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Cardiovascular events and all-cause mortality associated with sulfonylureas compared to other antihyperglycaemic drugs: A Bayesian meta-analysis of survival data

Steve Bain, MD[1] Eric Druyts, MSc[2,3] Chakrapani Balijepali, PhD[3,4] Carl A Baxter, PhD[5] Craig Currie, <insert degree>[6,7] Romita Das, <insert degree>[5] Richard Donnelly, MD[8] Kamlesh Khunti, PhD[9] Haya Langerman, MSc[5] Paul Leigh, MD[10] Matteo Monami, MD[11] Gaye Siliman, MSc[3] Jiten Vora, MD[12] Kristian Thorlund, PhD[3,13] Edward J Mills, PhD[3,14]

1. Diabetes Research Group, College of Medicine, Swansea University, Swansea, United Kingdom
2. Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
3. Redwood Outcomes, Vancouver, British Columbia, Canada
4. Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia, Canada
5. MSD Ltd, Hertford Road, Hoddesdon, United Kingdom
6. Global Epidemiology, Pharmatelligence, Cardiff, United Kingdom
7. Cochrane Institute of Primary Care and Public Health, Cardiff University, Cardiff, United Kingdom
8. School of Medical & Surgical Sciences, University of Nottingham, Derby, United Kingdom
9. University of Leicester, Leicester, United Kingdom
10. AstraZeneca, United Kingdom
11. Geriatric Cardiology, Careggi Teaching Hospital, Florence, Italy
12. Royal Liverpool University Hospital, Liverpool, United Kingdom
13. Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada

14. Stanford Prevention Research Center, Stanford University School of Medicine, Palo Alto, California, United States of America

Correspondence: Dr Edward Mills, 302-1505 West 2nd Ave, Vancouver, British Columbia, Canada; emills@redwoodoutcomes.com

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ABSTRACT

Importance: Antihyperglycaemic drugs can have different, often divergent, effects on cardiovascular risk and mortality.

Objective: To conduct a systematic review and meta-analysis to determine the risk of cardiovascular events and all-cause mortality associated with sulfonylureas versus other antihyperglycaemic drugs.

Data sources and study selection: A systematic review of Medline, Embase, Cochrane, and clinicaltrials.gov (Inception-December 2014) was conducted. Study selection occurred in duplicate. Eighty-two randomized clinical trials (RCTs) and 26 observational studies comparing sulfonylurea to placebo or other antihyperglycaemic drugs in patients with type 2 diabetes were included.

Data extraction and synthesis: Data were extracted in duplicate for study, intervention, patient characteristics, and outcomes. Since RCT outcomes data were reported as binary data, but at different time points, a *cloglog* model was employed in the Bayesian framework to obtain comparative hazard ratios between interventions. For the analysis of observational data, conventional fixed-effect pairwise meta-analyses were employed to pool adjusted hazard ratios for each pair wise treatment comparison.

Main outcomes and measures: The following outcomes were of interest: all-cause mortality, cardiovascular-related mortality, acute myocardial infarction, and stroke.

Results: Analyses of RCT data showed an increased risk of all-cause mortality and cardiovascular related mortality for sulfonylureas compared to all treatments combined (HR 1.26, 95% CI 1.10-1.44 and HR 1.46, 95% CI 1.21-1.77, respectively). These results were corroborated in the analyses of observational studies. The risk of myocardial infarction was significantly higher for sulfonylureas compared to DPP-4 inhibitors and SGLT-2 inhibitors (HR 2.54, 95% CI 1.14-6.57 and HR 41.80, 95% CI 1.64-360.4, respectively), but not in other classes of treatments. Observational studies confirmed an increased risk of myocardial infarction for sulfonylureas compared to all other treatments combined. The RCTs showed that the risk of stroke was significantly higher for sulfonylureas compared to DPP-4 inhibitors, GLP-1 agonists, TZDs, and insulin (HR 9.40, 95% CI 3.27-41.9; HR 45.40, 95% CI 1.99-362.7; HR 1.75, 95% CI 1.20-2.69; and HR 1.46, 95% CI 1.01-2.14, respectively).

Conclusions: This study shows that sulfonylurea therapy is generally associated with a higher risk of major cardiovascular disease-related events compared to other antihyperglycaemic drugs and this risk increases over time.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is known to increase the risk of cardiovascular (CV) disease, with a 3–5 fold increased risk of life-threatening events such as acute myocardial infarction (MI) and stroke.[1,2] Recent trials have shown that glucose-lowering treatments may have different, sometimes divergent, effects on CV risk.[3] Sulfonylureas (SUs) are among the most commonly used treatments for patients with T2DM, yet their long-term safety and their effects on CV outcomes remain uncertain and controversial.[4]

The possibility that SUs increase CV risk is rooted in clinical and experimental evidence that extra-pancreatic KATP channels and SU receptors are expressed abundantly in cardiac myocytes (SUR2A) and vascular smooth muscle cells (SUR2B). Off-target KATP channel blockade in the heart and vascular smooth muscle cells may lead to adverse CV events.[5] Animal and human studies have shown that SU binding to SUR2A and SUR2B receptors causes adverse effects on CV function, especially in the context of myocardial ischaemia.[6,7] SUs act on the myocardial ATP-sensitive potassium channel, which can impair the ability of myocardiocytes to adapt to ischaemia, thus affecting cardiac function in patients with ischaemic heart disease.[8] Furthermore, SUs may also have harmful, indirect effects on CV function, e.g. via hypoglycaemia-induced changes in QT-interval and arrhythmogenesis,[9] pro-thrombotic effects and endothelial dysfunction.[10,11]

There is no single published randomized clinical trial (RCT) that has examined the risk of CV events between SUs and a wide spectrum of commonly prescribed

antihyperglycaemic drugs. Several systematic reviews and meta-analyses have compared SUs with a variety of antihyperglycaemic drugs. However, findings of these studies are inconsistent; this is largely because of differences in study selection and statistical techniques used to analyze the data.[12-19] The most recent meta-analysis on this topic was presented by Rados et al at the American Diabetes Association 2015 Scientific Sessions.[19] These investigators generally concluded that SUs are not associated with increased mortality, with the exception of glipizide, which increased the risk for total and CV-related mortality. Another recent meta-analysis, by Monami et al,[13] showed increased mortality and a higher risk of stroke with SUs. However, the only comparison where results were statistically significant was the increased odds of a CV event for patients on a SU in comparison to those on a DPP-4 inhibitor. Furthermore, a study by Simpson et al focused on the difference in risk between SUs, and found that gliclazide and glimepiride were associated with a lower risk of all-cause and CV-related mortality when compared with glibenclamide.[20]

Using advanced meta-analytical techniques, the aim of this study was to assess the risk of CV-related outcomes associated with SUs versus other antihyperglycaemic drugs using data from RCTs and comparative observational studies. Analyses of survival data were performed separately for both RCT evidence and observational evidence to facilitate a multi-level inference approach.

METHODS

Overview

We conducted a systematic literature review to identify studies that compared SU monotherapy or a SU in combination with another antihyperglycaemic drug against placebo/no intervention or other antihyperglycaemic drugs. Data derived from the studies identified in the systematic literature review were used to compare the risk of CV events associated with the use of SUs and the other selected treatments.

Eligibility criteria

The eligibility criteria used to select studies in the systematic literature review are presented according to the PICOS (population, intervention, control, outcomes, study design) convention (**eTable 1**). In brief, RCTs and non-randomized comparative studies, including prospective or retrospective observational cohort studies and case-control studies, conducted among adult patients diagnosed with T2DM who were either treatment naïve or had prior exposure to antihyperglycaemic drugs were eligible for inclusion. Eligible interventions included SU monotherapy or a SU in combination with a biguanide or another antihyperglycaemic drug (i.e. biguanides, dipeptidyl peptidase protein-4 [DPP-4] inhibitors, glucagon-like peptide-1 [GLP-1] agonists, sodium-glucose linked transporter-2 [SGLT-2] inhibitors, thiazolidinediones [TZDs], insulin). Eligible comparators included placebo/no intervention or other antihyperglycaemic drugs. Outcomes of interest included all-cause mortality, CV-related mortality, acute MI, and stroke.

Literature search

A systematic search of the peer-reviewed literature was conducted in Medline, Embase, and Cochrane Register of Controlled Trials from inception to December 2014 (**eTable 2** presents the search strategy used). Additionally, clinicaltrials.gov was searched to identify potentially eligible RCTs with results that had not yet been published in a peer-reviewed journal.

Two investigators independently identified relevant abstracts and full-text publications based on the eligibility criteria. If any discrepancies occurred between the studies selected by the two investigators, a third investigator provided arbitration. For all the articles that were not published in English language, a separate search was conducted using the author names to see if a relevant publication in English exists. If not, non-English publications were discarded.

Data extraction

Two reviewers working independently extracted data on study characteristics, interventions, patient characteristics at baseline, and outcomes for the study populations of interest for the eligible studies. If discrepancies occurred between the data extracted by the two reviewers, these differences were reconciled by involving a third reviewer. In the event that the third reviewer could not resolve a disagreement, the authors of the publication were contacted for clarification.

Data on all outcomes were extracted as intention-to-treat analyses, where all dropouts were assumed to be treatment failures, wherever trial reporting allowed this. For studies that reported "per-protocol" results only, these were extracted and used in the analyses. For observational studies, we focused on extracting adjusted estimates representing comparative effects through hazard ratios, odds ratios, or relative risks as intention-to-treat and per-protocol issues were not relevant.

Study quality

For included RCTs, we assessed the validity of individual trials using the Risk of Bias instrument, endorsed by the Cochrane Collaboration.[21] This instrument is used to evaluate six key domains: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias.

For observational studies, we used the Newcastle-Ottawa scale. Using the scale, each study is judged on eight items, categorized into three groups: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. Stars awarded for each quality item serve as a quick visual assessment.

The same two reviewers extracting data conducted the quality assessment. If disagreements between the reviewers occurred, we resolved these by including a third

reviewer, and if necessary, contacting the authors of the publication for clarification. No studies were excluded on the basis of quality.

Evidence synthesis

Treatments were grouped according to drug class. First- and second-generation SUs were treated as one group. Other drug classes included biguanides, DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors, TZDs, and insulins. When biguanides were used as background therapy, the intervention therapy was analyzed as a monotherapy.

For all four outcomes (all-cause mortality, CV-related mortality, acute MI, and stroke), meta-analysis was employed to establish comparative efficacy between SU versus other drug classes. The hazard ratio was employed as a primary effect measure (i.e. primary analysis) to evaluate comparative efficacy. Analyses were performed separately for RCT evidence and observational evidence to facilitate a multi-level inference approach.

For the primary analysis of RCT data, a Bayesian hierarchical approach was employed in the framework of indirect treatment comparisons. The choice whether to use a fixed- or random-effects model was determined by comparing the values of the deviance information criterion for each model as well as assessing the heterogeneity variance provided in the random-effects model. Since RCT data were only available as binary data, but at differing time points, and since the effect measure of interest was the hazard ratio, a binomial model with a *cloglog* link function and a time offset (*cloglog* model) was employed in the Bayesian framework to obtain comparative hazard ratios between

interventions.[22] For the primary analysis of observational data, conventional fixed-effect pairwise meta-analyses were employed to pool adjusted hazard ratios for each pair-wise treatment comparison.

Since the outcomes typically only occurred once, we assumed that adjusted relative risks from observational studies could be considered similar to adjusted hazard ratios, and thus pooled the two where relevant. From the *cloglog* model of RCT data, we further estimated the survival functions for each of the interventions of interest. From these survival functions, we calculated the absolute difference in risk of each outcome between SU and each of the other interventions. We additionally calculated the same absolute differences in risk based on the observational data, using the estimated survival function for SU and the pooled (observational) hazard ratios to produce survival functions for the other interventions.

We produced two types of forest plots to graphically display the results. The first compared the study specific estimates provided in each study and the second compared the relative efficacies between treatments as estimated in the analysis. In traditional meta-analysis, forest plots are used to present the results from individual studies and the synthesized result from the analysis, providing a visual assessment of the statistical heterogeneity. Statistical heterogeneity is caused by differences in factors that influence the outcome or the intervention, such as prognostic factors. As explained above, our analyses account for an important effect modifier, namely time. Longer follow-up periods lead to higher probabilities of an event occurring.

Since rosiglitazone has been suspended in many settings due to concerns of CV safety,[3] a sensitivity analysis was conducted excluding this treatment from the TZD class.

All Bayesian analyses were performed in WinBUGS v3.1.4, and all conventional meta-analyses and figures were performed and produced using R v3.1.2.

RESULTS

Included studies

The systematic literature review yielded 14,841 abstracts for screening. Subsequently 830 full-text articles were reviewed, of which 722 were excluded: 64 due to an ineligible population, 93 due to an ineligible intervention, 36 due to an ineligible comparison, 393 due to lack of outcomes of interest, 126 due to an ineligible study design, and 10 for other (e.g. study not in English language). Of these, 108 studies were included (82 RCTs and 26 observational studies). The flow of study selection is presented in **eFigure 1**, and the summary of baseline characteristics and quality of included studies is presented in **eTable 3 – eTable 8**.

All-cause mortality

The results of the analysis of all-cause mortality for the RCT and observational evidence are detailed in **Table 1** and **Figure 1.A**. Additionally, **eFigure 2** presents the forest plot for showing individual study results. When considering RCT evidence, the results indicate an increased risk of all-cause mortality for SUs in comparison to all other active treatments (HR 1.26, 95% CI 1.10-1.44). Four of these comparisons were statistically significant: SUs versus biguanides (HR 1.37, 95% CI 1.03-1.84), DPP-4 inhibitors (HR 2.03, 95% CI 1.22-3.58), TZDs (HR 1.54, 95% CI 1.14-2.10), and insulins (HR 1.21, 95% CI 1.01-1.45). When compared to no active treatment, SUs demonstrated an increase in risk, however this was not statistically significant.

Where observational evidence was available, results trended in the same direction as the RCT evidence, with the exception of SUs versus insulins. Each comparison using observational evidence was statistically significant.

Cardiovascular-related mortality

The results of the analyses of the risk of CV-related mortality are presented in **Table 1** and **Figure 1.B**. In addition, **eFigure 3** provides the forest plot showing individual study results. Analyses of RCT evidence indicated that there is an increased risk of CV related mortality for SUs in comparison to all other active treatments (HR 1.46, 95% CI 1.21-1.77). These results were statistically significant for SUs versus DPP-4 inhibitors (HR 4.42, 95% CI 1.92-13.0), GLP-1 agonists (HR 45.4, 95% CI 2.07-362.8), SGLT-2 inhibitors (HR 42.6, 95% CI 1.71-359.1), TZDs (HR 3.05, 95% CI 1.79-5.54), and insulins (HR 1.30, 95% CI 1.02-1.66). When compared to no active treatment, SUs demonstrated an increase in risk, however this was not statistically significant.

Observational data were only available for the SU versus no treatment and insulin comparisons. Similar to the RCT evidence, SUs tended to have a greater risk of CV-related mortality with the observational evidence, however this was not statistically significant. When considering SUs versus insulins with observational evidence, the risk of CV-related mortality was in the opposite direction of the RCT data, although this estimate was not statistically significant.

Acute myocardial infarction

The results of the analyses of the risk of acute MI are provided in **Table 1** and **Figure 1.C**. Additionally, **eFigure 4** presents the forest plot showing the individual study results. The analyses of RCT evidence demonstrated that SUs increased the risk of acute MI in comparison to all other active treatments, with the exception of insulins. These results were statistically significant for SUs versus DPP-4 inhibitors (HR 2.54, 95% CI 1.14-6.57) and SGLT-2 inhibitors (HR 41.8, 95% CI 1.64-360.4). Although results indicate a decrease in the risk of acute MI for SUs compared to no active treatment, this comparison was not statistically significant.

Observational data were also available for the comparison of SUs versus TZDs. The increased risk of acute MI with the use of SUs compared to TZDs was statistically significant when considering observational evidence.

Stroke

The results of the analyses of the risk of stroke are provided in **Table 1** and **Figure 1.D.** In addition, **eFigure 5** presents the forest plot showing the individual study results. The analysis of RCT evidence indicated that SUs increased the risk of stroke relative to all other active treatments. These results were statistically significant for the comparisons of SUs versus DPP-4 inhibitors (HR 9.40, 95% CI 3.27-41.9), GLP-1 inhibitors (HR 45.4, 95% CI 1.99-362.7), TZDs (HR 1.75, 95% CI 1.20-2.69), and insulins (HR 1.46, 95% CI 1.01-2.14). When SUs were compared to no active treatment, there was an increase in

risk, however this estimate was not statistically significant. No observational data were available for this outcome.

Sensitivity analysis

When excluding rosiglitazone in the comparison of SUs versus TZDs, the risk of all-cause mortality (HR 3.58, 95% CI 1.87-7.87), CV-related mortality (HR 3.62, 95% CI 1.88-7.96), acute MI (HR 1.44, 95% CI 0.87-2.50), and stroke (HR 2.07, 95% CI 1.12-4.19) increased with the RCT evidence base. However, when removing rosiglitazone in the analyses of the observational evidence base, the results were comparable.

DISCUSSION

This study is the most comprehensive review of RCTs and observational studies to compare CV-related outcomes and all-cause mortality among patients with T2DM treated with a SU versus other antihyperglycaemic agents, including insulin and the newer drugs such as SGLT-2 inhibitors. Results for the RCT pooled hazard ratios indicate that treatment with a SU was associated with a significantly higher risk of all-cause mortality and CV-related mortality when compared to all other treatments. The differences ranged from a doubling of mortality risk versus a DPP-4 inhibitor to more modest differences relative to insulin or metformin treatment. Some of the confidence intervals were wide, but the significant results all trended in the same direction. All-cause mortality and CV-related mortality had the greatest number of statistically significant results and the analysis of observational studies generally supported the results from RCTs.

There were two major discrepancies between the observational and RCT analyses. First, the comparison of SU and insulin for the outcome of CV-related mortality; RCT results showed a significant increase in risk for SUs, while observational results showed a decrease in risk. The observational data were, however, sparse (only two trials available) which may explain the lack of statistical significance. The second was the comparison of SU and insulin for the outcome of all-cause mortality; the RCT results showed a significant increase in risk while the observational evidence suggested a significant decrease. However, the observational data exhibited significant heterogeneity as identified with the Cochrane-Q (p-value < 0.001), which may explain this discrepancy.

Several systematic reviews have addressed similar topics concerning SU therapy.[9,12-15,18,20,23,24] However, these studies had important methodological limitations, in particular grouping treatments with diverse safety profiles, imprecise study inclusion criteria, non-systematic searches, and important analytical limitations. Four of the studies reported similar results to ours for all-cause mortality and CV-related mortality.[12,15,18,24] Two of these studies only included subsets of SUs.[9,23] Two of these reviews were associated with methodological limitations, such as incorrect inclusions, inconsistent reporting, and lack of a rigorous search strategy.[13,14] Finally, one recent review assessed CV outcomes, however this meta-analysis only included SUs and aimed to report on differences within this treatment class.[20]

SU-mediated inhibition of ischaemic preconditioning and hypoglycaemia-related arrhythmogenesis are the principal mechanisms cited to support the biological plausibility of a harmful link between SUs and CV disease. However, very few RCTs with SUs have included CV endpoints and the trials to date have been relatively small and of short duration. Future trials, e.g. the TOSCA.IT[25] and CAROLINA,[26] may provide important information but not for several years. Furthermore, the large studies that have been performed in patients with type 2 diabetes treated with SUs, e.g. UKPDS[27] and ADVANCE,[28] are of limited value since these trials evaluated the effects of glycaemic control rather than the effects of specific antihyperglycaemic agents. Thus, in the absence of conclusive RCT data, the present meta-analysis offers the most comprehensive overview of SU trials using Bayesian techniques to quantify relative differences in major CV outcomes and all-cause mortality versus placebo (or no

treatment) and other classes of antihyperglycaemic drugs, including insulin therapy and the SGLT-2 inhibitors. Our analysis includes RCTs and observational studies, and overcomes many of the limitations of earlier analyses.

The current analysis also has some limitations. First, the number of analyses conducted may have introduced multiplicity, i.e. a type one error (false positive) may have occurred in a comparison estimate. Second, the minimal amount of data in some analyses did not allow for robust effect estimates. For instance, low event counts in some comparisons (i.e. SU versus GLP-1 for CV-related mortality and stroke, and SU versus SGLT-2 for CV-related mortality and acute MI) resulted in wide confidence intervals and potentially misleading large risk differences. Third, our analyses focused on class effects to ensure sufficient sample sizes to detect differences; however, it should be recognized that individual SU treatments may differ in terms of mortality risk.[20] Finally, there are inherent flaws in meta-analyses, which rely on high-quality study data. The current study used a rigorous search and extraction method to ensure high quality evidence was integrated appropriately. Risk of bias assessments were performed for both RCTs and observational studies to summarize study quality.

Our findings generally indicated a higher risk of cardiovascular-related events associated with sulfonylureas compared to other antihyperglycaemic drugs. This risk increased over time, and it was confirmed in analysis of both clinical trial and observational studies.

Author Contributions: Dr Edward Mills had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Bain, Druyts, Mills

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Thorlund, Siliman

Administrative, technical, or material support: Balijepali

Study supervision: Mills

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Figure Titles and Legends

Figure 1.A: Forest plot presenting hazard ratio estimates of all-cause mortality for sulfonylureas versus other antihyperglycemic drugs

Figure 1.B: Forest plot presenting hazard ratio estimates of cardiovascular-related mortality for sulfonylureas versus other antihyperglycemic drugs

Figure 1.C: Forest plot presenting hazard ratio estimates of acute myocardial infarction for sulfonylureas versus other antihyperglycemic drugs

Figure 1.D: Forest plot presenting hazard ratio estimates of stroke for sulfonylureas versus other antihyperglycemic drugs
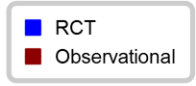
Table 1: Difference between sulfonylureas and other treatments for cardiovascular-related and mortality outcomes

Sulfonylurea vs	RCT	Observational	
	HR (95% CI)	HR (95% CI)	I^2 % (95% CI)
All-cause mortality			
No active treatment/ placebo	1.07 (0.90-1.28)	**1.13 (1.07-1.19)**	63.5 (14.2-79.3)[a]
Biguanide	**1.37 (1.03-1.84)**	**1.57 (1.48-1.66)**	0.00 (0.00-64.1)
DPP-4 inhibitor	**2.03 (1.22-3.58)**	**1.58 (1.36-1.83)**	0.00 (0.00-72.9)
GLP-1 agonist	1.85 (0.80-5.19)	-	-
SGLT-2 inhibitor	-	-	-
Thiazolidinedione	**1.54 (1.14-2.10)**	**1.50 (1.32-1.71)**	96.6 (93.9-97.8)[b]
Insulin	**1.21 (1.01-1.45)**	**0.82 (0.77-0.89)**	92.4 (86.7-95.0)[b]
Combined	**1.26 (1.10-1.44)**	**1.22 (1.18-1.26)**	92.4 (90.6-93.7)[b]
Cardiovascular-related mortality			
No active treatment/ placebo	1.25 (0.98-1.62)	1.16 (0.93-1.44)	73.9 (0.00-88.6)[a]
Biguanide	1.38 (0.90-2.16)	-	-
DPP-4 inhibitor	**4.42 (1.92-13.0)**	-	-
GLP-1 agonist	**45.4 (2.07-362.8)**	-	-
SGLT-2 inhibitor	**42.6 (1.71-359.1)**	-	-
Thiazolidinedione	**3.05 (1.79-5.54)**	-	-
Insulin	**1.30 (1.02-1.66)**	0.80 (0.52-1.24)	-
Combined	**1.46 (1.21-1.77)**	1.01 (0.89-1.14)	80.8 (58.6-88.6)[b]
Acute myocardial infarction			
No active treatment/ placebo	0.86 (0.70-1.06)	**-**	-
Biguanide	1.21 (0.78-1.99)	**-**	-
DPP-4 inhibitor	**2.54 (1.14-6.57)**	-	-
GLP-1 agonist	1.49 (0.45-5.41)	-	-
SGLT-2 inhibitor	**41.8 (1.64-360.4)**	-	-
Thiazolidinedione	1.13 (0.83-1.59)	**1.41 (1.23-1.62)**	36.7 (0.00-78.3)
Insulin	0.96 (0.78-1.18)	-	-
Combined	0.92 (0.78-1.08)	**1.34 (1.25-1.44)**	16.5 (0.00-67.1)
Stroke			
No active treatment/ placebo	1.26 (0.88-1.81)	-	-
Biguanide	1.40 (0.92-2.22)	-	-
DPP-4 inhibitor	**9.40 (3.27-41.9)**	-	-
GLP-1 agonist	**45.4 (1.99-362.7)**	-	-
SGLT-2 inhibitor	**-**	-	-
Thiazolidinedione	**1.75 (1.20-2.69)**	-	-
Insulin	**1.46 (1.01-2.14)**	-	-
Combined	1.09 (0.86-1.39)	-	-

Note: Bold text indicates statistical significance (95% confidence interval does not include 1.00); Pooled hazard ratios for RCTs were obtained by cloglog analysis; Random effect estimates were equivalent to fixed effect estimates for observational studies; Data reported is or the > 1 year time point; – not applicable due to lack of trial data; [a] - p-value < 0.01; [b] - p-value < 0.001

Figure 1.A: Forest plot presenting hazard ratio estimates of all-cause mortality for sulfonylureas versus other antihyperglycemic drugs
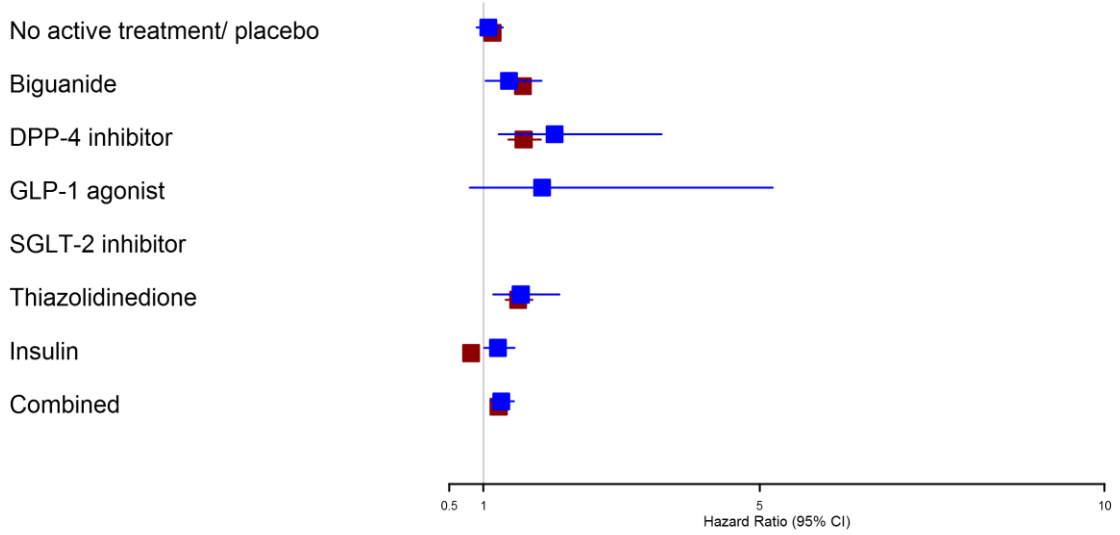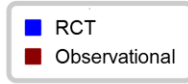
Figure 1.B: Forest plot presenting hazard ratio estimates of cardiovascular-related mortality for sulfonylureas versus other antihyperglycemic drugs
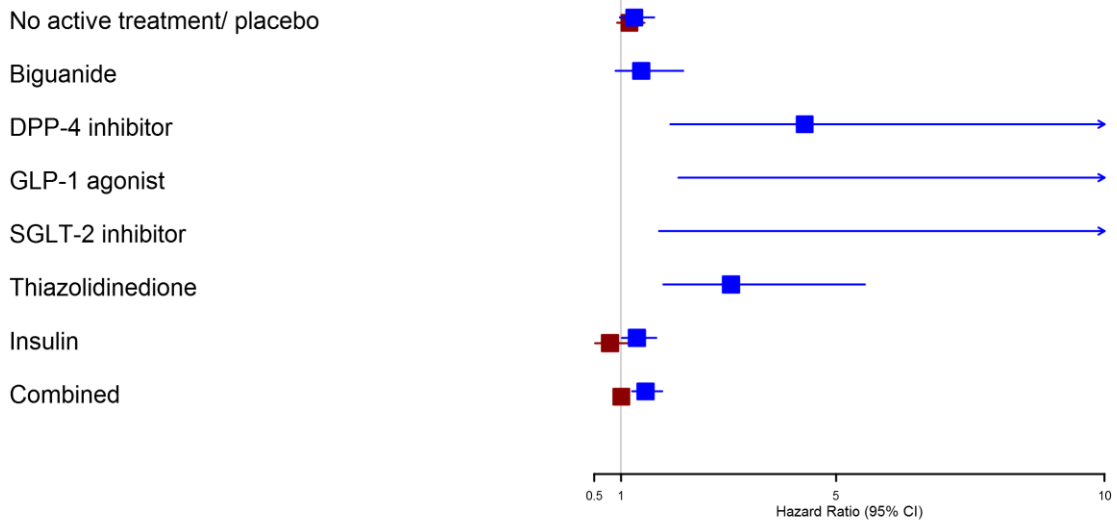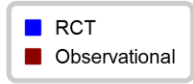
Figure 1.C: Forest plot presenting hazard ratio estimates of acute myocardial infarction for sulfonylureas versus other antihyperglycemic drugs
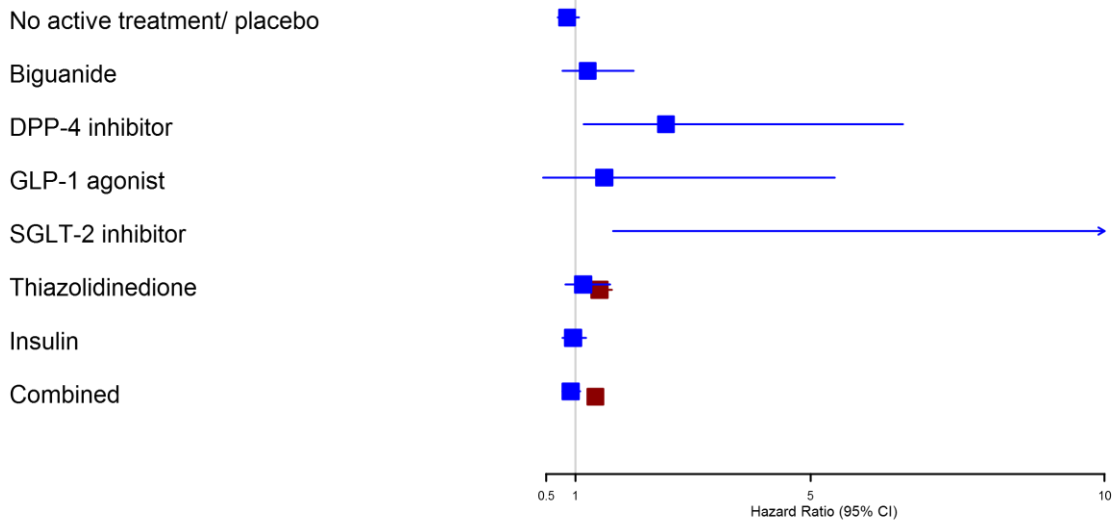
Figure 1.D: Forest plot presenting hazard ratio estimates of stroke for sulfonylureas versus other antihyperglycemic drugs