



Mortality risk among sulfonylureas: a systematic review and network meta-analysis

Scot H Simpson, Jayson Lee, Sabina Choi, Ben Vandermeer, Ahmed S Abdelmoneim, Travis R Featherstone

Summary

Background Sulfonylureas are common second-line options for management of type 2 diabetes; however, they are associated with a higher risk of cardiovascular events compared with other antidiabetic drugs. Since tissue selectivity and risk of hypoglycaemia differ among sulfonylureas, we aimed to assess whether mortality and the risk of cardiovascular events also varies.

Methods We searched Medline and Embase from inception to June 11, 2014, to identify controlled studies reporting the risk of all-cause mortality, cardiovascular-related mortality, or myocardial infarction for at least two sulfonylureas. We examined differences in cardiovascular event risk among sulfonylureas with random effects models for direct pairwise comparisons and network meta-analyses to incorporate direct and indirect data.

Findings 14 970 (9%) of 167 327 patients in 18 studies died: 841 (4%) of 19 334 gliclazide users, 5482 (11%) of 49 389 glimepiride users, 2106 (15%) of 14 464 glipizide users, 5296 (7%) of 77 169 glibenclamide users, 1066 (17%) of 6187 tolbutamide users, and 179 (23%) of 784 chlorpropamide users. Inconsistency was low for the network meta-analysis of all-cause mortality, and the relative risk of death compared with glibenclamide was 0.65 (95% credible interval 0.53–0.79) for gliclazide, 0.83 (0.68–1.00) for glimepiride, 0.98 (0.80–1.19) for glipizide, 1.13 (0.90–1.42) for tolbutamide, and 1.34 (0.98–1.86) for chlorpropamide. Similar associations were noted for cardiovascular-related mortality: the relative risk compared with glibenclamide was 0.60 (95% credible interval 0.45–0.84) for gliclazide, 0.79 (0.57–1.11) for glimepiride, 1.01 (0.72–1.43) for glipizide, 1.11 (0.79–1.55) for tolbutamide, and 1.45 (0.88–2.44) for chlorpropamide.

Interpretation Gliclazide and glimepiride were associated with a lower risk of all-cause and cardiovascular-related mortality compared with glibenclamide. Clinicians should consider possible differences in risk of mortality when selecting a sulfonylurea.

Funding None.

Introduction

Sulfonylureas are recommended in clinical practice guidelines for management of patients with type 2 diabetes because they effectively lower blood glucose and reduce the risk of microvascular complications such as nephropathy and retinopathy.^{1–3} However, debate regarding the cardiovascular safety of sulfonylureas is ongoing.⁴ Findings from several studies and meta-analyses suggest that sulfonylureas are associated with a significantly higher risk of mortality and adverse cardiovascular events than metformin and other antidiabetic drugs.^{5–15}

Two mechanisms are often proposed to explain the higher risk of adverse cardiovascular effects associated with sulfonylureas. The first plausible biological mechanism centres on an extension of the beneficial pharmacological action of sulfonylureas. These drugs bind to sulfonylurea receptors (SUR1) on pancreatic β cells and inhibit ATP-sensitive potassium channels; this process promotes insulin release and lowers blood glucose concentrations.¹⁶ However, sulfonylureas also bind to receptors on myocardial (SUR2A) and vascular smooth muscle (SUR2B) cells, so can inhibit cardiac ATP-sensitive potassium channels.^{16,17} Binding of sulfonylureas to SUR2A or SUR2B receptors can

interfere with ischaemic conditioning—an endogenous cardiac protective mechanism—and possibly with cardiac conduction.^{18,19} Findings from studies of animal models have shown that sulfonylureas binding to SUR2A or SUR2B receptors can abolish the beneficial effects of ischaemic conditioning.^{20,21} The affinity characteristics seem to vary among sulfonylureas towards SUR1, SUR2A, and SUR2B, with some—such as gliclazide—binding selectively to SUR1 when given at usual therapeutic doses, and others—such as glibenclamide—binding to sulfonylurea receptors in both the heart and pancreas when given at therapeutic doses.^{16,19,22}

The second plausible mechanism for the higher risk of adverse cardiovascular effects associated with sulfonylureas involves hypoglycaemia—a common, well known adverse effect of sulfonylurea treatment. Episodes of hypoglycaemia can prolong the QT interval and are associated with cardiac ischaemia.^{23,24} A prolonged QT interval and cardiac ischaemia can increase the risk of adverse cardiovascular events, such as ventricular arrhythmias, myocardial infarction, and sudden cardiac death.²⁵ Differences in SUR1 receptor affinity and pharmacokinetic properties seem to create

Lancet Diabetes Endocrinol 2014

Published Online

October 23, 2014

[http://dx.doi.org/10.1016/S2213-8587\(14\)70213-X](http://dx.doi.org/10.1016/S2213-8587(14)70213-X)

See Online/Comment

[http://dx.doi.org/10.1016/S2213-8587\(14\)70217-7](http://dx.doi.org/10.1016/S2213-8587(14)70217-7)

Faculty of Pharmacy and Pharmaceutical Sciences

(Prof S H Simpson MSc,

J Lee BSc, S Choi BSc,

A S Abdelmoneim MSc,

T R Featherstone BSc) and

Alberta Research Centre for

Health Evidence, Faculty of

Medicine (B Vandermeer MSc),

University of Alberta,

Edmonton, AB, Canada

Correspondence to:

Prof Scot H Simpson, Faculty of

Pharmacy and Pharmaceutical

Sciences, 3-171 Edmonton Clinic

Health Academy, University of

Alberta, Edmonton, AB T6G 1C9,

Canada

scot@ualberta.ca

differences in the risk of hypoglycaemia, with glibenclamide, which has the highest affinity for SUR1,²² having the highest risk among the sulfonylureas.^{26,27} Other mechanisms that might explain the increased risk of cardiovascular events with sulfonylureas compared with other antidiabetic drugs include increased secretion of intact proinsulin, increased amount of visceral adipose tissue, and weight gain.^{28,29}

Despite this controversy regarding cardiovascular safety, sulfonylureas remain the most commonly used second-line oral antidiabetic drugs in patients with type 2 diabetes when metformin monotherapy does not successfully control blood glucose or is contraindicated.^{30–33} Regardless of the mechanism, assessment of whether the risk of adverse cardiovascular events is similar among sulfonylureas is important. Ideally, the question of relative cardiovascular safety among sulfonylureas should be tested in a randomised controlled trial. Although seven studies have randomly allocated patients to more than one sulfonylurea and reported deaths or cardiovascular events, there are important limitations to this source of evidence.^{3,34–39} First, the UK Prospective Diabetes Study (UKPDS)³ was the only trial to report cardiovascular events as prespecified outcomes. Second, the remaining six randomised controlled trials^{34–39} were not designed to examine risk of adverse cardiovascular events and therefore had insufficient power because of small sample sizes (30–1044 patients enrolled), short follow-up (median 6 months), and few reported events (24 deaths in total). In the absence of definitive evidence from randomised controlled trials, observational studies and meta-analyses of these data can provide information to help guide treatment decisions.⁴⁰

Network meta-analyses are regarded as an important source of information to compare the safety or efficacy of several treatment options.⁴¹ This analytical technique is increasingly used to synthesise evidence from both direct and indirect comparisons to assess the effect of different treatment options on an outcome of interest.^{42,43}

We undertook a network meta-analysis to compare the relative risk of mortality and adverse cardiovascular events among sulfonylureas. On the basis of our previous findings,^{22,44} we hypothesised that gliclazide use would be associated with a significantly lower risk of mortality and adverse cardiovascular events compared with glibenclamide use.

Methods

Search strategy and selection criteria

We followed standard methodology to undertake and report a systematic review and network meta-analysis.^{45–48} We searched Medline and Embase from inception to June 11, 2014, with database-appropriate terms and text words for type 2 diabetes, sulfonylureas, and comparative study; we excluded review articles, editorials, commentaries, and animal studies (appendix). We

supplemented the electronic database search by examining reference lists of potentially relevant studies and review articles that discussed cardiovascular safety of oral antidiabetic drugs.

All citations were eligible for inclusion regardless of language or publication year. Review authors worked in pairs to screen and review articles. The pairs differed at each stage of article selection. After duplicate citations were removed, two review authors independently screened the titles and abstracts to identify potentially relevant citations. A copy of the published article from each potentially relevant citation was obtained and examined independently by two review authors to establish whether it met all prespecified inclusion criteria: patients were adults with type 2 diabetes; group allocation was based on sulfonylurea use; the study reported at least two different sulfonylurea groups; patients were followed up for at least 30 days; and the number of all-cause deaths, cardiovascular-related deaths, or myocardial infarctions were reported according to individual sulfonylurea. We excluded studies examining only one sulfonylurea to ensure that we gathered data for direct, within-study comparisons between two or more sulfonylureas for the network meta-analysis. Study authors were contacted by email to obtain additional details if the publication did not contain all required information. Disagreements regarding study inclusion or exclusion were resolved by review by a third review author.

Data extraction and synthesis

One review author used a standardised form to extract data from each included study and a second review author verified accuracy and completeness. The following study characteristics were recorded: lead author and year of publication, study design, country, period of study, antidiabetic drug use at enrolment, age, percentage of male participants, duration of diabetes, duration of follow-up, outcomes measured, sulfonylureas under study, number of patients who used each sulfonylurea, and number of patients who experienced each outcome. When an adjusted hazard ratio was reported in an observational study, we recorded the point estimate and 95% CI, reference group, and the other variables included in the fully adjusted model. Antidiabetic drug exposure was defined according to each study and categorised as new user (follow-up began with first ever sulfonylurea prescription) or prevalent user (exposure assessed during a fixed timepoint).

We assessed study quality with the 27-item Downs and Black⁴⁹ checklist because we included a mixture of randomised controlled trials and observational studies. Two review authors (two of SHS, ASA, or TRF) independently assessed each included study and agreement on a quality score was reached by consensus.

After reviewing the included studies, we found that two studies from the USA enrolled patients from the same clinic database,^{50,51} three studies from Italy enrolled

patients from the same clinic database,^{52–54} and four studies from Denmark enrolled patients from the Danish National Health Service databases.^{55–58} The two studies from the USA identified patients visiting the Cleveland Clinic main campus or family health centres between 1998 and 2006.^{50,51} However, one study included patients receiving sulfonylureas as monotherapy⁵⁰ and the other included patients receiving sulfonylureas in combination with metformin.⁵¹ We retained both studies in our analyses because the same patient was unlikely to have been included in both studies. By contrast, there was a greater possibility of counting the same patient more than once if we used data from all three of the Italian studies^{52–54} and all four of the Danish studies.^{55–58} Although the enrolment periods did not completely overlap, and the types of sulfonylureas and numbers of patients using each sulfonylurea varied among these studies, we chose to only include in the main analysis the Danish study with the largest number of patients and longest follow-up⁵⁸ and the Italian study with the largest number of patients.⁵³

Our review of the included studies also identified that the study by Schramm and colleagues⁵⁸ reported separate analyses for patients with and without cardiovascular disease at enrolment; we entered data from these two analyses as two separate studies to preserve this strata-specific information.

Statistical analysis

As an initial examination of the data, we undertook traditional meta-analyses by combining evidence from direct, within-study comparisons between sulfonylureas (eg, glibenclamide and gliclazide users included in the same study) with random effects models in RevMan 5.1 (The Cochrane Collaboration, Copenhagen, Denmark).⁵⁹ We measured heterogeneity with the I^2 statistic. We then constructed network meta-analyses to improve precision of the comparisons among sulfonylureas by combining direct and indirect evidence.⁴⁸ We followed the methods described by Lu and Ades⁴³ to compare risk of all sulfonylureas simultaneously in a Bayesian random effects model. We modelled log risk ratios or log hazard ratios with non-informative prior distributions. A normal prior with mean of 0 and large variance (10 000) was used for each of the trial mean log ratios, whereas a uniform prior with a range of 0–10 was used as a prior for the between-study variance component. These priors were checked for effect in a sensitivity analysis. We did Markov Chain Monte Carlo simulations in WinBugs software (Medical Research Council, Biostatistics Unit, Cambridge, UK) to obtain consistent and simultaneous estimates of all interventions. The first 20 000 iterations were discarded to minimise bias of initial values as the chain reaches its target distribution. We used information from the subsequent 200 000 iterations to compute the estimates. Results were reported with 95% credible intervals. Model inconsistency was assessed in Stata

(StataCorp LP, College Station, TX, USA) by contrasting direct and indirect estimates in each triangular loop by the methods described by Veroniki and colleagues.⁶⁰ We constructed separate network meta-analyses to estimate the relative risk of all-cause mortality, cardiovascular-related mortality, and myocardial infarction among sulfonylureas, with glibenclamide use serving as the reference group.

We did three sensitivity analyses with all-cause mortality as the outcome. First, we were concerned that uncontrolled confounding would affect our findings because we used raw event count data from the included cohort studies. We therefore used the adjusted hazard ratio data from cohort studies rather than the raw count data and combined these with the randomised controlled trial data. Second, since selection bias could create important differences between patients receiving metformin, chlorpropamide, and tolbutamide, we excluded these treatment nodes from the network meta-analysis. Third, we used data from all studies that met our inclusion criteria, regardless of the possible overlap

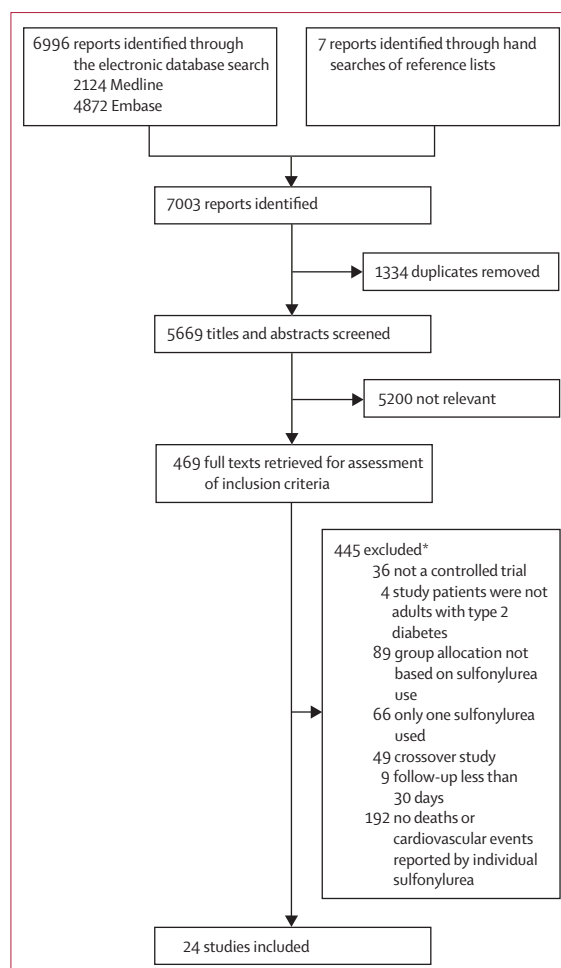


Figure 1: Flow diagram of citations

*Listed according to the most responsible reason for exclusion.

of included patients from studies by the same author groups or same database.

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The literature search identified 5669 unique citations; after screening the titles and abstracts, 469 papers were deemed potentially relevant (figure 1). We requested additional information from the authors of 46 studies (9.8%) and disagreed on the inclusion of eight (1.7%) articles. 24 studies met all inclusion criteria.

The table summarises characteristics of the seven studies that randomly allocated patients to different sulfonylureas^{3,34–39} and 17 observational studies in which patients were grouped by sulfonylurea for analyses.^{50–58,61–68} The case-control study by Johnsen and colleagues⁵⁵ met our inclusion criteria because the 30-day case fatality rate after hospital admission for myocardial infarction was reported by individual sulfonylurea. Authors from nine studies provided additional information to supplement the data published in their articles.^{50,51,53,54,63–65,67,68} In three observational studies, incident sulfonylurea users were enrolled because recruitment was on the basis of the first known prescription for a sulfonylurea.^{50,51,58} In the remaining 14 observational studies, prevalent users were enrolled because patients were using a sulfonylurea before study enrolment.^{52–57,61–68} In five randomised controlled trials, patients who were using sulfonylureas were enrolled,^{34,36–39} one study randomly allocated patients

newly diagnosed with type 2 diabetes to a sulfonylurea treatment group,³ and sulfonylurea use before enrolment was not reported in one trial.³⁵ The Downs and Black⁴⁹ quality score ranged from 16 to 25 (median 18).

Three studies used metformin monotherapy as the reference group when analysing the association between sulfonylurea use and risk of adverse cardiovascular outcomes.^{50,57,58} This information was used in the network meta-analyses for indirect estimates of mortality and myocardial infarction risk among sulfonylureas. However, we have not reported the associations for metformin generated from the network meta-analyses because of concerns regarding selection bias between metformin and sulfonylureas.

The analyses of all-cause mortality risk included data from 18 studies reporting 14970 (9%) deaths in 167327 patients who used a sulfonylurea.^{3,34–37,39,50,51,53,58,61–68} 841 (4%) of 19334 gliclazide users, 5482 (11%) of 49389 glimepiride users, 2106 (15%) of 14464 glipizide users, 5296 (7%) of 77169 glibenclamide users, 1066 (17%) of 6187 tolbutamide users, and 179 (23%) of 784 chlorpropamide users died. Figure 2 presents results of the traditional meta-analyses of direct evidence from within-study comparisons. Gliclazide seemed to have the lowest risk of mortality compared with the other sulfonylureas, followed by glimepiride, glipizide, glibenclamide, tolbutamide, and chlorpropamide. The network meta-analysis, which incorporated both direct and indirect evidence, had a low level of incoherence (appendix) and is presented in figure 3. Gliclazide and glimepiride use was associated with a significantly lower risk of mortality compared with glibenclamide, whereas glipizide use had a similar risk.

Country	Study period (follow-up duration)*	Antidiabetic drug exposure	Number of patients	Age* (years)	Men	Diabetes duration* (years)	Glycated haemoglobin*	BMI* (Kg/m ²)	History of CVD	Quality score†	
Patients randomly assigned to a sulfonylurea											
UK Prospective Diabetes Study Group (1998) ³	UK	1977–97 (10 years)‡	New users (started within 2 months of type 2 diabetes diagnosis)	1234	54	60.0%	Newly diagnosed	6.3%	27.2	0%	25
Draeger et al (1996) ³⁹	Various	NR (1 year)	Prevalent users (all patients used glibenclamide at enrolment)	1044	60.2	63.7%	5‡	8.1%	26.5	NR	22
Jennings et al (1992) ³⁸	Scotland, UK	NR (0.5 years)	Prevalent users (all patients used glibenclamide at enrolment)	30	58.1	66.7%	8	8.7%	NR	0%	19
Kilo et al (1992) ³⁷	USA	NR (0.2 years)	Prevalent users (all patients on a sulfonylurea at enrolment)	34	55.8	73.5%	NR	7.7%	30.4	NR	18
Baba et al (1983) ³⁶	Japan	NR (0.5 years)	47% were prevalent users	289	≤59§	48.0%	≤9§	NR	NR	NR	19
Tan et al (1977) ³⁵	USA	NR (4 years)	NR	120	43.0	100%	NR	NR	NR	NR	18
Katz and Bissel (1965) ³⁴	USA	NR (0.3–2.9 years)	Prevalent users (proportion of antidiabetic drug users at enrolment NR)	121	NR	NR	NR	NR	NR	NR	20

(Table continues on next page)

	Country	Study period (follow-up duration)*	Antidiabetic drug exposure	Number of patients	Age* (years)	Men	Diabetes duration* (years)	Glycated haemoglobin*	BMI* (Kg/m ²)	History of CVD	Quality score†
(Continued from previous page)											
Patients grouped according to sulfonylurea use											
Bo et al (2013) ⁶⁴	Italy	1996–2011 (14 years)	Prevalent users (on treatment at study enrolment)	1277	65.7	42.9%	9	6.7%	28.6	28.7%	17
Juurlink et al (2012) ⁶²	Canada	2007–10 (0.9 years glibenclamide; 0.6 years gliclazide)‡	Prevalent users (within 90 days of index hospital admission)	2674	66–85§	63.5%	NR	NR	NR	8.4%	19
Pantalone et al (2012) ^{60¶}	USA	1998–2006 (2.2 years)‡	New users (first-known prescription of monotherapy)	23 915	61.9	50.4%	NR	7.6%	32.2	11.4%	18
Pantalone et al (2012) ^{61¶}	USA	1998–2006 (2.4 years)‡	New users (first-known prescription of combination with metformin)	7320	62.1	53.3%	NR	8.2%	32.6	12.0%	18
Jørgensen et al (2011) ⁵⁷	Denmark	1997–2006 (1 year)	Prevalent users (within 180 days of index hospital admission)	400	64.9	67.2%	5.6	NR	NR	NR	20
Schramm et al (2011) ⁵⁸	Denmark	1997–2006 (2.0 years no previous MI; 2.2 years with previous MI)	New users (first-known prescription)	110 374 (no previous MI), 96 466 (with previous MI)	58.1 (no previous MI), 69.3 (with previous MI)	53.4% (no previous MI), 70.7% (with previous MI)	2.0 (no previous MI), 2.0 (with previous MI)	NR	NR	9.8%	20
Sillars et al (2010) ^{63¶}	Australia	1993–2007 (10.4 years)	Prevalent users (on treatment at study enrolment)	303	64.2	48.8%	4.0	7.7%	28.8	28.4%	21
Khalangot et al (2009) ^{64¶}	Ukraine	1998–2007 (1.5 years)	Prevalent users (on treatment at study enrolment)	64 288	67.8	31.2%	8.6	NR	28.2	NR	18
Horsdal et al (2009) ⁵⁶	Denmark	1996–2004 (1 year)	Prevalent users (within 90 days of index hospital admission)	3448	73.9	58.6%	≤5§	7.7%	NR	NR	21
Arruda-Olson et al (2009) ^{65¶}	USA	1985–2002 (4.9 years)	Prevalent users (on treatment at admission)	120	68	57%	12.9	NR	30.0	NR	18
Gerstein et al (2008) ^{66**}	Various	2001–08 (4.9 years)	Prevalent users (on treatment at study enrolment)	2375	61.9	59.8%	9.6	8.4%	32.2	32.6%	22
Mellbin et al (2008) ^{67¶}	Sweden	1998–2003 (2.1 years)‡	Prevalent users (on treatment at admission)	416	68.4	66.8%	7.9	7.7%	28.4	NR	18
Monami et al (2007) ⁵²	Italy	1998–2001 (5.0 years for mortality, 4.4 years for cardiac events)	Prevalent users (on treatment at study enrolment)	568	65.3	49.6%	11.4	8.1%	27.8	NR	18
Monami et al (2006) ^{53¶}	Italy	1993–2004 (2.6 years)	Prevalent users (on treatment in combination with metformin at study enrolment)	587	65.8	49.9%	14.4	8.6%	28.7	NR	18
Johnsen et al (2006) ^{55††}	Denmark	1994–2002 (30 days)	Prevalent users (within 90 days of index date)	6738 cases	69.5	61.7%	NR	NR	NR	NR	18
Mannucci et al (2004) ^{54¶}	Italy	1993–2003 (4.6 years)	Prevalent users (on treatment in combination with a biguanide at study enrolment)	374	66.0	47.6%	14.2	8.8%	28.3	NR	18
Pogatsa et al (1992) ^{68¶}	Hungary	1967–91 (8 years)	Prevalent users (on treatment at study enrolment)	351	55	46.3%	8	6.9%	27.2	15.9%	16

CVD=cardiovascular disease. MI=myocardial infarction. NR=not reported. *Mean reported unless otherwise specified. †Score out of 27 on the Downs and Black checklist;⁴⁹ higher scores suggest better study quality. ‡Median. §Over 50% of the study group were within this range. ¶Authors provided additional information. ||Events counted in the first year after index hospital admission. **Patients who used only one sulfonylurea during the ACCORD trial (data were taken from the ACCORD Research Materials obtained from the National Heart, Lung and Blood Institute). ††30-day fatality rate reported for all 6738 cases, of whom 361 were using a sulfonylurea.

Table: Characteristics of included studies

Cardiovascular-related mortality analyses were based on data from 13 studies reporting 7158 (5%) deaths in 145 916 patients who used a sulfonylurea.^{3,34,36,37,39,52,58,61,63,64,66-68} The traditional meta-analysis of direct evidence from within-study comparisons between sulfonylureas was similar to the analysis of all-cause mortality (appendix). There was a low level of inconsistency between direct and indirect evidence in the network meta-analysis of cardiovascular mortality risk among sulfonylureas (appendix) and the results are presented in figure 4. Gliclazide use was associated with a significantly lower risk of cardiovascular-related mortality compared with glibenclamide. Glimepiride use was associated with a numerically lower risk, but the difference compared with glibenclamide was not significant.

Myocardial infarction analyses were based on 1012 (12%) events in 8124 patients receiving a sulfonylurea who were enrolled in seven studies.^{3,34,38,56,62,67,68} There were no significant differences among sulfonylureas when direct evidence was pooled by traditional meta-analyses or when direct and indirect evidence were combined in a network meta-analysis (appendix).

Seven studies used adjusted hazard ratios to compare the risk of all-cause mortality between different sulfonylureas.^{50-52,58,61,62,64} The results of a network

meta-analysis of these adjusted hazard ratios and data from the randomised controlled trials^{3,34-37,39} are similar to the main analysis (appendix). Removing metformin, tolbutamide, and chlorpropamide from the network meta-analysis did not change the direction, magnitude, or significance of our main analysis (appendix). Although two studies from Italy^{52,54} and three studies from Denmark⁵⁵⁻⁵⁷ could have drawn patients from the same sampling frame as studies included in the main analyses,^{53,58} there were important differences in the types of sulfonylureas used across these studies and the number of patients using each sulfonylurea. Incorporating data from all 23 studies that reported all-cause mortality rates did not change the direction, magnitude, or significance of our main findings (appendix).

Discussion

In this systematic review, we identified 24 controlled studies that reported the risk of adverse cardiovascular outcomes for two or more sulfonylureas. We were able to combine mortality data from 23 of these studies that enrolled a total of 172 349 patients who used a sulfonylurea; 18 of these studies (167 327 patients) were included in our main analyses. In all direct or indirect analyses, gliclazide use was associated with a significantly lower risk of all-cause and cardiovascular-related mortality

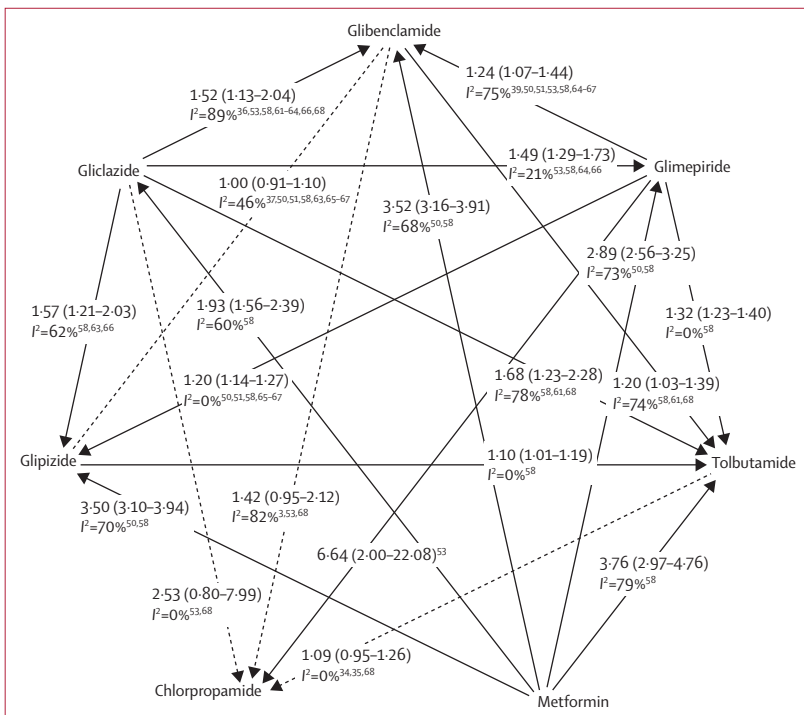


Figure 2: Comparison of all-cause mortality between sulfonylureas using direct evidence
Data are taken from 18 studies that reported direct evidence of the risk of all-cause mortality for two or more sulfonylureas and are compared by meta-analyses.^{3,34-37,39,50,51,53,58,61-68} The pooled relative risks with 95% CIs are reported for each pairwise comparison. A solid line shows the association is statistically significant and a dotted line shows the association is not statistically significant. Arrowheads point to the drug with higher risk within each pair. The number of arrowheads pointing to each drug gives an approximation of the overall risk of mortality relative to the others.

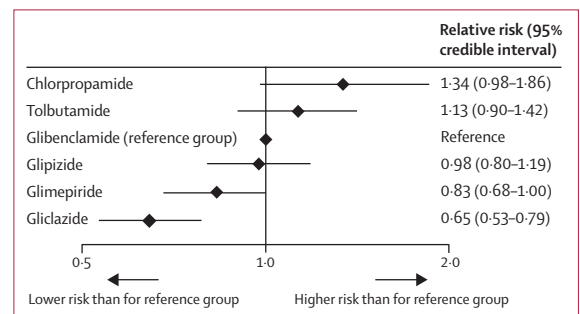


Figure 3: Comparison of all-cause mortality between sulfonylureas using direct and indirect evidence
Data are pooled relative risks and 95% credible intervals calculated by network meta-analysis of direct and indirect evidence from 18 studies.^{3,34-37,39,50,51,53,58,61-68}

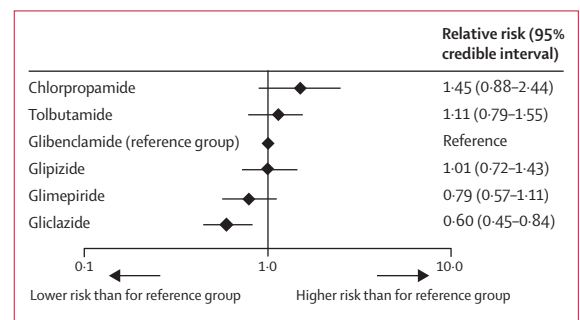


Figure 4: Comparison of cardiovascular-related mortality between sulfonylureas using direct and indirect evidence
Data are pooled relative risks and 95% credible intervals calculated by network meta-analysis of direct and indirect evidence from 13 studies.^{3,34,36,37,39,52,58,61,63,64,66-68}

compared with glibenclamide use. Glimepiride use was associated with a lower risk of all-cause mortality compared with glibenclamide use. Glipizide use was associated with a similar risk of all-cause and cardiovascular-related mortality compared with glibenclamide use. There were no clear significant differences in risk of myocardial infarction among the sulfonylureas.

Previous observational studies that examined the possible adverse cardiovascular effects of sulfonylureas have, for the most part, grouped these drugs together.^{5-7,63,65,67,68} As our understanding of the differences in pharmacological properties among these drugs increases, a growing number of studies are assessing each sulfonylurea separately against a non-sulfonylurea reference group, such as metformin,^{50,55,57,58,69} or with one sulfonylurea serving as the reference group.^{44,51,52,56,61,62,64} Although a higher risk of mortality and adverse cardiovascular events has consistently been reported with sulfonylurea use compared with other diabetic drugs,^{12,14,15} findings of differences among sulfonylureas have been inconsistent.^{44,51,52,56,61,62,64} Variations in study design, choice of reference group, sample size, cardiovascular history, duration of follow-up, exposure status and duration, and number of events reported might explain the inconsistent findings. By combining both direct and indirect data from these studies in network meta-analyses, we noted significant differences in all-cause and cardiovascular-related mortality among several individual sulfonylureas.

We expected some inconsistency between the direct and indirect data since most studies included in this systematic review were observational studies. Several factors could contribute to the inconsistencies noted in the main analysis. For example, duration of diabetes ranged from newly diagnosed³ to 14 years,³³ patients could either be new sulfonylurea users or prevalent users at study enrolment, and the duration of follow-up ranged from 30 days⁵⁴ to 14 years.⁶¹ Despite these variations, the reported associations in the network meta-analysis of adjusted hazard ratios were consistent with the associations noted in the main analysis—that gliclazide use was associated with a significantly lower risk of all-cause and cardiovascular-related mortality compared with glibenclamide.

Several limitations should be considered when interpreting our findings. First and foremost, selection bias could have affected the reported associations because data for these network meta-analyses were taken mainly from cohort studies. Although concerns about selection bias affecting reported differences between metformin and sulfonylureas are well known, removal of metformin from our analysis did not have a substantial effect on the associations among the commonly used sulfonylureas. Perhaps more relevant to our study would be factors that affect the choice of a specific sulfonylurea, such as cost. More expensive

sulfonylureas, such as glimepiride and gliclazide, which were only available in trade name formulations during many of the study periods, might have been selectively used in patients with a higher socioeconomic status. Although this factor might partially explain the differences seen between these two sulfonylureas and glibenclamide, we also noted important differences between gliclazide and glimepiride.

Second, the main analyses examined the relative risks using raw event count data and, therefore, we did not control for any potential confounding, both within the studies and across studies. Although a sensitivity analysis of all-cause mortality using adjusted hazard ratios produced similar results, residual confounding is still an important factor to consider. Many of the included observational studies could not account for important clinical measures such as blood glucose concentrations, history of hypoglycaemia, blood pressure, lipid concentrations, renal function, left ventricular function, and smoking status in the adjusted hazard ratios. Third, some patients who stopped using a sulfonylurea might have been misclassified as exposed. For example, several trials used a time-fixed definition to allocate patients to a sulfonylurea group and excluded patients if there was evidence of switching to or concurrent use of a second sulfonylurea.^{50,51,57,61,62} Schramm and colleagues⁵⁸ study was the only one in which investigators checked at regular intervals to ensure patients continued to use a sulfonylurea during the observation period. Fourth, the limited amount of available information did not allow us to examine other factors that could affect risk of adverse effects. For example, different formulations of sulfonylureas, such as the regular and modified-release formulations of gliclazide, and regular and extended-release formulations of glipizide, could have different levels of cardiovascular risk because of possible differences in risk of hypoglycaemia. For these reasons, findings from this study should be considered hypothesis generating and need to be verified in a properly designed randomised clinical trial. Although ongoing trials are not designed to specifically examine the question of safety among sulfonylureas, we believe results of the TOSCA IT (NCT00700856) and CAROLINA (NCT01243424) trials will help answer some questions regarding the role of sulfonylureas in diabetes management.^{70,71}

In addition to the concerns noted earlier, our study shares the limitations of other systematic reviews because we were unable to obtain usable information from all relevant studies. Although our search strategy identified 469 potentially relevant studies, including the well known clinical trials ACCORD,⁶⁶ ADVANCE,⁷² BARI 2D,⁷³ RECORD,⁷⁴ and UKPDS,³ 192 (41%) were excluded because mortality or cardiovascular outcomes were not reported for individual sulfonylureas. Moreover, we only included published studies, which could introduce bias since these studies are more likely to report differences compared with unpublished studies.

Contributors

SHS conceived and designed the study, acquired data, analysed and interpreted data, and drafted and critically revised the manuscript. JL and SC acquired data, interpreted data, and drafted and critically revised the manuscript. BV analysed and interpreted data, and critically revised the manuscript. ASA and TRF acquired data, interpreted data, and critically revised the manuscript.

Declaration of interests

SHS has received speaker honoraria from Eli Lilly. JL, SC, BV, ASA, and TRF declare no competing interests.

Acknowledgments

We are very grateful for the additional information provided by the authors of nine studies included in this report. We also thank the authors of 23 studies who took time to check their databases, but were unable to retrieve the information we requested. ASA is supported by studentships through the Alberta Diabetes Institute and the Alliance for Canadian Health Outcomes Research in Diabetes Strategic Training Program in Diabetic Research, and holds an Izaak Walton Killam Memorial Scholarship and Canadian Diabetes Association Doctoral Studentship.

References

- Harper W, Clement M, Goldenberg R, et al. Pharmacologic management of type 2 diabetes. *Can J Diabetes* 2013; 37(suppl 1): S61–68.
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; 35: 1364–79.
- UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837–53.
- Bell DS. Do sulfonylurea drugs increase the risk of cardiac events? *Can Med Assoc J* 2006; 174: 185–86.
- Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR Jr. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1999; 33: 119–24.
- Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. *Diabetes Care* 2002; 25: 2244–48.
- Evans JM, Ogston SA, Emslie-Smith A, Morris AD. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulphonylureas and metformin. *Diabetologia* 2006; 49: 930–36.
- Pantalone KM, Kattan MW, Yu C, et al. The risk of overall mortality in patients with type 2 diabetes receiving glipizide, glyburide, or glimepiride monotherapy: a retrospective analysis. *Diabetes Care* 2010; 33: 1224–29.
- Gallwitz B, Rosenstock J, Rauch T, et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. *Lancet* 2012; 380: 475–83.
- Rao AD, Kuhadiya N, Reynolds K, Fonseca VA. Is the combination of sulphonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies. *Diabetes Care* 2008; 31: 1672–78.
- Selvin E, Bolen S, Yeh HC, et al. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. *Arch Intern Med* 2008; 168: 2070–80.
- Forst T, Hanefeld M, Jacob S, et al. Association of sulphonylurea treatment with all-cause and cardiovascular mortality: a systematic review and meta-analysis of observational studies. *Diab Vasc Dis Res* 2013; 10: 302–14.
- Hemmingsen B, Schroll J, Lund S, et al. Sulphonylurea monotherapy for patients with type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2013; 4: CD009008.
- Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulphonylureas: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab* 2013; 15: 938–53.
- Phung OJ, Schwartzman E, Allen RW, Engel SS, Rajpathak SN. Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis. *Diabet Med* 2013; 30: 1160–71.
- Ashcroft FM, Gribble FM. Tissue-specific effects of sulphonylureas: lessons from studies of cloned K(ATP) channels. *J Diabetes Complications* 2000; 14: 192–96.
- Bolli R. Preconditioning: a paradigm shift in the biology of myocardial ischemia. *Am J Physiol Heart Circ Physiol* 2007; 292: H19–27.
- Hausenloy DJ, Yellon DM. Preconditioning and postconditioning: new strategies for cardioprotection. *Diabetes Obes Metab* 2008; 10: 451–59.
- Thisted H, Johnsen SP, Rungby J. Sulphonylureas and the risk of myocardial infarction. *Metabolism* 2006; 55 (5 suppl 1): S16–19.
- Gross GJ, Auchampach JA. Blockade of ATP-sensitive potassium channels prevents myocardial preconditioning in dogs. *Circ Res* 1992; 70: 223–33.
- Kristiansen SB, Lofgren B, Nielsen JM, et al. Comparison of two sulphonylureas with high and low myocardial K(ATP) channel affinity on myocardial infarct size and metabolism in a rat model of type 2 diabetes. *Diabetologia* 2011; 54: 451–58.
- Abdelmoneim AS, Hasenbank SE, Seubert JM, Brocks DR, Light PE, Simpson SH. Variations in tissue selectivity amongst insulin secretagogues: a systematic review. *Diabetes Obes Metab* 2012; 14: 130–38.
- Landstedt-Hallin L, Englund A, Adamson U, Lins PE. Increased QT dispersion during hypoglycaemia in patients with type 2 diabetes mellitus. *J Intern Med* 1999; 246: 299–307.
- Desouza C, Salazar H, Cheong B, Murgu J, Fonseca V. Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. *Diabetes Care* 2003; 26: 1485–89.
- Nordin C. The proarrhythmic effect of hypoglycemia: evidence for increased risk from ischemia and bradycardia. *Acta Diabetol* 2014; 51: 5–14.
- Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. *Eur J Clin Invest* 2004; 34: 535–42.
- Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. *Diabetes Care* 2007; 30: 389–94.
- Hermann LS, Ranstam J, Vaaler S, Melander A. Effects of antihyperglycaemic therapies on proinsulin and relation between proinsulin and cardiovascular risk factors in type 2 diabetes. *Diabetes Obes Metab* 1999; 1: 227–32.
- Gallwitz B, Haupt A, Kraus P, et al. Changes in body composition after 9 months of treatment with exenatide twice daily versus glimepiride: comment letter on Jendle et al. *Diabetes Obes Metab* 2010; 12: 1127–28.
- Abdelmoneim AS, Eurich DT, Gamble JM, Simpson SH. Use patterns of antidiabetic regimens by patients with type 2 diabetes. *Can J Diabetes* 2013; 37: 394–400.
- Leiter LA, Berard L, Bowering CK, et al. Type 2 diabetes mellitus management in Canada: is it improving? *Can J Diabetes* 2013; 37: 82–89.
- Filion KB, Joseph L, Boivin JF, Suissa S, Brophy JM. Trends in the prescription of anti-diabetic medications in the United Kingdom: a population-based analysis. *Pharmacoepidemiol Drug Saf* 2009; 18: 973–76.
- Alexander GC, Sehgal NL, Moloney RM, Stafford RS. National trends in treatment of type 2 diabetes mellitus, 1994–2007. *Arch Intern Med* 2008; 168: 2088–94.
- Katz HM, Bissel G. Blood sugar lowering effects of chlorpropamide and tolbutamide. A double blind cooperative study. *Diabetes* 1965; 14: 650–57.
- Tan MH, Graham CA, Bradley RF, Gleason RE, Soeldner JS. The effects of long-term therapy with oral hypoglycemic agents on the oral glucose tolerance test dynamics in male chemical diabetics. *Diabetes* 1977; 26: 561–70.
- Baba S, Nakagawa S, Takebe K, et al. Comparison of gliclazide and glibenclamide treatment in non-insulin-dependent diabetes. *Tohoku J Exp Med* 1983; 141 (suppl): 693–706.

- 37 Kilo C, Meenan A, Bloomgarden Z. Glyburide versus glipizide in the treatment of patients with non-insulin-dependent diabetes mellitus. *Clin Ther* 1992; **14**: 801–12.
- 38 Jennings PE, Scott NA, Saniabadi AR, Belch JJ. Effects of gliclazide on platelet reactivity and free radicals in type II diabetic patients: clinical assessment. *Metabolism* 1992; **41** (5 suppl 1): 36–39.
- 39 Draeger KE, Wernicke-Panten K, Lomp HJ, Schuler E, Roskamp R. Long-term treatment of type 2 diabetic patients with the new oral antidiabetic agent glimepiride (Amaryl): a double-blind comparison with glibenclamide. *Horm Metab Res* 1996; **28**: 419–25.
- 40 Potts M, Prata N, Walsh J, Grossman A. Parachute approach to evidence based medicine. *Br Med J* 2006; **333**: 701–03.
- 41 Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012; **3**: 80–97.
- 42 Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med* 2002; **21**: 2313–24.
- 43 Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004; **23**: 3105–24.
- 44 Abdelmoneim AS, Eurich DT, Gamble JM, et al. Risk of acute coronary events associated with glyburide compared with gliclazide use in patients with type 2 diabetes: a nested case-control study. *Diabetes Obes Metab* 2014; **16**: 22–29.
- 45 Higgins JP, Green S, eds. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration, 2011. www.cochrane-handbook.org (accessed Aug 1, 2014).
- 46 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic reviews and Meta-Analyses: the PRISMA statement. *PLoS Medicine* 2009; **6**: e1000097.
- 47 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008–12.
- 48 Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health* 2011; **14**: 429–37.
- 49 Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998; **52**: 377–84.
- 50 Pantalone KM, Kattan MW, Yu C, et al. Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. *Diabetes Obes Metab* 2012; **14**: 803–09.
- 51 Pantalone KM, Kattan MW, Yu C, et al. The risk of overall mortality in patients with type 2 diabetes receiving different combinations of sulfonylureas and metformin: a retrospective analysis. *Diabet Med* 2012; **29**: 1029–35.
- 52 Monami M, Balzi D, Lamanna C, et al. Are sulphonylureas all the same? A cohort study on cardiovascular and cancer-related mortality. *Diabetes Metab Res Rev* 2007; **23**: 479–84.
- 53 Monami M, Luzzi C, Lamanna C, et al. Three-year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin. *Diabetes Metab Res Rev* 2006; **22**: 477–82.
- 54 Mannucci E, Monami M, Masotti G, Marchionni N. All-cause mortality in diabetic patients treated with combinations of sulfonylureas and biguanides. *Diabetes Metab Res Rev* 2004; **20**: 44–47.
- 55 Johnsen SP, Monster TB, Olsen ML, et al. Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. *Am J Ther* 2006; **13**: 134–40.
- 56 Horsdal HT, Johnsen SP, Sondergaard F, et al. Sulfonylureas and prognosis after myocardial infarction in patients with diabetes: a population-based follow-up study. *Diabetes Metab Res Rev* 2009; **25**: 515–22.
- 57 Jorgensen CH, Gislason GH, Bretler D, et al. Glyburide increases risk in patients with diabetes mellitus after emergent percutaneous intervention for myocardial infarction—a nationwide study. *Int J Cardiol* 2011; **152**: 327–31.
- 58 Schramm TK, Gislason GH, Vaag A, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. *Eur Heart J* 2011; **32**: 1900–08.
- 59 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Cont Clin Trials* 1986; **7**: 177–88.
- 60 Veroniki AA, Vasiliadis HS, Higgins JP, Salanti G. Evaluation of inconsistency in networks of interventions. *Int J Epidemiol* 2013; **42**: 332–45.
- 61 Bo S, Castiglione A, Ghigo E, et al. Mortality outcomes of different sulphonylurea drugs: the results of a 14-year cohort study of type 2 diabetic patients. *Eur J Endocrinol* 2013; **169**: 117–26.
- 62 Juurlink DN, Gomes T, Shah BR, Mamdani MM. Adverse cardiovascular events during treatment with glyburide (glibenclamide) or gliclazide in a high-risk population. *Diabet Med* 2012; **29**: 1524–28.
- 63 Sillars B, Davis WA, Hirsch IB, Davis TM. Sulphonylurea–metformin combination therapy, cardiovascular disease and all-cause mortality: the Fremantle Diabetes Study. *Diabetes Obes Metab* 2010; **12**: 757–65.
- 64 Khalangot M, Tronko M, Kravchenko V, Kovtun V. Glibenclamide-related excess in total and cardiovascular mortality risks: data from large Ukrainian observational cohort study. *Diabetes Res Clin Pract* 2009; **86**: 247–53.
- 65 Arruda-Olson AM, Patch RK 3rd, Leibson CL, et al. Effect of second-generation sulfonylureas on survival in patients with diabetes mellitus after myocardial infarction. *Mayo Clin Proc* 2009; **84**: 28–33.
- 66 Gerstein HC, Miller ME, Byington RP, et al, for the ACCORD Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545–59.
- 67 Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L, for the DIGAMI 2 Investigators. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. *Eur Heart J* 2008; **29**: 166–76.
- 68 Pogatsa G, Koltai MZ, Jermendy G, Simon J, Aranyi Z, Ballagi-Pordany G. The effect of sulphonylurea therapy on the outcome of coronary heart diseases in diabetic patients. *Acta Med Hung* 1992; **49**: 39–51.
- 69 Horsdal HT, Sondergaard F, Johnsen SP, Rungby J. Antidiabetic treatments and risk of hospitalisation with myocardial infarction: a nationwide case-control study. *Pharmacoepidemiol Drug Safety* 2011; **20**: 331–37.
- 70 Vaccaro O, Masulli M, Bonora E, et al. Addition of either pioglitazone or a sulfonylurea in type 2 diabetic patients inadequately controlled with metformin alone: impact on cardiovascular events. A randomized controlled trial. *Nutr Metab Cardiovasc Dis* 2012; **22**: 997–1006.
- 71 Rosenstock J, Marx N, Kahn SE, et al. Cardiovascular outcome trials in type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. *Diab Vasc Dis Res* 2013; **10**: 289–301.
- 72 Patel A, MacMahon S, Chalmers J, et al, for the ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**: 2560–72.
- 73 Chaitman BR, Hardison RM, Adler D, et al, for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Study Group. The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes mellitus with stable ischemic heart disease: impact of treatment strategy on cardiac mortality and myocardial infarction. *Circulation* 2009; **120**: 2529–40.
- 74 Home PD, Pocock SJ, Beck-Nielsen H, et al, for the RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009; **373**: 2125–35.

Does mortality risk vary among sulfonylureas?

The University Group Diabetes Program raised concern in 1970 when it reported an increased risk of cardiovascular mortality in patients who received tolbutamide.¹ It was this finding that largely prompted the initiation of the UK Prospective Diabetes Study (UKPDS),² the findings of which did not support the suggestion that sulfonylurea treatment was associated with an increased risk of cardiovascular death. However, sulfonylurea use has been controversial ever since and many retrospective studies have subsequently reported an increased risk of adverse cardiovascular outcomes, mortality, or both, with sulfonylurea treatment, specifically when compared with metformin.

Sulfonylureas have historically been analysed as a drug class, despite the fact that there are vast differences in pharmacological properties among the individual sulfonylureas: hypoglycaemic risk, sulfonylurea receptor (SUR) subtype specificity and affinity, and the ability to abolish ischaemic preconditioning. Glibenclamide is the sulfonylurea most commonly associated with hypoglycaemia.³ Some sulfonylureas (gliclazide and glipizide) are specific for the pancreatic SUR1 receptors, thereby principally stimulating insulin secretion. Other sulfonylureas (glimepiride and glibenclamide) are not pancreas specific; these drugs agonise both the pancreatic SUR1 receptors and the SUR2 receptors found on cardiac myocytes and vascular smooth muscle cells—mediating effects in the heart and smooth muscles.^{4,5} Although both glimepiride and glibenclamide agonise the SUR2 receptors, only glibenclamide abolishes ischaemic preconditioning, a cardioprotective phenomenon whereby repeated episodes of ischaemia help to protect the heart against subsequent episodes, thereby potentially limiting ischaemic injury or infarct size.⁶

Substantial differences clearly exist in terms of the pharmacological properties inherent to the individual sulfonylureas, but whether these differences translate into differences in the risk of adverse cardiovascular outcomes, mortality, or both, remained unclear. Conflicting reports have emerged concerning whether an increased overall or cardiovascular mortality risk accompanies the various sulfonylureas.⁷⁻⁹ The reason for this discrepancy is probably multifactorial, because these reports differ in terms of their design, study populations, and choice of variables for which

adjustments were made. These discrepancies have limited our ability to draw reliable conclusions, which is why the results of the report by Scot Simpson and colleagues¹⁰ in *The Lancet Diabetes & Endocrinology* are so important. The investigators thoroughly reviewed the published work and undertook a network meta-analysis, the results of which summarise the totality of the literature effectively. They reported that the relative risk of death versus glibenclamide was 0.65 (95% credible interval 0.53–0.79) for gliclazide, 0.83 (0.68–1.00) for glimepiride, 0.98 (0.80–1.19) for glipizide, 1.13 (0.90–1.42) for tolbutamide, and 1.34 (0.98–1.86) for chlorpropamide. Similar associations were noted for cardiovascular-related mortality. Simpson and colleagues concluded that gliclazide and glimepiride use were associated with a lower risk of mortality compared with glibenclamide use. Although many of the trials included in the meta-analysis were observational, and thus subject to possible selection bias, this is a limitation of the available data rather than a limitation of their meta-analysis. The investigators appropriately recommended that clinicians consider these possible risk differences when selecting a sulfonylurea; however, they cautioned that this hypothesis needs to be tested in a randomised clinical trial. Although I could not agree more with this conclusion, the results of this meta-analysis are nonetheless extremely important. Sulfonylureas are readily available as generics, are extremely cheap, or both. Therefore, it is very unlikely that a prospective randomised clinical trial will ever be done to assess whether the differences in pharmacological properties inherent to individual sulfonylureas translate into differences in the risk of adverse cardiovascular outcomes or mortality, or both. These data would be especially relevant for patients with pre-existing coronary artery disease, who are most at risk of mortality or an adverse cardiovascular event from a sulfonylurea that inhibits ischaemic preconditioning. One conclusion seems to be clear from the available literature in this area: since other sulfonylureas are readily available, and at a similar cost to the patient, continuing to prescribe glibenclamide seems inappropriate in view of its higher risk of hypoglycaemia and ability to abolish ischaemic preconditioning, even if the jury is still out regarding whether or not it is



Christina Pedrazini/Science Photo Library

Lancet Diabetes Endocrinol 2014

Published Online

October 23, 2014

[http://dx.doi.org/10.1016/S2213-8587\(14\)70217-7](http://dx.doi.org/10.1016/S2213-8587(14)70217-7)

[http://dx.doi.org/10.1016/S2213-8587\(14\)70217-7](http://dx.doi.org/10.1016/S2213-8587(14)70217-7)

See Online/Articles

[http://dx.doi.org/10.1016/S2213-8587\(14\)70213-X](http://dx.doi.org/10.1016/S2213-8587(14)70213-X)

[http://dx.doi.org/10.1016/S2213-8587\(14\)70213-X](http://dx.doi.org/10.1016/S2213-8587(14)70213-X)

associated with a higher risk of adverse cardiovascular outcomes or mortality versus other sulfonylureas.

Kevin M Pantalone

Cleveland Clinic, Cleveland, OH 44195, USA

pantalk@ccf.org

I have received honoraria for participating in speaker bureaus of Bristol-Myers Squibb, AstraZeneca, and Eli Lilly, and for serving as a consultant for Novo Nordisk, Eli Lilly, Sanofi, and Merck.

- 1 University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. *Diabetes* 1970; **19** (suppl 2): 747-830.
- 2 UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352**: 837-53.
- 3 Gangji AS, Cukierman T, Gerstein HC, et al. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. *Diabetes Care* 2007; **30**: 389-94.
- 4 Gribble FM, Reimann F. Sulphonylurea action revisited: the post-cloning era. *Diabetologia* 2003; **46**: 875-91.
- 5 Evans JM, Ogston SA, Reimann F, Gribble FM, Morris AD, Pearson ER. No differences in mortality between users of pancreatic-specific and non-pancreatic-specific sulphonylureas: a cohort analysis. *Diabetes Obes Metab* 2008; **10**: 350-52.
- 6 Klepzig H, Kober G, Matter C, et al. Sulfonylureas and ischaemic preconditioning; a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. *Eur Heart J* 1999; **20**: 439-46.
- 7 Horsdal HT, Johnsen SP, Sondergaard F, et al. Sulfonylureas and prognosis after myocardial infarction in patients with diabetes: a population-based follow-up study. *Diabetes Metab Res Rev* 2009; **25**: 515-22.
- 8 Pantalone KM, Kattan MW, Yu C, et al. The risk of overall mortality in patients with type 2 diabetes receiving glipizide, glyburide, or glimepiride monotherapy: a retrospective analysis. *Diabetes Care* 2010; **33**: 1224-29.
- 9 Zeller M, Danchin N, Simon D, et al. Impact of type of preadmission sulfonylureas on mortality and cardiovascular outcomes in diabetic patients with acute myocardial infarction. *J Clin Endocrinol Metab* 2010; **95**: 4993-5002.
- 10 Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. *Lancet Diabetes Endocrinol* 2014; published online Oct 23. [http://dx.doi.org/10.1016/S2213-8587\(14\)70213-X](http://dx.doi.org/10.1016/S2213-8587(14)70213-X).