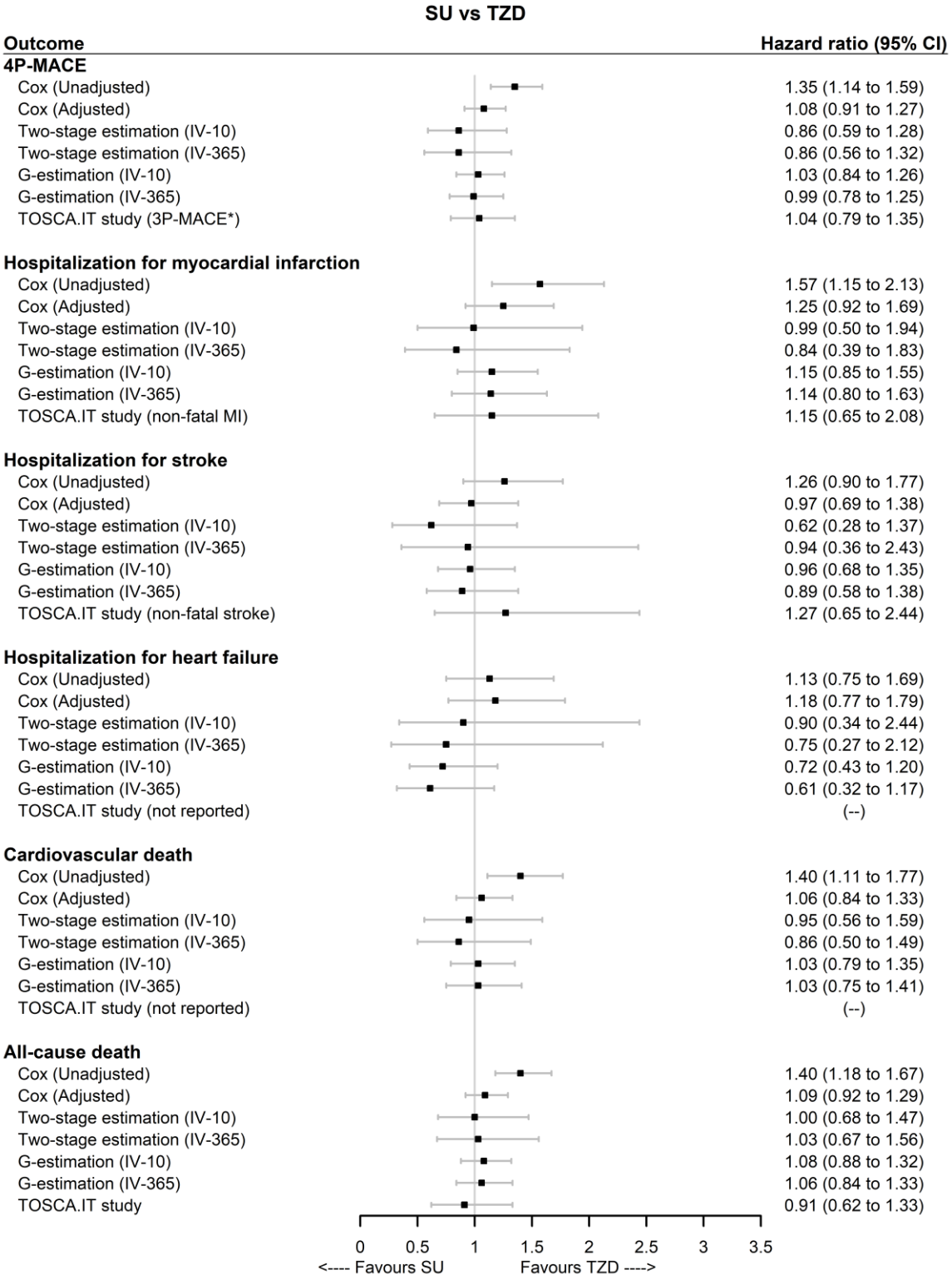


Figure 2. Forest plot summarising the comparison of outcome rates between sulphonylureas (SU) and DPP-4 inhibitors (DPP4i) as second-line treatment in addition to metformin between 2010 and 2017.



*3P-MACE in the CAROLINA study includes non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death.

Figure 3. Forest plot summarising the comparison of outcome rates between sulphonylureas (SU) and thiazolidinediones (TZD) as second-line treatment in addition to metformin between 2010 and 2017.



*3P-MACE in the TOSCA.IT study includes non-fatal myocardial infarction, non-fatal stroke, urgent coronary revascularisation, or all-cause death.

Supplementary Materials

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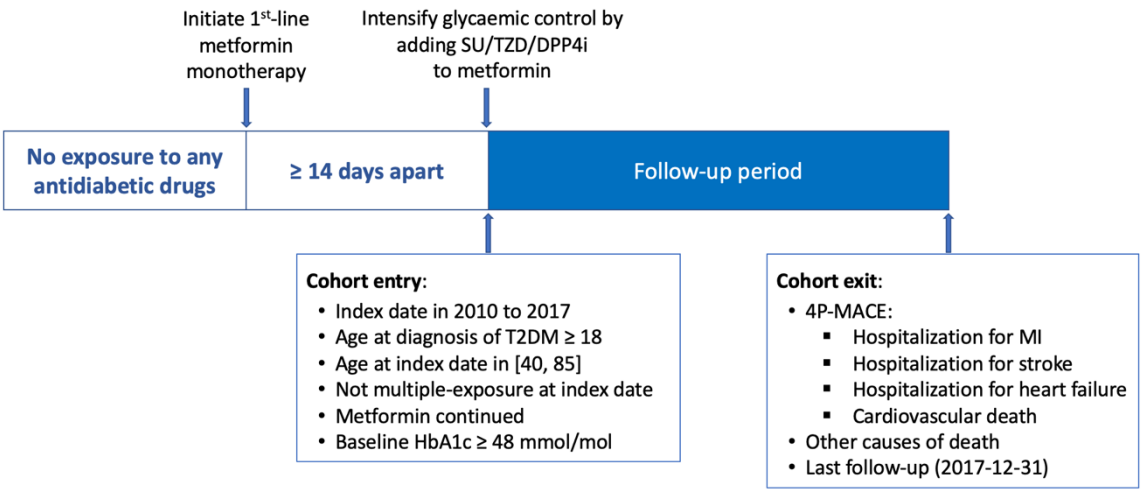

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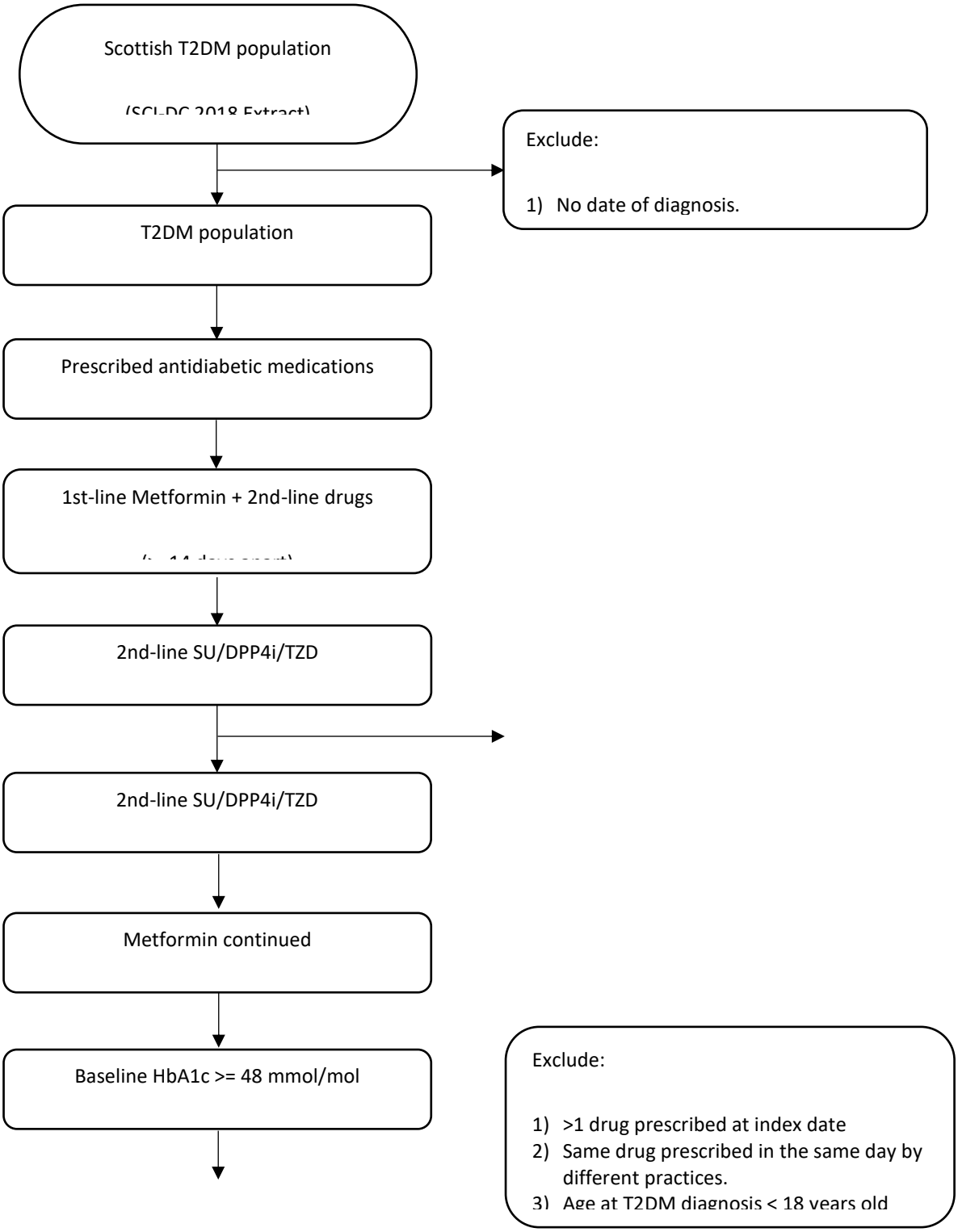
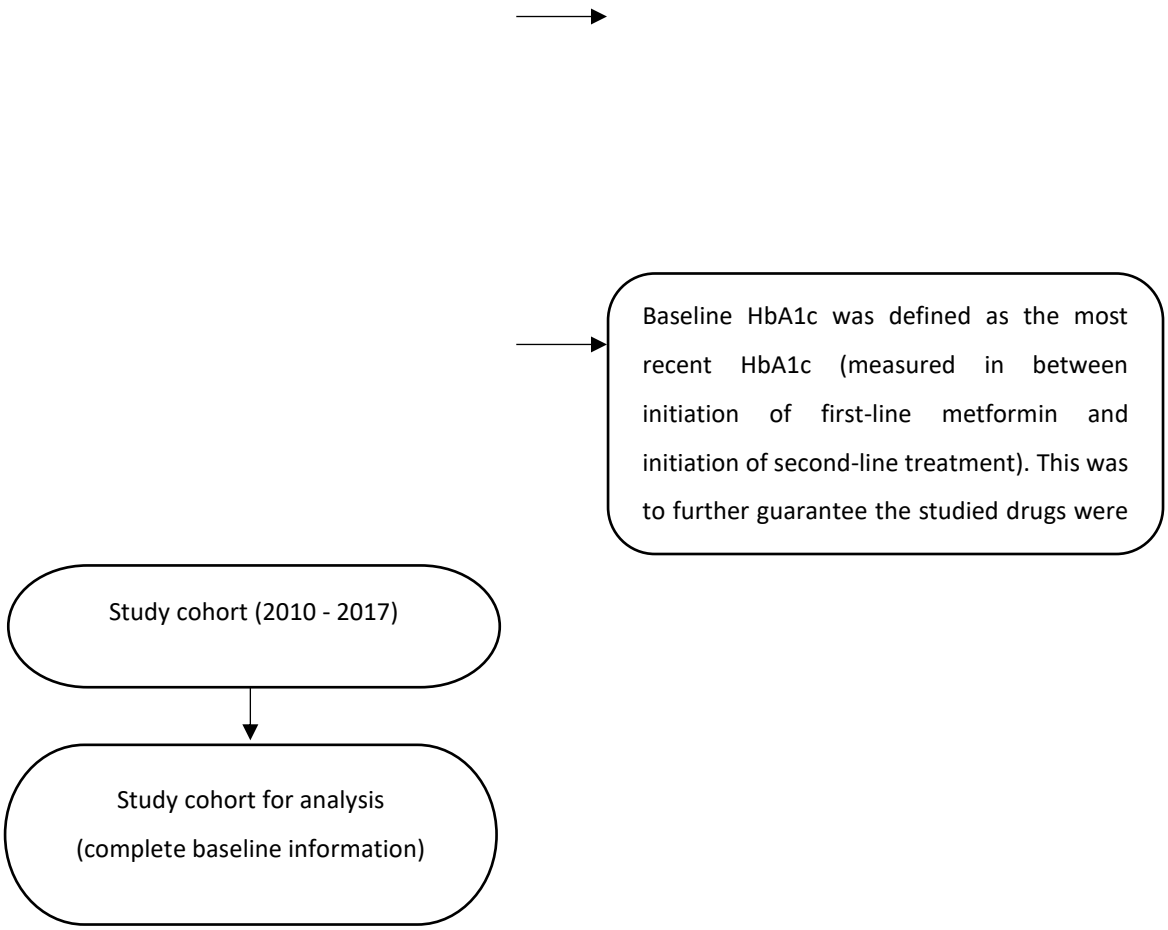
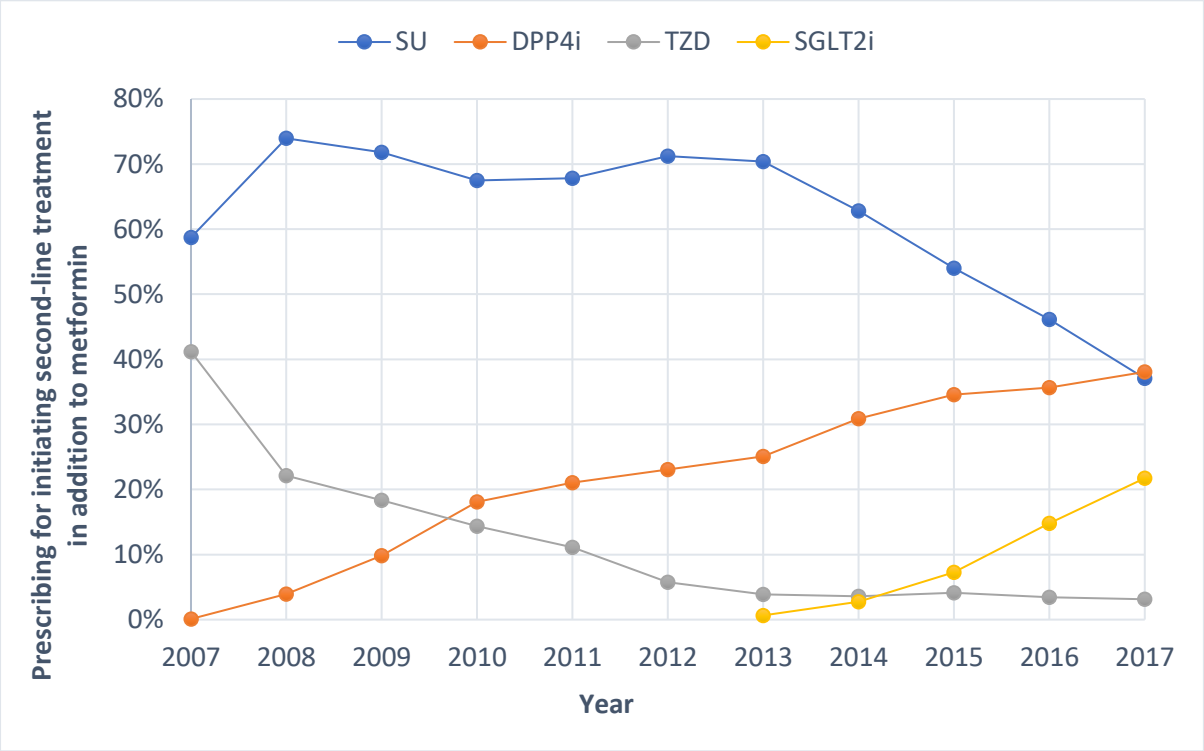


'Metformin continued' was defined as:

1) Metformin was co-prescribed at index date; or
2) Metformin was prescribed within 60 days post index date & before prescribing

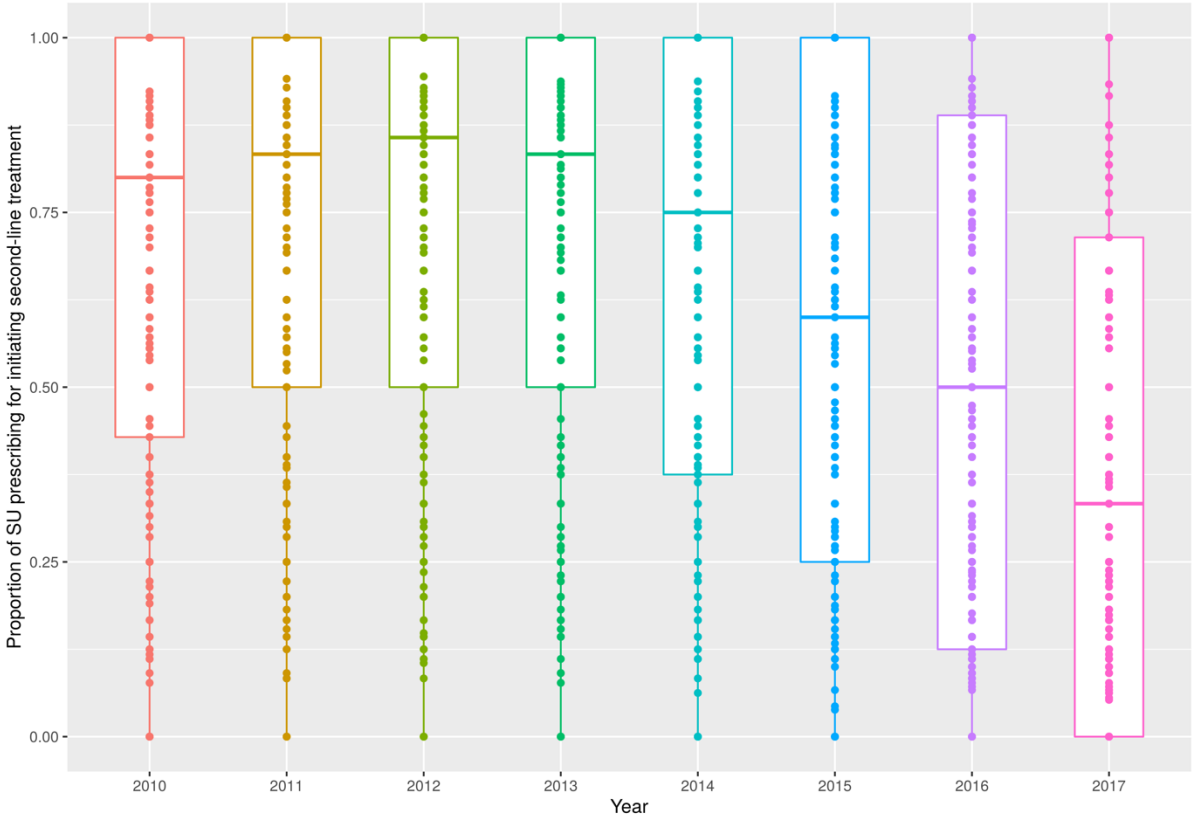

Baseline HbA1c was defined as the most recent HbA1c (measured in between initiation of first-line metformin and initiation of second-line treatment). This was to further guarantee the studied drugs were
Study cohort (2010 - 2017)
Study cohort for analysis
(complete baseline information)

sFigure 3. Temporal trends of prescribing for second-line treatment in addition to metformin for people with type 2 diabetes in Scotland between 2007 and 2017.



The patterns of prescribing for initiating treatment intensification varied substantially. Between 2010 and 2013, SU accounted for around 70% of all the second-line treatment initiations. This percentage declined dramatically after 2013, and in 2017 SU accounted for 37% of the second-line treatment initiations, slightly less than DPP4i (38%). Prescribing for TZD remained low during the study period with a declining trend from 14% in 2010 to only 3% in 2017. Prescribing for SGLT2i started from 2013 in Scotland and has increased rapidly after guideline recommendation in 2015. In 2017, SGLT2i accounted for nearly 22% of the second-line initiated drugs. However, due to the low absolute number of prescriptions, insufficient follow-up time, and established cardio-protective effects, SGLT2i were not included as one of the comparators in further analyses.

sFigure 4. Boxplots of practice-level proportion of SU prescribing for initiating second-line treatment in addition to metformin among people with type 2 diabetes in Scotland between 2010 and 2017.



Between-practice variation of SU prescribing for initiating second-line treatment was found to be substantial. Within each year between 2007 to 2017, some practices only prescribed SU, while some others hardly ever prescribed SU. This suggests that the practice-level proportion of SU prescriptions is a good instrument for our IV analyses.

sTable 1. Incidence rates of study outcomes among people with type 2 diabetes in Scotland treated with sulphonylureas (SU), DPP-4 inhibitors (DPP4i) or thiazolidinediones (TZD) as second-line treatment in addition to metformin between 2010 and 2017.

	No. patients	No. events	Person years	Median (IQR) follow-up years	Incidence rate (95% CI) per 1000 person years
4P-MACE					
SU	18531	1709	72958.6	3.9 (2.1 to 5.7)	23.4 (22.3 to 24.6)
Non-SU	10987	701	37567.8	3.0 (1.5 to 5.2)	18.7 (17.3 to 20.1)
DPP4i	9114	541	28611.9	2.8 (1.3 to 4.7)	18.9 (17.3 to 20.6)
TZD	1873	160	8955.8	5.3 (2.7 to 6.9)	17.9 (15.2 to 20.9)
Hospitalization for MI					
SU	18531	528	74233.3	4.0 (2.2 to 5.7)	7.1 (6.5 to 7.7)
Non-SU	10987	211	38063.2	3.1 (1.6 to 5.3)	5.5 (4.8 to 6.3)
DPP4i	9114	169	28965.8	2.8 (1.4 to 4.8)	5.8 (5.0 to 6.8)
TZD	1873	42	9097.4	5.5 (2.8 to 6.9)	4.6 (3.3 to 6.2)
Hospitalization for stroke					
SU	18531	379	74653.0	4.1 (2.2 to 5.8)	5.1 (4.6 to 5.6)
Non-SU	10987	183	38132.2	3.1 (1.6 to 5.3)	4.8 (4.1 to 5.5)
DPP4i	9114	144	29011.5	2.8 (1.4 to 4.8)	5.0 (4.2 to 5.8)
TZD	1873	39	9120.7	5.5 (2.8 to 6.9)	4.3 (3.0 to 5.8)
Hospitalization for HF					
SU	18531	257	74555.1	4.1 (2.2 to 5.8)	3.4 (3.0 to 3.9)
Non-SU	10987	79	38207.5	3.1 (1.6 to 5.4)	2.1 (1.6 to 2.6)
DPP4i	9114	54	29112.6	2.8 (1.4 to 4.8)	1.9 (1.4 to 2.4)
TZD	1873	25	9094.9	5.5 (2.8 to 6.9)	2.7 (1.8 to 4.1)
Cardiovascular death					

SU	18531	916	75346.1	4.1 (2.3 to 5.8)	12.2 (11.4 to 13.0)
Non-SU	10987	355	38462.5	3.1 (1.6 to 5.4)	9.2 (8.3 to 10.2)
DPP4i	9114	269	29268.8	2.8 (1.4 to 4.8)	9.2 (8.1 to 10.4)
TZD	1873	86	9193.7	5.6 (2.9 to 6.9)	9.4 (7.5 to 11.6)
All-cause death					
SU	18531	1601	75346.1	4.1 (2.3 to 5.8)	21.2 (20.2 to 22.3)
Non-SU	10987	618	38462.5	3.1 (1.6 to 5.4)	16.1 (14.8 to 17.4)
DPP4i	9114	469	29268.8	2.8 (1.4 to 4.8)	16.0 (14.6 to 17.5)
TZD	1873	149	9193.7	5.6 (2.9 to 6.9)	16.2 (13.7 to 19.0)

sMethod 1. Subgroup analyses

sTable 2. Comparison of outcome rates between sulphonylureas (SU) and non-SU agents (DPP4i or TZD) in subgroups of cohort stratified by prior history of MACE, age, BMI, and subtypes of SU.

	4P-MACE	Hospitalization for MI	Hospitalization for stroke	Hospitalization for heart failure	Cardiovascular death	All-cause death
MACE history						
No prior MACE (n = 25,943)	1.05 (0.94 to 1.17)	1.19 (0.98 to 1.44)	0.89 (0.72 to 1.10)	1.37 (0.97 to 1.93)	1.05 (0.90 to 1.24)	1.05 (0.94 to 1.18)
Prior MACE (n = 3,575)	0.89 (0.75 to 1.05)	0.86 (0.63 to 1.18)	0.73 (0.52 to 1.03)	0.95 (0.67 to 1.34)	0.87 (0.70 to 1.08)	0.93 (0.77 to 1.12)
Age group						
Age < 70 (n = 22,985)	0.97 (0.86 to 1.10)	1.09 (0.89 to 1.32)	0.88 (0.69 to 1.13)	1.20 (0.85 to 1.72)	0.95 (0.80 to 1.14)	1.04 (0.91 to 1.19)
Age >= 70 (n = 6,533)	1.04 (0.89 to 1.20)	1.10 (0.80 to 1.50)	0.78 (0.59 to 1.02)	1.16 (0.80 to 1.67)	1.02 (0.85 to 1.22)	1.01 (0.88 to 1.16)
BMI category						
BMI < 30 (n = 9,811)	1.06 (0.91 to 1.23)	1.23 (0.93 to 1.63)	0.78 (0.59 to 1.04)	1.52 (0.88 to 2.64)	1.07 (0.87 to 1.32)	1.03 (0.88 to 1.21)

BMI >= 30 (n = 19,707)	0.97 (0.87 to 1.09)	1.04 (0.85 to 1.28)	0.86 (0.70 to 1.06)	1.10 (0.83 to 1.46)	0.96 (0.82 to 1.12)	1.04 (0.92 to 1.17)
Subtypes of SU						
Gliclazide (n = 16,152)	1.01 (0.93 to 1.10)	1.12 (0.94 to 1.33)	0.85 (0.71 to 1.01)	1.18 (0.92 to 1.51)	1.00 (0.88 to 1.13)	1.04 (0.95 to 1.15)
Glimepiride (n = 1,540)	0.94 (0.77 to 1.16)	1.00 (0.67 to 1.50)	0.77 (0.47 to 1.25)	1.16 (0.69 to 1.95)	0.98 (0.75 to 1.28)	0.96 (0.77 to 1.19)
Glipizide (n = 818)	0.93 (0.75 to 1.16)	0.81 (0.50 to 1.32)	0.68 (0.40 to 1.14)	1.17 (0.63 to 2.18)	1.02 (0.77 to 1.35)	0.97 (0.77 to 1.22)
Glibenclamide* (n = 21)	(--)	(--)	(--)	(--)	(--)	(--)

*Hazard ratios for glibenclamide were not evaluated due to the extremely small sample size.

sTable 3. Comparison of outcome rates between sulphonylureas (SU) and DPP-4 inhibitors (DPP4i) in subgroups of cohort stratified by prior history of MACE, age, BMI, and subtypes of SU.

	4P-MACE	Hospitalization for MI	Hospitalization for stroke	Hospitalization for heart failure	Cardiovascular death	All-cause death
MACE history						
No prior MACE (n = 24,277)	1.02 (0.91 to 1.16)	1.14 (0.92 to 1.42)	0.85 (0.67 to 1.08)	1.28 (0.87 to 1.90)	1.05 (0.88 to 1.26)	1.03 (0.91 to 1.17)
Prior MACE (n = 3,444)	0.89 (0.75 to 1.06)	0.84 (0.60 to 1.18)	0.70 (0.48 to 1.01)	1.10 (0.74 to 1.63)	0.86 (0.68 to 1.09)	0.92 (0.75 to 1.12)
Age group						
Age < 70 (n = 21,436)	0.94 (0.82 to 1.07)	1.04 (0.83 to 1.31)	0.86 (0.66 to 1.14)	1.14 (0.77 to 1.69)	0.92 (0.75 to 1.12)	1.02 (0.87 to 1.18)
Age >= 70 (n = 6,209)	1.05 (0.89 to 1.23)	1.05 (0.75 to 1.46)	0.72 (0.53 to 0.97)	1.30 (0.85 to 1.97)	1.03 (0.84 to 1.26)	0.99 (0.85 to 1.16)
BMI category						
BMI < 30 (n = 9,245)	1.05 (0.88 to 1.25)	1.27 (0.92 to 1.76)	0.66 (0.48 to 0.91)	1.95 (0.94 to 4.06)	1.05 (0.83 to 1.34)	1.02 (0.85 to 1.22)
BMI >= 30 (n = 18,400)	0.95 (0.84 to 1.08)	0.97 (0.78 to 1.22)	0.88 (0.69 to 1.11)	1.07 (0.78 to 1.47)	0.96 (0.80 to 1.14)	1.01 (0.89 to 1.15)
Subtypes of SU						

Gliclazide (n = 16,152)	0.99 (0.89 to 1.09)	1.07 (0.88 to 1.30)	0.80 (0.66 to 0.97)	1.19 (0.90 to 1.57)	0.98 (0.85 to 1.13)	1.02 (0.92 to 1.14)
Glimepiride (n = 1,540)	0.95 (0.77 to 1.17)	0.98 (0.64 to 1.49)	0.71 (0.42 to 1.18)	1.28 (0.73 to 2.23)	0.99 (0.75 to 1.30)	0.93 (0.75 to 1.16)
Glipizide (n = 818)	0.91 (0.72 to 1.15)	0.76 (0.46 to 1.26)	0.62 (0.36 to 1.06)	1.33 (0.72 to 2.46)	1.02 (0.76 to 1.37)	0.95 (0.75 to 1.21)
Glibenclamide* (n = 21)	(--)	(--)	(--)	(--)	(--)	(--)

*Hazard ratios for glibenclamide were not evaluated due to the extremely small sample size.

sTable 4. Comparison of outcome rates between sulphonylureas (SU) and thiazolidinediones (TZD) in subgroups of cohort stratified by prior history of MACE, age, BMI, and subtypes of SU.

	4P-MACE	Hospitalization for MI	Hospitalization for stroke	Hospitalization for heart failure	Cardiovascular death	All-cause death
MACE history						
No prior MACE (n = 17,939)	1.11 (0.92 to 1.34)	1.32 (0.94 to 1.85)	1.01 (0.68 to 1.51)	1.55 (0.85 to 2.81)	1.07 (0.81 to 1.42)	1.10 (0.91 to 1.34)
Prior MACE (n = 2,465)	0.87 (0.60 to 1.28)	0.98 (0.48 to 2.01)	0.83 (0.39 to 1.76)	0.62 (0.31 to 1.24)	0.90 (0.56 to 1.44)	0.96 (0.64 to 1.42)
Age group						
Age < 70 (n = 15,753)	1.13 (0.93 to 1.37)	1.22 (0.86 to 1.73)	0.96 (0.61 to 1.51)	1.48 (0.81 to 2.70)	1.13 (0.84 to 1.52)	1.10 (0.87 to 1.40)
Age >= 70 (n = 4,651)	1.01 (0.76 to 1.34)	1.30 (0.69 to 2.44)	0.99 (0.58 to 1.71)	0.94 (0.52 to 1.72)	1.00 (0.71 to 1.40)	1.07 (0.82 to 1.39)
BMI category						
BMI < 30 (n = 7,314)	1.07 (0.81 to 1.41)	1.12 (0.68 to 1.84)	1.29 (0.69 to 2.39)	1.08 (0.49 to 2.41)	1.10 (0.76 to 1.61)	1.02 (0.77 to 1.36)
BMI >= 30 (n = 13,090)	1.09 (0.89 to 1.33)	1.35 (0.89 to 2.04)	0.85 (0.57 to 1.27)	1.24 (0.76 to 2.04)	1.05 (0.80 to 1.37)	1.15 (0.94 to 1.41)
Subtypes of SU						
Gliclazide (n = 16,152)	1.09 (0.93 to 1.29)	1.30 (0.95 to 1.77)	1.00 (0.70 to 1.43)	1.18 (0.76 to 1.81)	1.05 (0.84 to 1.32)	1.10 (0.93 to 1.30)
Glimepiride (n = 1,540)	0.94 (0.72 to 1.22)	1.13 (0.70 to 1.82)	0.90 (0.51 to 1.59)	1.12 (0.54 to 2.32)	0.89 (0.61 to 1.28)	0.96 (0.74 to 1.25)

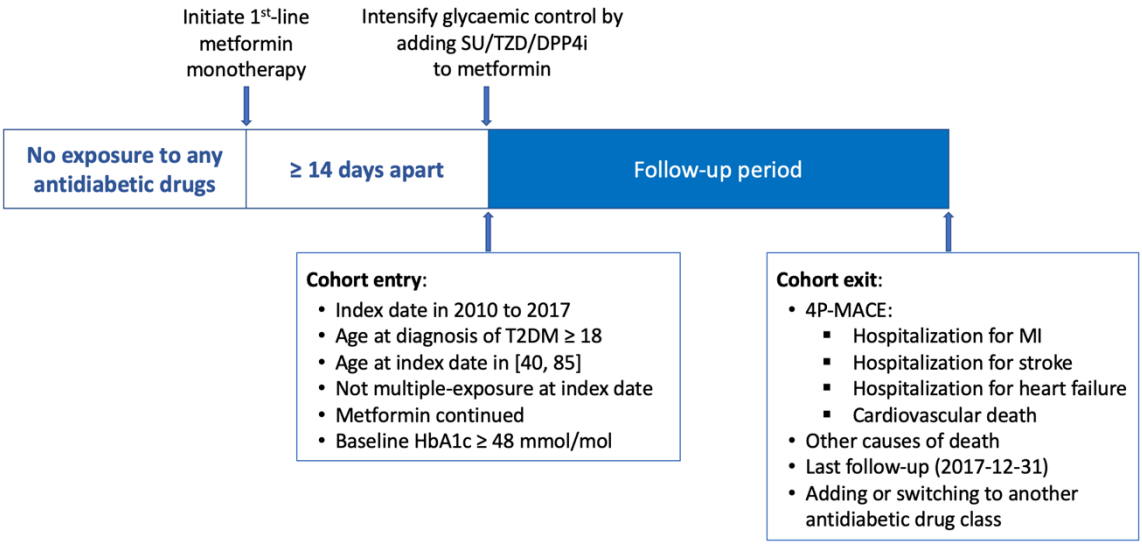
Glipizide (n = 818)	1.10 (0.78 to 1.30)	1.06 (0.63 to 1.79)	0.88 (0.48 to 1.60)	0.95 (0.44 to 2.08)	1.10 (0.78 to 1.57)	1.02 (0.77 to 1.35)
Glibenclamide (n = 21)	(--)	(--)	(--)	(--)	(--)	(--)

*Hazard ratios for glibenclamide were not evaluated due to the extremely small sample size.

sMethod 2. Sensitivity analyses

In the sensitivity analyses, follow-up was additionally censored at adding or switching to a third class of antidiabetic medication (different from metformin and the second-line treatment currently received). Please see the sFigure 3 below for details.

sFigure 5. Illustration of study design for the sensitivity analyses.

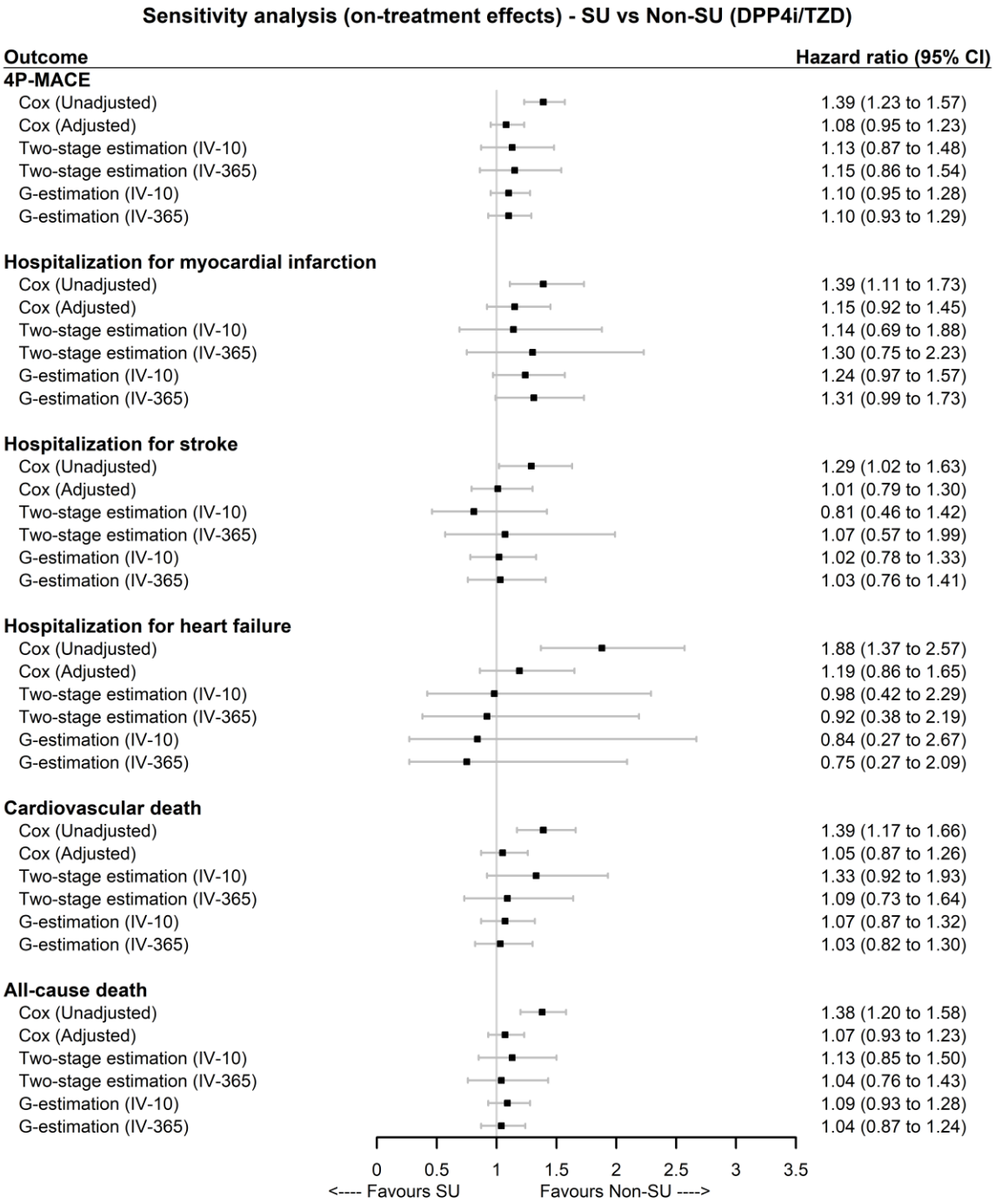


sTable 5. Incidence rates of study outcomes (follow up was additionally censored at adding or switching to a third class of antidiabetic medication).

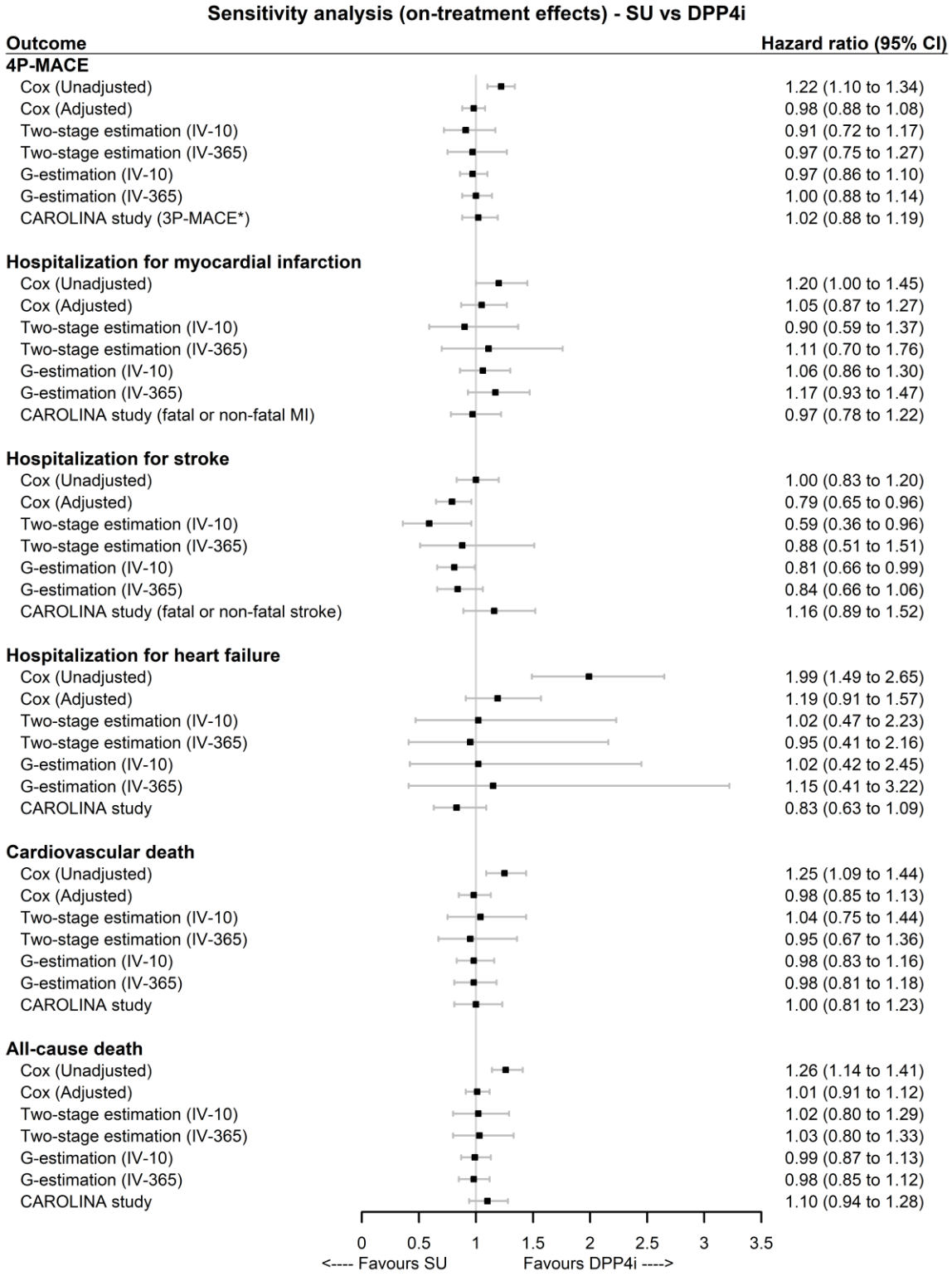
	No. patients	No. events	Person years	Median (IQR) follow-up years	Incidence rate (95% CI) per 1000 person years
4P-MACE					
SU	18531	998	42623.9	1.8 (0.6 to 3.6)	23.4 (22.0 to 24.9)
Non-SU	10987	361	21793.9	1.4 (0.6 to 2.8)	16.6 (14.9 to 18.4)
DPP4i	9114	280	16625.7	1.3 (0.6 to 2.6)	16.8 (14.9 to 18.9)
TZD	1873	80	5168.3	2.1 (0.8 to 4.5)	15.5 (12.3 to 19.3)
Hospitalization for MI					
SU	18531	303	43236.8	1.9 (0.6 to 3.7)	7.0 (6.2 to 7.8)
Non-SU	10987	111	21999.6	1.4 (0.6 to 2.8)	5.0 (4.2 to 6.1)
DPP4i	9114	90	16775.1	1.3 (0.6 to 2.6)	5.4 (4.3 to 6.6)
TZD	1873	21	5224.5	2.1 (0.8 to 4.6)	4.0 (2.5 to 6.1)
Hospitalization for stroke					
SU	18531	223	43364.0	1.9 (0.6 to 3.7)	5.1 (4.5 to 5.9)
Non-SU	10987	86	21986.5	1.4 (0.6 to 2.8)	3.9 (3.1 to 4.8)
DPP4i	9114	69	16756.1	1.3 (0.6 to 2.6)	4.1 (3.2 to 5.2)
TZD	1873	17	5230.4	2.1 (0.8 to 4.6)	3.3 (1.9 to 5.2)
Hospitalization for HF					
SU	18531	176	43333.4	1.9 (0.6 to 3.7)	4.1 (3.5 to 4.7)
Non-SU	10987	50	22027.5	1.4 (0.6 to 2.8)	2.3 (1.7 to 3.0)

DPP4i	9114	35	16809.1	1.3 (0.6 to 2.6)	2.1 (1.5 to 2.9)
TZD	1873	15	5218.4	2.1 (0.8 to 4.6)	2.9 (1.6 to 4.7)
Cardiovascular death					
SU	18531	510	43701.3	1.9 (0.6 to 3.7)	11.7 (10.7 to 12.7)
Non-SU	10987	174	22121.6	1.4 (0.6 to 2.9)	7.9 (6.7 to 9.1)
DPP4i	9114	136	16867.0	1.3 (0.6 to 2.6)	8.1 (6.8 to 9.5)
TZD	1873	38	5254.6	2.1 (0.8 to 4.6)	7.2 (5.1 to 9.9)
All-cause death					
SU	18531	871	43701.3	1.9 (0.6 to 3.7)	19.9 (18.6 to 21.3)
Non-SU	10987	301	22121.6	1.4 (0.6 to 2.9)	13.6 (12.1 to 15.2)
DPP4i	9114	230	16867.0	1.3 (0.6 to 2.6)	13.6 (11.9 to 15.5)
TZD	1873	71	5254.6	2.1 (0.8 to 4.6)	13.5 (10.6 to 17.0)

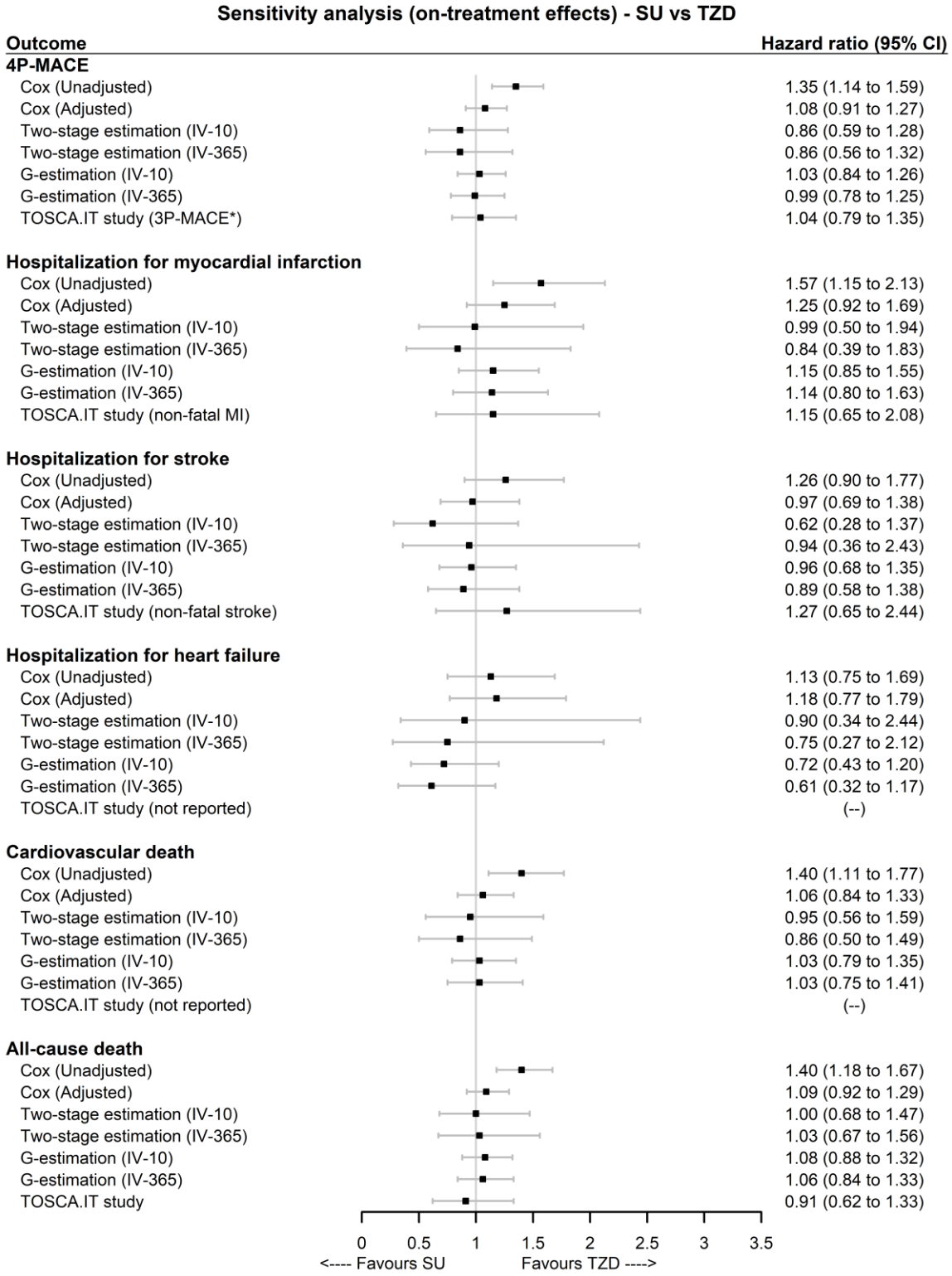
sFigure 6. Comparison of outcome rates between SU and non-SU agents (DPP4i or TZD).



sFigure 7. Comparison of outcome rates between SU and DPP4i.



sFigure 8. Comparison of outcome rates between SU and TZD.



sMethod 3. Assessment of instrumental variable (IV) conditions

The three essential IV conditions are: (i) 'Relevance' – the IV is associated with the exposure of interest; (ii) 'Exclusion restriction' – the IV does not affect the outcome except through its potential effect on the exposure; and (iii) 'Exchangeability' – the IV and the outcome have no common causes. For the proposed two IVs, condition (i) was tested under the two-stage setting by performing likelihood ratio test, analogous to reporting the partial *F* statistic for the linear framework. Point-biserial correlation was used to quantify the strength of the IVs. Moreover, logistic regression models were built with SU prescription as the outcome, regressing on the *z*-transformed IV with and without including year of cohort entry. The strength of the IV can be assured if the odds ratio of the *z*-transformed IV remains large with or without including year of cohort entry. Condition (ii) was assumed to be met because the prescribing preference at practice level was unlikely to affect a new patient's CV risk or mortality other than through the actual prescription issued. Condition (iii) was falsified by using the standardized difference (SDif), an intuitive measure for assessing covariates balance. If measured covariates are well balanced, it is reasonable to assume that such balance may also be achieved in the potential unmeasured confounders.(1) As our IVs are continuous proportions, the balance was assessed across the quartiles. The maximum SDif for each covariate was reported, with small values (e.g. < 0.1) indicating better balance.(2)

In addition to the three essential IV conditions above, obtaining a point estimate for the causal exposure effect requires a further fourth condition of either treatment effect homogeneity or monotonicity.(3) Here we assumed the monotonicity was established, that is, all study participants were assumed to comply with the preference of their practices. In other words, patients registered with a practice with stronger preference for a given drug would be more likely to receive that drug in comparison to the other drugs. Under this assumption, the estimated exposure effect would be interpreted as the average causal effect in those who complied with practice preference (also known as the local average treatment effect).

sTable 6. Assessment of IV condition (i): IV strength evaluated using likelihood ratio test and point biserial correlation.

Instrumental variable	Deviance of the first stage model[1]		Likelihood ratio test *p* value	Point-biserial correlation
	Without IV	With IV		
IV-10	35467	28829	< 0.001	0.497
IV-365	27111	21697	< 0.001	0.516

[1]First stage model: Exposure to SU (yes/no) ~ Instrument (IV-10 or IV-365) + year of cohort entry.

sTable 7. Assessment of IV condition (i): IV strength evaluated using logistic regression.

Instrumental variable	Crude odds ratio[1] (95% CI)	Adjusted odds ratio[2] (95% CI)	*p* value (Wald's test)	*p* value (Likelihood ratio test)
IV-10	3.25 (3.15 – 3.36)	3.19 (3.09 – 3.29)	< 0.001	< 0.001
IV-365	3.45 (3.33 – 3.58)	3.39 (3.26 – 3.52)	< 0.001	< 0.001

[1]Crude odds ratios were obtained from the univariate logistic model: Exposure to SU (yes/no) ~ *z*-transformed Instrument (IV-10 or IV-365).
[2]Adjusted odds ratios were obtained from the multivariate logistic model: Exposure to SU (yes/no) ~ *z*-transformed Instrument (IV-10 or IV-365) + year of cohort entry.

sTable 8. Falsification of IV condition (iii): assessing covariate balance.

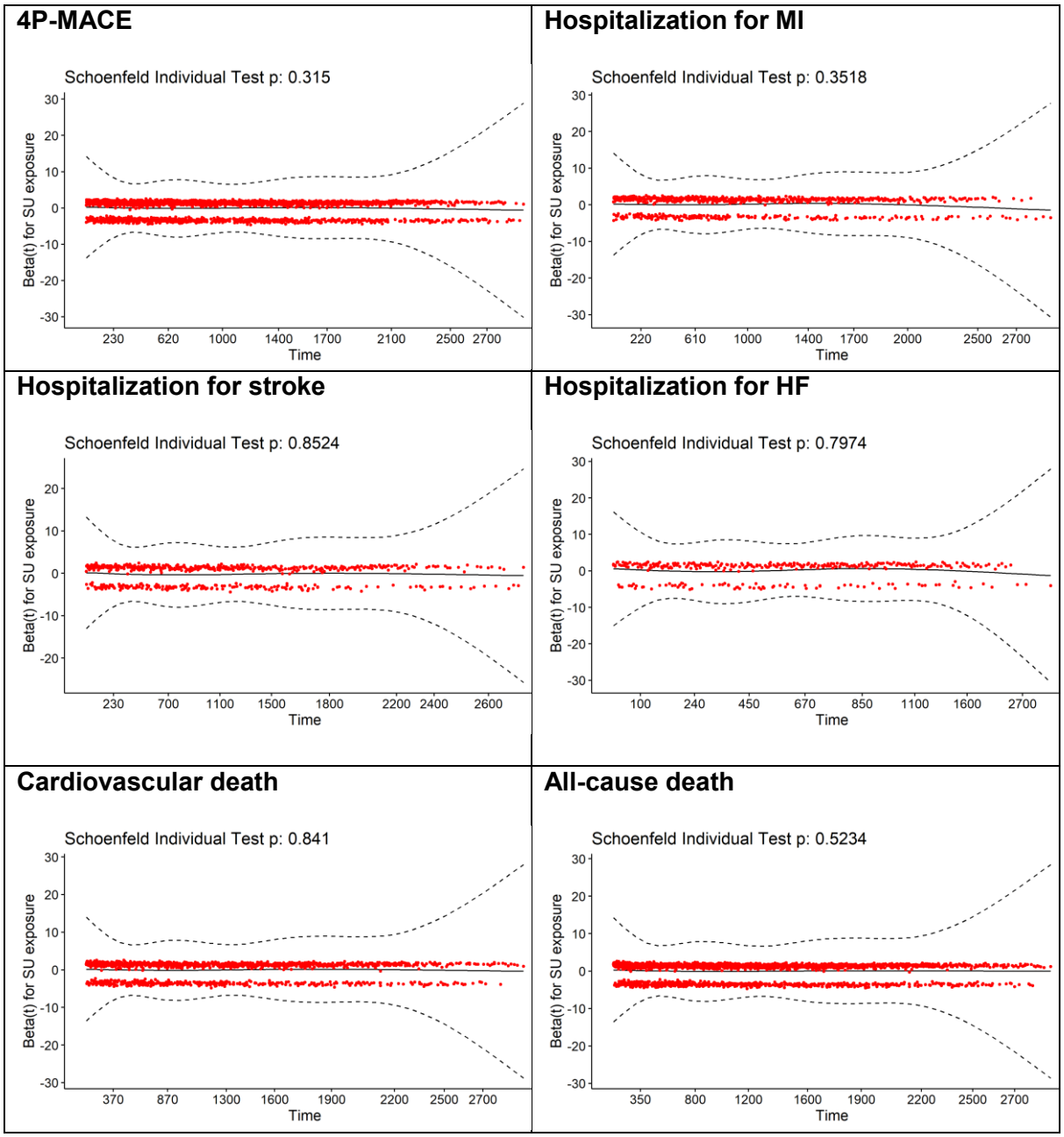
	Standardised mean difference (SDif)	Maximum pairwise standardised mean difference (SDif) across IV quartiles	
Covariates	**Exposure (SU vs non-SU)**	**IV-10**	**IV-365**
Age	**0.105**	0.053	0.064
Sex	0.009	0.007	0.015
Ethnicity	0.022	0.053	0.041
Duration of diabetes	-0.014	0.029	0.051
HbA1c	**0.220**	0.098	0.097

Total cholesterol/HDL ratio	0.044	0.065	0.093
Systolic blood pressure	-0.012	0.044	0.071
Baseline eGFR (CKD-EPI)			
≥90	-0.011	0.033	0.037
60-89	0.006	0.027	0.019
45-59	0.004	0.004	0.015
<45	0.002	0.005	0.007
Body mass index (kg/m^2)			
<25	0.032	0.003	0.008
25-29	0.053	0.009	0.013
30-34	-0.004	0.009	0.006
35-40	-0.031	0.010	0.008
>=40	-0.050	0.008	0.009
Smoking status			
Never	-0.026	0.009	0.012
Ever	-0.001	0.011	0.009
Current	0.027	0.017	0.017
SIMD quintile			
1	-0.011	0.029	0.023
2	-0.012	0.023	0.020
3	0.008	0.026	0.005
4	0.006	0.015	0.020
5	0.010	0.014	0.017
History of conditions:			
Arterial fibrillations	0.009	0.004	0.003
Coronary artery disease	0.025	0.007	0.005
Cancer	0.018	0.008	0.011

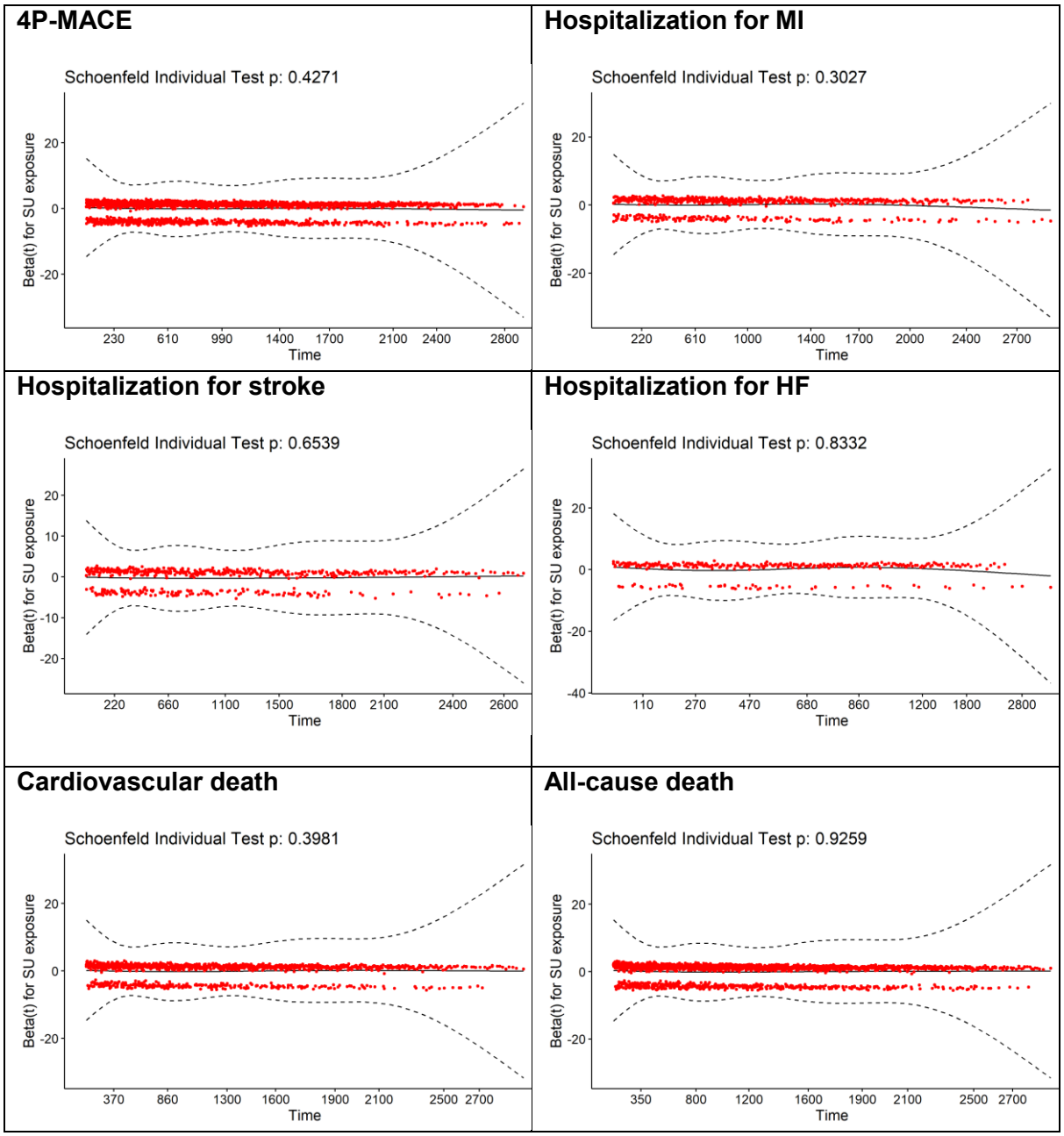
COPD	0.013	0.008	0.014
Diabetic retinopathy	0.012	0.032	0.025
Hypertension (ICD-coded)	0.021	0.011	0.010
Myocardial infarction	0.011	0.009	0.002
Stroke	0.004	0.004	0.005
Heart failure	0.010	0.002	0.001
Currently used drugs:			
ACEis/ARBs	-0.021	0.014	0.009
Beta blockers	0.024	0.017	0.015
Calcium channel blockers	-0.004	0.011	0.024
Diuretics	0.013	0.008	0.009
Cardiac glycosides	0.006	0.003	0.005
Nitrates	0.011	0.002	0.003
Oral anticoagulants	0.005	0.004	0.004
Antiplatelets	0.041	0.031	0.026
Lipid lowering drugs	-0.008	0.009	0.010

sMethod 4. Assessment of proportional hazard assumptions

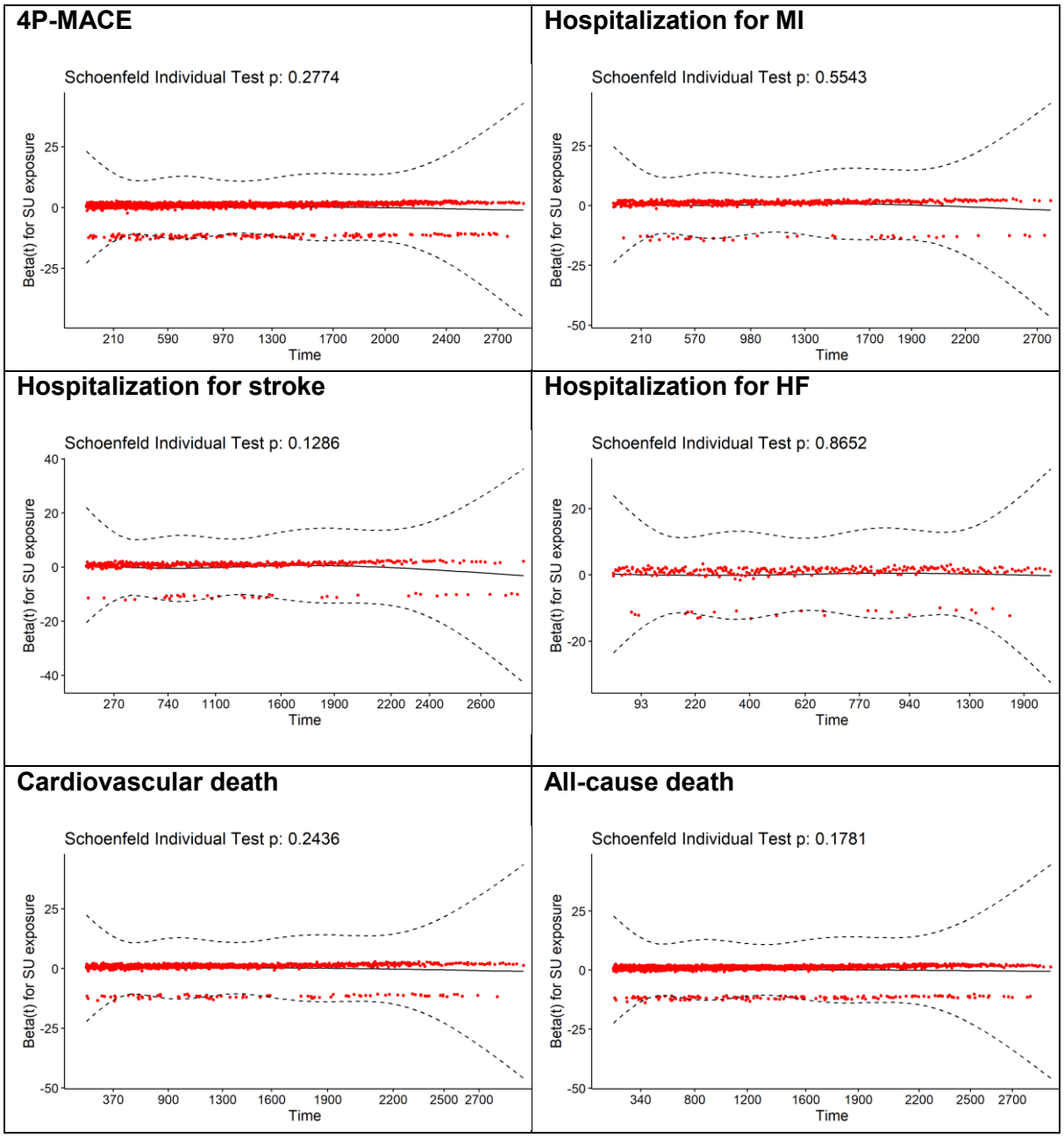
sTable 9. Plot of Schoenfeld residuals for the comparison between SU vs non-SU agents (DPP4i or TZD).



sTable 10. Plot of Schoenfeld residuals for the comparison between SU vs DPP4i.



sTable 11. Plot of Schoenfeld residuals for the comparison between SU vs TZD.



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