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Comparative risk of major cardiovascular events associated with second-line antidiabetic treatments: a retrospective cohort study using UK primary care data linked to hospitalisation and mortality records

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Aims The cardiovascular benefits of second-line regimens after metformin are uncertain. The aim of this study was to examine the risk of major cardiovascular events associated with second-line diabetes therapies, in patients with type 2 diabetes, after adjusting for known cardiovascular risk factors.

Methods A retrospective cohort study of patients prescribed second-line regimens between 1998 and 2011 following first-line metformin. The UK Clinical Practice Research Datalink (CPRD) with linked national hospitalisation and mortality data were used up to December 2013. Inverse probability of treatment weighted time-varying Cox regression models estimated HR and 95% confidence intervals (CI) for developing a major cardiovascular event (cardiovascular death, myocardial infarction, stroke, acute coronary syndrome, unstable angina, or coronary revascularization) associated with second-line therapies. Analyses adjusted for patient demographic characteristics, co-morbidities, glycated haemoglobin (HbA_{1c}), socio-economic status, ethnicity, smoking status and concurrent medications.

Results A total of 10,118 initiators of a second-line add-on to metformin of either a sulphonylurea (n=6,740), dipeptidyl peptidase-4 inhibitor (DPP-4i) (n=1,030) or thiazolidinedione (n=2,348) were identified. After a mean (SD) 2.4 (1.9) years of follow-up, 386, 36 and 95 major cardiovascular events occurred in sulphonylurea, DPP-4i and thiazolidinedione initiators, respectively. In comparison to the metformin-sulphonylurea regimen, adjusted HRs were 0.78 (95% CI 0.55; 1.11) for metformin-DPP-4i regimen and 0.68 (95% CI 0.54; 0.85) for metformin-thiazolidinedione regimen.

Conclusions Thiazolidinedione add-on treatments to metformin were associated with lower risks for major cardiovascular disease or cardiovascular death compared to sulphonylurea combination with metformin. Lower, but non-statistically significant, risks were also found with DPP-4i add-on therapies.

Introduction

Metformin is the standard first-line drug therapy for patients with type 2 diabetes [1, 2]. An escalation to a second-line therapy after initial metformin is, however, inevitable in the majority of patients, due to the progressive nature of diabetes. The recently updated position statement on diabetes management suggested a number of treatment options after metformin monotherapy [2]. However, the selection of an optimal second-line therapy is widely debated, primarily due to safety concerns, efficacy issues and costs [3, 4].

In people with type 2 diabetes, the risk for cardiovascular disease (CVD) complications is two-fold higher [1] than in the general population, where CVD is the leading cause of mortality (nearly 50% of all deaths) [5]. Given the increasing worldwide prevalence of type 2 diabetes, the associated increased cardiovascular risk and the availability of a wide range of different treatment options, there is a need to compare the impact of these different treatment regimens on major cardiovascular outcomes. Previous studies have investigated the cardiovascular risk of diabetes medications, but conclusions have been unclear due to small sample size [3, 6]; inadequate control for baseline disparities in clinical characteristics between treatment groups [7-9]; or failure to account for clinically important time-varying covariates [10-13] though may have modelled time-varying-exposures. Given the limitations observed in earlier studies, we hypothesised that there would be no differences in the cardiovascular risk associated with different second-line therapies. The aim of this large cohort study was therefore to compare the risk of major cardiovascular events occurring during different second-line diabetes treatment regimens in comparison to the most-commonly prescribed regimen after controlling for known cardiovascular risk factors in patients with type 2 diabetes.

Methods

Data source

The study cohort was identified using the Clinical Practice Research Datalink (CPRD). CPRD is a longitudinal electronic medical record database of patients registered in general practices (GPs) in the United Kingdom [14]. The database includes anonymised information on patients' demographics, diagnoses, consultations, specialist referrals, prescribed medications and biomedical laboratory tests. CPRD data have been used extensively in pharmacoepidemiology research [15-17] and previous validation studies have reported on the accuracy of diagnostic data [18]. In CPRD and linked datasets, clinical events are coded using Read codes (a hierarchical clinical classification system) and ICD (international classification of diseases) codes. Given our overall study period is between 1998 and 2013 and the ICD coding update in January 2001, both the ninth (ICD-9) and tenth (ICD-10) code revisions were used. The medical codes for diabetes, co-morbidities, and outcomes used in this study are listed in the online repository (ClinicalCodes.org) [19]. Currently, 75% of the English practices in CPRD have consented to contribute to the CPRD data linkage scheme [14]. In this study, we obtained access to linked hospitalisation records via Hospital Episode Statistics (HES); cause-specific mortality data collected by the Office for National Statistics (ONS); and the socio-economic status by index of multiple deprivation (IMD) 2010 quintiles (assigned at small-area locality level by linking to patient's residential postcode). The IMD is a composite score calculated as the weighted sum of the individual indices of seven domains of deprivation including: finance, education, health, access to services and crime [20].

Study population

Using CPRD, we identified a cohort of individuals with at least one diagnostic medical code for type 2 diabetes; aged ≥40 years at diagnosis before December 2011; and prescribed 90 days or more first-line metformin monotherapy. Among this cohort, patients were eligible for inclusion if they were prescribed a second-line antidiabetic treatment between 1st January 1998 and 31st December 2011, with at least 3 months of registration period in an up-to-standard general practice. Patients with type 2 diabetes who ever had a medical record for type 1 diabetes or non-specific diabetes were excluded. Eligible cases were followed up from index date (the initiation date of the second-line therapy) until a major cardiovascular event or censoring. Patients were censored at the earliest date of the following occurrences: change of prescribed second-line diabetes therapy; transfer out of the practice; death or end of the study (31st December 2013).

Exposures

Patients prescribed metformin monotherapy after an earlier diagnostic record for type 2 diabetes were identified as metformin initiators. Patients were excluded if they had initiated diabetes treatment with any other treatment regimen (including metformin combinations). Using therapy records, the duration of metformin therapy was calculated by summing the duration of individual repeat prescriptions of metformin monotherapy. Metformin initiators were eligible for inclusion if the total duration of metformin monotherapy prescriptions was ≥ 90 days. Eligible metformin initiators were then followed over time until the addition of a second-line medication. Incident exposure to second-line therapy was determined by the earliest date of an add-on medication (index date). Metformin-containing dual therapies (i.e. add-on regimens) were defined when a new diabetes medication was prescribed from day 91 onwards after first-line

metformin accompanied with subsequent refill(s) of metformin prescription(s) within 90 days of the earliest prescription of the new medication. To enhance statistical power, only dual second-line therapies with at least 1,000 cases were included in the analysis. Concurrent non-diabetes medications were defined if they were prescribed within 90 days before index date. Post-index co-medications were modelled as a binary time-varying covariate (yes vs. no) by assessing the prescription status at 6-month time-points during the follow-up period.

Outcome

The primary composite cardiovascular outcome was the earliest major cardiovascular event including: cardiovascular death, myocardial infarction, stroke, unstable angina, acute coronary syndrome, coronary artery bypass graft (CABG), or percutaneous transluminal coronary angioplasty (PTCA).

Covariates

We extracted baseline information on the following demographic and clinical risk factors: age, gender, BMI, smoking status, HbA_{1c}, ethnicity, IMD quintile, diabetes duration, duration of metformin therapy, calendar index year, co-morbidities and concomitant medications. Smoking status and exposure to the following co-medications were examined at baseline and as a time-varying covariates throughout follow-up: diuretics, α- & β-adrenoceptor blockers, calcium-channel blockers, ACE inhibitors, angiotensin-II receptor blockers (ARBs), hydroxyl-3-methylglutaryl coenzyme-A reductase inhibitors (statins), antiplatelet drugs (abciximab, aspirin, clopidogrel, dipyridamole, eptifibatide, prasugrel, ticagrelor, ticlopidine, tirofiban), and non-steroidal anti-inflammatory drugs (NSAIDs). The comorbid conditions included history of hypertension, myocardial infarction, stroke, heart failure, atrial fibrillation/flutter,

peripheral vascular disease (PVD), microvascular complications (retinopathy, neuropathy, nephropathy and foot complications), rheumatoid arthritis, and chronic kidney disease (stages 3, 4 and 5).

Statistical analyses

Descriptive statistics were used to analyse the baseline demographic and clinical characteristics of second-line therapy initiators. Mean (±SD) and proportions (percentage) were calculated for continuous and categorical variables, respectively. A multinomial logistic regression model was used to predict the probability of being prescribed a specific second-line therapy given the patient's baseline characteristics, analogous to the propensity score. We then calculated the inverse-probability of treatment weights (IPTWs) as the reciprocal of the patient's predicted probability of receiving their own second-line regimen. Inverse-probability of treatment weights were only estimated for patients with predicted probabilities within the common support (i.e. cases with probabilities overlapping with the probabilities of the referent group). The most-commonly prescribed regimen (sulphonylurea add-on to metformin) was chosen as the referent group. The IPTW analysis can be conceptualised as a process of re-weighting the data so the distribution of confounders becomes the same in the referent and comparator groups [21], and so the predicted probability of a chosen second-line therapy after metformin is based on balanced differences in baseline covariates. Standardised differences of means (for continuous variables) and proportions (for categorical variables) between each treatment group and the referent group (metformin plus sulphonylurea) were then calculated after propensity score estimation to assess the covariate balance between both groups. Standardised difference of <0.1 was used to denote balance between groups.

In addition to controlling for baseline co-medications in the IPTW calculation, co-medications were also modelled as a time-varying covariate by assessing their status on a 6-monthly basis for the full length of follow-up for each individual. Missing baseline BMI was imputed by an interpolation algorithm that has been used in previous studies using CPRD [22]. An algorithm for data cleaning was also used to manage smoking status inconsistencies and model smoking as a time-varying covariate in order to capture changes during follow-up.

The analysis was based on constructing survival (time-to-event) models to compare time to the pre-defined CVD outcome for comparator second-line regimens versus the referent second-line treatment group. Time to event was defined as the time between the index date to the earliest event among the composite cardiovascular outcome and the censoring date, whichever occurred first. Inverse probability of treatment weighted time-varying Cox regression was performed to estimate adjusted hazard ratios and 95% CI for the cardiovascular outcome. This analysis indicated the relative hazard of developing the endpoint upon exposure to each treatment regimen versus the referent regimen (metformin plus sulphonylurea). Two additional analyses were performed to assess the robustness of our findings. Firstly, we restricted our cohort to patients who entered the study from 2007 onwards to account for the availability of DPP-4 inhibitors. Secondly, we assessed the risk of major cardiovascular events in users of pioglitazone and rosiglitazone add-ons to metformin separately. We were unable to consider other individual drugs due to low numbers of patients prescribed these drugs. Schoenfeld residuals were used to test the assumption of proportional hazards. In all study comparisons, a two-sided p-value of <0.05 was used to denote statistical significance. All statistical analyses were performed using Stata v.13 (StataCorp LP, College Station, Texas, USA).

Results

A prevalent cohort of 82,568 patients diagnosed with type 2 diabetes before 31st December 2011 and registered in linked general practices was identified (Figure 1). Among this cohort, 56,737 patients were prescribed metformin monotherapy after diabetes diagnosis. Of these, 13,576 second-line therapy initiators within the study period were eligible for inclusion. Baseline BMI, Black ethnicity (versus White), low or unknown economic status, smoking, history of microvascular complications were significant predictors of the prescribed therapy. Three second-line add-on therapies with at least 1,000 users were identified among this cohort and accounted for 97.4% of all add-ons to metformin therapy. These were sulphonylurea (SU), dipeptidyl peptidase (DPP)-4 inhibitor or thiazolidinedione (pioglitazone or rosiglitazone) add-ons to initial metformin monotherapy (n=10,473). Among these patients, only those prescribed a DPP-4 inhibitor or a thiazolidinedione with estimated weights (based on overlapped probabilities with the referent group) were included in the analysis (n=10,118). Included patients were prescribed a sulphonylurea (n=6,740, 66.6%), a DPP-4 inhibitor (n=1,030, 10.2%) or a thiazolidinedione (n=2,348, 23.2%) add-on to metformin (Table 1). The patterns of the prescribed second-line medications are provided in the supplementary data. Overall, 87% of sulphonylurea users were prescribed gliclazide; 78% of DPP-4 inhibitor users were prescribed sitagliptin; and 54% of thiazolidinedione users were prescribed rosiglitazone. Overall, mean (±SD) age at index was 61.7 years (±10.5); 39% were females; 78% White; duration on metformin monotherapy 2.2 years (±1.9); and HbA_{1c} 8.7% (±1.5) [71.2mmol/mol (±15.9)]. Estimated standardised differences showed a markedly improved covariate balance in comparison to before IPTWs calculation.

During mean 2.4 (±1.9) years of overall follow-up (total of 23,789 person-years), 517 major cardiovascular events occurred. The number of observed events in the add-ons of sulphonylurea, DPP-4 inhibitor and thiazolidinedione were 386; 36; and 95 occurred during 2.4 (±2.0) years; 1.9 (±1.3) years and 2.5 (±2.0) years of follow-up, respectively. Crude event rates (95% CI) for cardiovascular events per 1,000 person-years were 24.4 (22.04; 26.91) in patients prescribed metformin and sulphonylurea; 18.4 (13.26; 25.48) in patients treated with metformin and DPP-4 inhibitor; and 15.9 (12.99; 19.42) in patients prescribed metformin and thiazolidinedione. Figure 2 shows Kaplan–Meier survival plots and the number of patients at risk in the three treatment groups. In comparison to metformin-sulphonylurea initiators, fully-adjusted HRs (95% CI) for the composite major cardiovascular outcome were 0.78 (0.55; 1.11) [P=0.17] when adding a DPP-4 inhibitor and 0.68 (0.54; 0.85) [P=0.001] when adding a thiazolidinedione to metformin. Individuals from the most-disadvantaged areas had higher cardiovascular risk than individuals from affluent areas [HR: 1.49, 95% CI 1.11; 2.00, P=0.008]. Adjusted HRs (95% CI) for time-varying co-medications and smoking status were also estimated (Table 2). The overall proportionality test revealed a non-violated proportional hazard assumption [P=0.47].

The two additional analyses showed similar estimates to those reported in the main analysis. By restricting our cohort to patients who initiated second-line therapies ≥2007 the risk estimates remained the same as in the main analysis. In the sensitivity analysis where thiazolidinediones regimens were examined separately, adjusted HR (95% CI) was 0.58 (0.41; 0.80) [P=0.001] for pioglitazone users and 0.79 (0.58; 1.06) [P=0.115] for rosiglitazone users in comparison to sulphonylurea users. The proportional hazard assumption was met in both analyses [P=0.80 and P=0.53, respectively].

Discussion

Main findings

In this population-based study, data linkage to secondary care data and mortality records was utilised. Using a well-defined cohort and advanced statistical methods, we showed that patients who added a thiazolidinedione as a second-line agent to metformin had lower risk of a major cardiovascular event than those who added sulphonylurea. Although non-statistically significant, DPP-4 inhibitor add-on to metformin was also associated with lower cardiovascular risks in comparison to sulphonylurea add-on to metformin. These findings suggest cardiovascular benefits of thiazolidinediones added as second-line therapy over sulphonylureas, whereas there was no statistically significant cardiovascular benefit in patients treated with DPP-4 inhibitors.

Strengths and limitations

Our study has several important strengths. First, our population-based data from CPRD was linked to hospital episode statistics (HES) data and the Office for National Statistics (ONS) death registry data to maximise capture of recorded events and ascertain cardiovascular deaths. This is critically important because a substantial proportion (20-25%) of coronary events are missed when using individual datasets [23]. Second, we assessed the cardiovascular safety of several second-line regimens, after initiation of basal metformin to make our results relevant to clinical practice. Third, we applied conservative inclusion and exclusion criteria to increase the validity of our results. Fourth, our cases were identified using diagnostic clinical code lists reviewed by expert clinicians. This is important because some published reports used diabetes prescriptions only to identify patients with type 2 diabetes. Fifth, we used propensity score analyses to minimise confounding by indication; advanced multiple imputation

technique to impute missing BMI values; and also adjusted for important clinical time-varying risk factors such as concurrent medications and smoking status. Sixth, we controlled for index year to adjust for the introduction of newer drug classes and improvements in clinical management of CVD over time. Seventh, the supplementary analyses confirmed the robustness of our findings. Finally, in addition to adjusting for primary risk factors such as HbA_{1c} and BMI, omitted in some previous studies, we adjusted for ethnicity and socio-economic class as important cardiovascular risk factors.

We acknowledge some limitations of our work. First, the study had a relatively short duration of follow-up as treatment change was the main cause of censoring. Second, data on alcohol use and hypoglycaemia are not adequately captured in CPRD and therefore we could not assess their association with the outcome. Third, the use of prescription refills as a proxy to define exposure may have resulted in possible exposure misclassification, due to variable adherence to prescribed medications, and dichotomisation of exposure to post-index co-medications may not fully account for exposure. Fourth, although our study cohort is widely representative of the UK population, our findings may not be generalizable to some patients with type 2 diabetes such as those who did not start on metformin monotherapy. Fifth, point estimates indicate possible cardiovascular benefits with DPP-4i add-on but our study appeared underpowered to demonstrate this. Finally, although we adjusted for many potential confounders, we cannot exclude the possibility of residual confounding due to unmeasured confounders.

Prior studies

Selecting the optimal medication among the available therapies is a challenging decision for practitioners because there have been few studies that have compared the long-term effects of these therapies. Past studies examining the cardiovascular risk

profile of diabetes therapies may have been limited by not accounting for subsequent treatment changes [24]; selection bias [25] such as immortal time bias [26] or using all-cause mortality as a surrogate measure for cardiovascular mortality [9, 26].

Our findings are similar to some prior observational studies assessing the cardiovascular risk associated with sulphonylurea therapy. Despite the reported cardiovascular benefits of sulphonylureas in the United Kingdom Prospective Diabetes Study (UKPDS) 80 [27], concerns were raised regarding some cardiovascular adverse effects of sulphonylurea compared to other therapies [13, 28]. A large retrospective study observed significantly higher risk of congestive heart failure and all-cause mortality in sulphonylurea-treated patients compared to those treated with metformin [29]. However, the study was potentially limited by issues in defining drug exposure intervals.

In another cohort study of 5,730 newly-diagnosed patients with type 2 diabetes in Tayside, Scotland, the risks of cardiovascular hospitalisation, all-cause and cardiovascular deaths were significantly higher with sulphonylurea therapy alone or with a sulphonylurea-metformin combination when compared to metformin therapy alone [30]. However, the study design used allowed some patients to contribute to two exposures and no robust measures were taken to account for the observed baseline differences among participants.

Based on these reports it is possible to assume that the higher risk associated with metformin-sulphonylurea combination observed in our study might be attributed to the adverse effects of the sulphonylurea component, as previously proposed; a position that is supported by the known cardiovascular benefits of metformin [31, 32]. The adverse cardiovascular outcomes associated with sulphonylureas could be mediated by closure of the cardioprotective K_{ATP} channels in myocytes which could promote myocardial ischemia [33]. However, in contrast to our findings, a CPRD-based study

published in 2004 showed no evidence of a higher mortality risk with the sulphonylurea-metformin combination when compared to metformin or sulphonylurea alone [34]. Although adjusting for prevalent coronary heart disease and cardiovascular medications at baseline and considering treatment changes over time, the study had a smaller sample size (n=8,488), shorter follow-up (20,783 person years) than our presented study. Also, it did not take account of important risk factors such as HbA_{1c}, BMI, smoking status and other cardiovascular co-morbidities.

The results of the Nissen & Wolski (2007) meta-analysis [35] raised concerns about the cardiovascular safety of rosiglitazone, but our results showed cardiovascular benefits with thiazolidinediones when added to metformin. The observed benefits remained unchanged when we examined pioglitazone and rosiglitazone add-ons separately. This is consistent with a number of studies published after 2007 showing reduced or not increased cardiovascular risk with pioglitazone [25] and rosiglitazone [29].

In agreement with our results, previous studies have shown cardiovascular safety with DPP-4 inhibitors. Three recent randomised trials showed no significant effect of DPP-4 inhibitors on cardiovascular risk [36-38]. A meta-analysis of eight Phase 3 studies showed that treatment with linagliptin was associated with a lower risk of major cardiovascular events than active or placebo comparators [39]. Our results are generally in keeping with these studies but we are unable to exclude clinically significant effects due to the cohort's relatively small size and short follow-up (mean 1.9(±1.3) years). More recently, a study showed significant cardiovascular benefits of DPP-4 inhibitor versus sulphonylurea add-on therapies to metformin [17]. But, there were some methodological differences between both studies where we benefited from additional linkages to HES and ONS data to avoid outcome misclassification; our DPP-

4 inhibitor add-on cohort was smaller as we intentionally only included patients who were fully balanced on baseline covariates with the referent cohort.

Clinical implications and future research

Overall, our findings show significantly lower cardiovascular risk in patients treated with thiazolidinedione add-on therapies when compared to sulphonylurea. For pioglitazone, the risk was significantly lower, but for rosiglitazone this was numerically, but not significantly lower. These cardiovascular benefits were observed in a real-world setting and are highly relevant to clinical practice and should be considered, along with the other known benefits and risks of thiazolidinediones, when making a decision about second-line therapies in this patient population, where future thiazolidinediones trials may be greatly limited in scope and number. The reported findings are also of particular importance given the current suspension of rosiglitazone by the EMA and the strict conditions of use announced in 2013 by the FDA. Future research should focus on identifying the optimal target population for thiazolidinediones among type 2 diabetes patients. A pragmatic clinical trial, expected to complete in 2020, will compare the glucose-lowering effects and outcomes of sulphonylurea, DPP-4 inhibitors, glucagon-like peptide-1 analogues and insulin in newly-diagnosed patients treated with metformin [40]. The trial's results are expected to provide valuable data to inform future guidelines.

Conclusions

Our retrospective cohort study based on UK primary care linked records assessed the cardiovascular risk associated with common dual second-line diabetes therapies and showed cardiovascular benefits of thiazolidinedione add-on therapy to metformin in comparison to sulphonylurea-metformin combination. DPP-4 inhibitors-metformin

combination was also associated with lower, but non-significant, cardiovascular risks than sulphonylurea-metformin combination. This finding may suggests cardiovascular benefits of DPP-4 inhibitors if examined in larger and long-term studies.

With the ongoing uncertainty regarding the optimal second-line therapy, our observations present new evidence on the cardiovascular safety of thiazolidinediones. The high cardiovascular risk in type 2 diabetes patient population calls for further randomised controlled trials and larger observational studies with longer follow-up to provide further data on the cardiovascular safety and efficacy of different glucose lowering regimens.

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Conflict of interest

DMA reports grant funding from Abbvie and serving on advisory boards for Pfizer and GSK. MKR reports grant funding from GSK, Novo Nordisk and Pfizer, modest stock

ownership in GSK and education support funding from MSD and Novo Nordisk. DTS, RAE, and SSZ state no conflict of interest.

Contribution statement

DTS, DMA, MKR and SSZ contributed to the study design. SSZ extracted and analysed the data and wrote the initial manuscript, and all authors reviewed and edited the manuscript before submission. SSZ performed all the statistical analyses supervised by DTS, DMA and RAE. SSZ had full access to all the study data and takes responsibility for the integrity of the data and the accuracy of data analyses. SSZ's sponsor was not involved in the study design, data collection, analysis of the results, or preparation of the manuscript.

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Figure legends:

Figure 1: Flow diagram of the study cohort (CRD: current registrations date; DPP: dipeptidyl peptidase; GP: general practice; SU: sulphonylurea; TZD: thiazolidinedione; UTS: up-to-standard

Figure 2: Kaplan-Meier survival plots and the number at risk for the composite cardiovascular endpoint among 10,118 patients treated with DPP-4i (dipeptidyl peptidase-4 inhibitors) (red solid line) or thiazolidinediones (green dashed line) compared to SU (sulphonylureas) (blue dotted line) when added to Met (metformin) monotherapy.

Table 1: Baseline characteristics of second-line therapy initiators

Characteristic	Metformin +SU (n= 6,740)	Metformin +DPP-4i (n= 1,030)	Standardised difference[a]	Metformin +TZD (n= 2,348)	Standardised difference[a]
Age (years)	62.5±10.8	60.0±10.0	-0.062	60.1±9.8	-0.031
Gender, female	2,644(39.2)	420 (40.8)	-0.042	869 (37.0)	0.016
IMD (quintiles)[b]					
Quintile 1	1,316(19.5)	208 (20.2)	-0.007	449 (19.1)	-0.006
Quintile 2	1,538(22.8)	210 (20.4)	-0.023	521 (22.2)	-0.024
Quintile 3	1,291(19.2)	217 (21.0)	0.043	468 (19.9)	0.015
Quintile 4	1,360(20.2)	175 (17.0)	-0.025	391 (16.7)	-0.009
Quintile 5	1,092(16.2)	183 (17.8)	-0.009	433 (18.4)	0.020
Unknown	143 (2.1)	37 (3.6)	0.049	86 (3.7)	0.017
Ethnicity					
White	5,242(77.8)	787 (76.4)	0.003	1,830 (77.9)	0.001
Black	149 (2.2)	11 (1.1)	-0.018	22 (0.9)	-0.021
Asian	308 (4.6)	56 (5.4)	0.001	82 (3.5)	0.009
Other	92 (1.4)	11 (1.1)	-0.020	32 (1.4)	-0.005
Unknown	949(14.0)	165 (16.0)	0.010	382 (16.3)	0.005
Diabetes duration (years)	3.7±3.1	3.7±2.7	-0.021	3.2±2.7	0.009
Duration of metformin treatment (years)	2.3±1.9	2.5±2.0	-0.012	2.0±1.6	0.013
BMI (kg/m^2)	31.9±6.1	34.1±6.5	0.054	33.3±6.4	0.056
HbA_{1c} (%) [mmol/mol][c]	8.7±1.5 [71.7±16.6]	8.5±1.3 [69.7±14.5]	-0.024[d]	8.6±1.3 [70.4±14.3]	-0.013[d]
Current smokers	1,152(17.1)	135 (13.1)	-0.016	412 (17.6)	-0.017
Co-medications					
Diuretics	1,938(28.8)	279 (27.1)	-0.016	689 (29.3)	-0.016
α- receptor blockers	401 (6.0)	47 (4.6)	-0.007	150 (6.4)	-0.022
β- receptor blockers	1,486(22.1)	195 (18.9)	0.022	495 (21.1)	-0.017
Calcium channel blockers	1,809(26.8)	273 (26.5)	0.005	604 (25.7)	0.016
ACE inhibitors	3,009(44.6)	453 (44.0)	0.023	1,075 (45.8)	0.002
ARBs	889(13.2)	186 (18.1)	-0.010	316 (13.5)	0.031
Antiplatelet drugs	2,833(42.0)	340 (33.0)	0.003	1,051 (44.8)	-0.034
Statins	5,174(76.8)	822 (79.8)	0.039	1,866 (79.5)	0.006
NSAIDs	695(10.3)	110 (10.7)	0.005	279 (11.9)	0.003
Co-morbidities					
Myocardial infarction	424 (6.3)	52 (5.1)	0.030	125 (5.3)	0.004
Stroke	211 (3.1)	22 (2.1)	-0.016	53 (2.3)	-0.013
Heart failure	205 (3.0)	24 (2.3)	0.008	36 (1.5)	-0.005
Atrial fibrillation/flutter	347 (5.2)	41 (4.0)	-0.030	87 (3.7)	-0.014
Hypertension	4,000(59.4)	606 (58.8)	-0.010	1,395 (59.4)	-0.005
PVD	218 (3.2)	28 (2.7)	0.006	48 (2.0)	-0.014
Microvascular complications	905(13.4)	164 (15.9)	-0.032	207 (8.8)	0.007
Chronic kidney disease	546 (8.1)	70 (6.8)	-0.011	87 (3.7)	-0.001
Rheumatoid arthritis	75 (1.1)	12 (1.2)	-0.005	25 (1.1)	0.004

Data are reported as means±SD and n (%). Abbreviations: **ARB**: angiotensin-II receptor blocker; **DPP-4i**: dipeptidyl peptidase-4 inhibitor; **IMD**: index of multiple deprivation; **NSAID**: non-steroidal anti-inflammatory drug; **PVD**: peripheral vascular disease; **SU**: sulphonylurea; **TZD**: thiazolidinedione. [a]Standardised differences of means (continuous variables) and proportions (categorical variables) between each treatment group and the metformin plus SU referent group. [b]IMD quintile 1 is the least deprived area and quintile 5 is the most deprived area. [c]The most recent measure over the last 12 months. [d]Standardised difference based on the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units (mmol/mol).

Table 2: Adjusted hazard ratios (HR) and 95% CI associated with second-line therapies for developing a major cardiovascular event

Covariate	HR (95% CI) [P value]
Metformin + Sulphonylurea	1.00
Metformin + DPP-4 inhibitor	0.78 (0.55; 1.11) [P=0.17]
Metformin + Thiazolidinedione	0.68 (0.54; 0.85) [P=0.001]
Time-varying smoking status	
• **Non-smoker**	1.00
• **Ex- smoker**	1.35 (0.93; 1.97) [P=0.12]
• **Current smoker**	1.91 (1.26; 2.90) [P=0.002]
• **Unknown status**	1.76 (1.24; 2.51) [P=0.002]
Time-varying co-prescriptions	
• **α-adrenoceptor blockers**	0.82 (0.60; 1.14) [P=0.24]
• **β-adrenoceptor blockers**	2.65 (2.21; 3.18) [P=0.000]
• **Calcium channel blockers**	1.24 (1.03; 1.50) [P=0.02]
• **ACE inhibitors**	1.19 (0.98; 1.45) [P=0.08]
• **ARBs**	1.03 (0.79; 1.33) [P=0.83]
• **Diuretics**	1.15 (0.96; 1.39) [P=0.13]
• **Statins**	0.74 (0.59; 0.94) [P=0.01]
• **Antiplatelet agents**	2.47 (2.02; 3.01) [P=0.000]
• **NSAIDs**	0.91 (0.70; 1.19) [P=0.48]

Abbreviations: **ARB**: angiotensin-II receptor blocker; **DPP**: dipeptidyl peptidase; **NSAID**; non-steroidal anti-inflammatory drug.

Figure 1

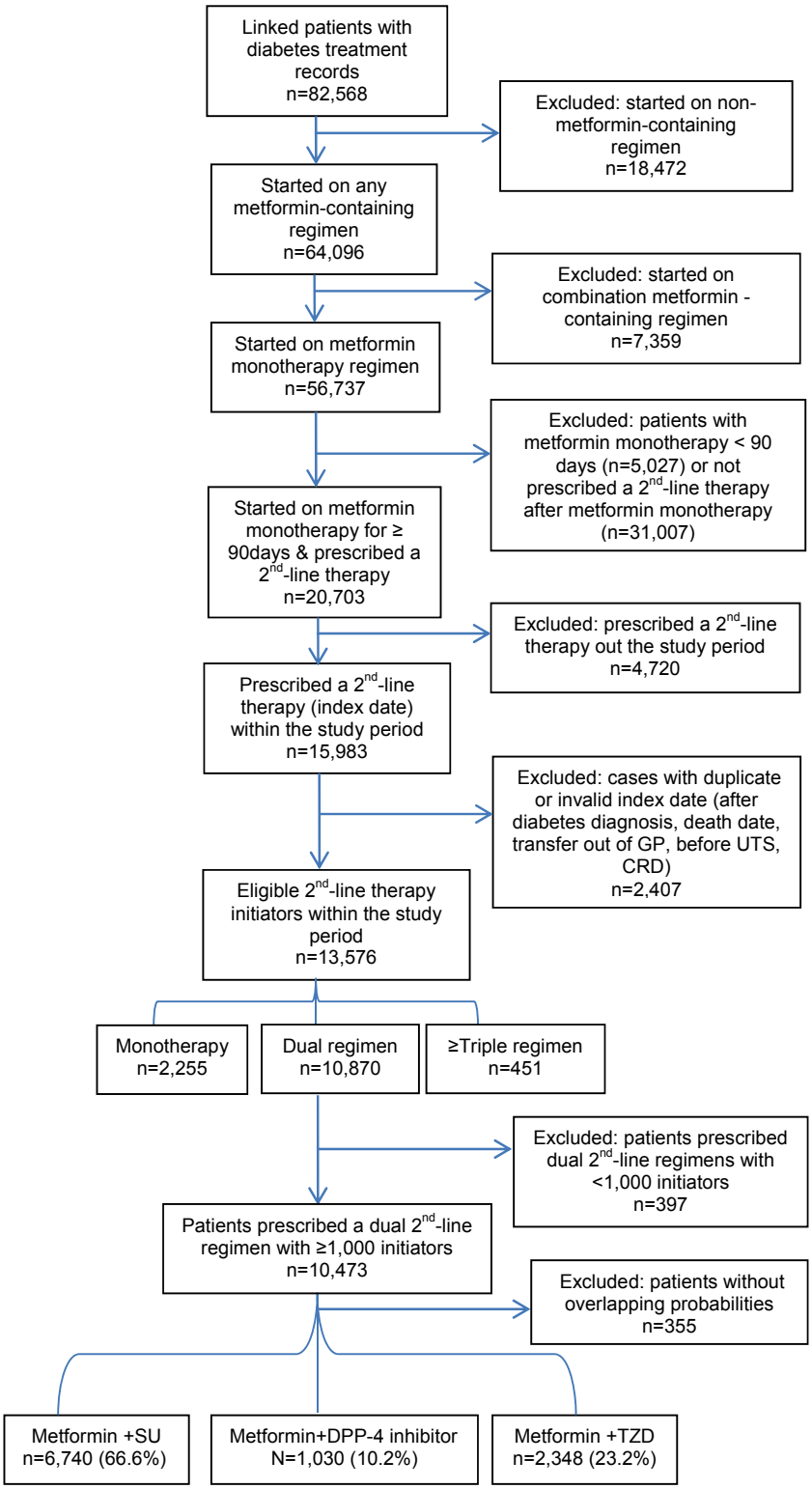
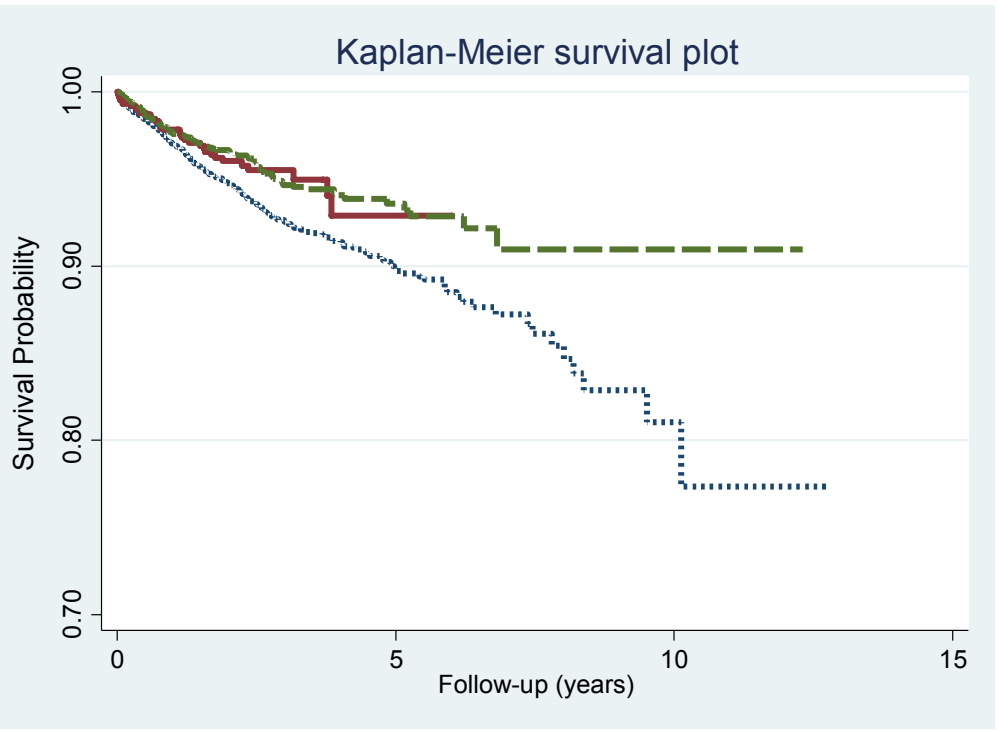


Figure 2



Number at risk								
Met+SU	6740	3313	1223	352	114	26	5	<5
Met+DPP-4i	1030	484	68	<5	<5	<5	<5	<5
Met+TZD	2348	1235	495	152	26	<5	<5	<5