Sulfonylureas and the Risks of Cardiovascular Events and Death: A Methodological Meta-Regression Analysis of the Observational Studies

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Recent randomized trials have compared the newer antidiabetic agents to treatments involving sulfonylureas, drugs associated with increased cardiovascular risks and mortality in some observational studies with conflicting results. We reviewed the methodology of these observational studies by searching MEDLINE from inception to December 2015 for all studies of the association between sulfonylureas and cardiovascular events or mortality. Each study was appraised with respect to the comparator, the outcome, and study design–related sources of bias. A meta-regression analysis was used to evaluate heterogeneity. A total of 19 studies were identified, of which six had no major design-related biases. Sulfonylureas were associated with an increased risk of cardiovascular events and mortality in five of these studies (relative risks 1.16–1.55). Overall, the 19 studies resulted in 36 relative risks as some studies assessed multiple outcomes or comparators. Of the 36 analyses, metformin was the comparator in 27 (75%) and death was the outcome in 24 (67%). The relative risk was higher by 13% when the comparator was metformin, by 20% when death was the outcome, and by 7% when the studies had design-related biases. The lowest predicted relative risk was for studies with no major bias, comparator other than metformin, and cardiovascular outcome (1.06 [95% CI 0.92–1.23]), whereas the highest was for studies with bias, metformin comparator, and mortality outcome (1.53 [95% CI 1.43–1.65]). In summary, sulfonylureas were associated with an increased risk of cardiovascular events and mortality in the majority of studies with no major design-related biases. Among studies with important biases, the association varied significantly with respect to the comparator, the outcome, and the type of bias. With the introduction of new antidiabetic drugs, the use of appropriate design and analytical tools will provide their more accurate cardiovascular safety assessment in the real-world setting.

REVIEW

It is well established that type 2 diabetes is associated with an increased risk of cardiovascular morbidity and mortality (1). Although much of this association can be attributed to the long-term complications of this disease, there has been growing interest in determining whether certain antidiabetic drugs influence this risk. In particular, over the years, there have been concerns regarding the cardiovascular safety of sulfonylureas, the second most commonly used antidiabetic drugs after metformin. These safety concerns initiated with the University Group Diabetes Program (UGDP) conducted in the 1960s, where tolbutamide (a first-generation sulfonylurea) was

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associated with an increased risk of all-cause and cardiovascular mortality compared with placebo (2). Indeed, sulfonylureas have been associated with weight gain, fluid retention, and hypoglycemia, which are all known cardiovascular risk factors (3). In contrast, meta-analyses of sulfonylurea randomized controlled trials (RCTs) have produced conflicting findings with respect to cardiovascular events and mortality (4–6). However, none of these RCTs were designed or powered to detect cardiovascular events and the RCTs used different comparators, including other oral agents or placebo.

In contrast to the RCTs, several observational studies have associated sulfonylureas with an increased risk of cardiovascular events and death (7). However, these observational studies used varying approaches to study design and data analysis that could have introduced several biases. With the introduction of new antidiabetic drugs, such as dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) analogs, and sodium–glucose cotransporter 2 (SGLT2) inhibitors, drugs that will likely undergo the same scrutiny as sulfonylureas, there is a need to understand how bias can be introduced (and avoided) in observational studies assessing the safety of second- to third-line treatments. Moreover, many RCTs of the newer drugs have included and will include sulfonylureas in the comparator group.

The objective of this methodological review is to detail the most important methodological limitations of observational studies assessing the cardiovascular safety of sulfonylureas and identify the most robust observational studies of the association between sulfonylureas and the risk of cardiovascular events. This review will thus provide guidance for future studies on the use of robust methods to minimize bias in assessing the cardiovascular safety of newer antidiabetic drugs.

RESEARCH DESIGN AND METHODS

Search Strategy

A MEDLINE search was conducted to identify all observational studies assessing the effects of sulfonylureas on the incidence of cardiovascular and cerebrovascular events, cardiovascular mortality, and all-cause mortality. The search terms included "sulfonylureas," "cardiovascular," "myocardial infarction," "coronary artery disease," "stroke," and "mortality." The search was limited to studies published in English before 31 December 2015.

Inclusion Criteria

To be included in this methodological review, the observational studies had to have *1*) compared at least one sulfonylurea (alone or in combination with other antidiabetic drugs) with specific antidiabetic drugs or no use of sulfonylureas and *2*) reported on at least one of the outcomes of interest (cardiovascular events, cerebrovascular events, and cardiovascular-specific and all-cause mortality). Studies comparing different sulfonylureas to each other or to patients without diabetes were not included, as were those conducted within selected cardiovascular populations, such as among those previously hospitalized for myocardial infarction. The latter represent distinct populations that assessed the effects of sulfonylureas on the risk of recurrent events. Such studies have their own set of methodological challenges, which are outside the scope of this review.

Sources of Bias

One of the major threats to observational studies is confounding bias, which presents important challenges in their conduct. Indeed, any study evaluating the risk of sulfonylureas will have to ensure that the comparator group of patients is practically identical to the patients using sulfonylureas. Thus, in contrast with RCTs where such comparability is inherently established by randomization, observational studies must rely on matching or statistical adjustment techniques to minimize the potential for confounding bias and determine comparability. Although most observational studies accomplish this quite well within the limitations of the available data, there are other sources of bias that can arise in their study design, which can have a greater impact on their results. In this article, we focus mainly on some of these study design limitations that could lead to bias other than from confounding, namely exposure misclassification, time-lag bias, and selection bias. In addition, we discuss the role of the comparator used in these studies.

Data Analysis

A meta-regression analysis was used to evaluate the heterogeneity among the relative risks. A multivariate log-linear regression model was used to fit the relative risks as a function of the three study design factors, namely the presence of major bias, the comparator being metformin or other, and the outcome being mortality versus cardiovascular events. The model was weighted by the inverse of the variance of the logarithm of each relative risk. This analysis estimated the ratio of relative risks (RRR) associated independently with each of the three factors, along with the 95% CIs. From this model, we also estimated the lowest and highest predicted relative risks (PRRs) and their 95% CIs on the basis of the three study design factors.

RESULTS

As of 31 December 2015, we identified a total of 44 observational studies that assessed the cardiovascular safety of sulfonylureas (8–51). Of those, 15 studies assessed outcomes within selected populations with cardiovascular complications (8,15,16,23,24,27,30–33,35,40,41,44,49), 6 studies performed within-class comparisons (9,19,28,34,39,47), and 4 studies used patients without type 2 diabetes as comparators (10,18,50,51). The remaining 19 studies were conducted within unselected populations (11–14,17,20–22,25,26,29,36–38,42,43,45,46,48). These 19 studies were assessed independently by the two authors for their study design quality.

The aforementioned studies were classified into one of four categories: exposure misclassification (17,36,42), time-lag bias (12,13,20,25,26,37,42,45,48), selection bias (14,22), and studies with no major biases (11,21,29,38,43,46). Overall, the relative risks ranged between 1.37 and 1.70 in studies with exposure misclassification, between 0.95 and 2.08 in studies with time-lag bias, between 1.23 and 1.24 in studies with selection bias, and between 0.95 and 1.55 in studies with no major biases. These studies are listed in Tables 1 and 2, and their biases are described in detail below along with some illustrative examples.

Exposure Misclassification

Exposure misclassification is invariably a limitation of all observational studies. However, in many studies investigating the association between the use of sulfonylureas and cardiovascular outcomes, this exposure misclassification was magnified by using intent-to-treat (ITT) analyses (17,36,42). Just as with

Table 1—Methodological limitations of observational studies investigating the effects of sulfonylureas alone or in combination with other antidiabetic drugs on the incidence of cardiovascular events or mortality

Author	Study design	Comparison	Outcome(s)	Relative risk[a] (95% CI)
Exposure misclassification				
Evans et al. (17)	Cohort	Sulfonylureas vs. metformin	All-cause mortality	1.43 (1.15–1.77)
		Sulfonylureas vs. metformin	Cardiovascular mortality	1.70 (1.18–2.45)
Corrao et al. (36)	Cohort	Sulfonylureas vs. metformin	All-cause mortality	1.37 (1.26–1.49)
Pantalone et al. (42)	Cohort	Glipizide vs. metformin	All-cause mortality	1.64 (1.39–1.94)
		Glyburide vs. metformin	All-cause mortality	1.59 (1.35–1.88)
		Glimepiride vs. metformin	All-cause mortality	1.68 (1.37–2.06)
Time-lag bias				
Mannucci et al. (12)	Cohort	Sulfonylurea + metformin vs. other antidiabetic drugs	All-cause mortality	2.08 (1.18–3.67)[b] 1.68 (1.01–2.79)[c]
Koro et al. (13)	Nested case-control	Sulfonylureas vs. no treatment	CHF	1.19 (1.02–1.39)
Kahler et al. (20)	Cohort	Sulfonylureas vs. metformin	All-cause mortality	1.15 (0.91–1.47)[d]
		Sulfonylureas vs. TZD	All-cause mortality	1.04 (0.75–1.46)[d]
Tzoulaki et al. (25)	Cohort	Sulfonylureas vs. metformin	All-cause mortality	1.37 (1.11–1.71)[e]
		Sulfonylureas vs. metformin	All-cause mortality	1.24 (1.14–1.35)[f]
Pantalone et al. (26)	Cohort	Sulfonylureas vs. metformin	CHF	1.32 (1.10–1.56)[d]
		Sulfonylureas vs. metformin	All-cause mortality	1.85 (1.56–2.17)[d]
		Sulfonylureas vs. pioglitazone	All-cause mortality	1.69 (1.23–2.33)[d]
Horsdal et al. (37)	Case-control	Sulfonylureas vs. metformin	Myocardial infarction	1.16 (1.05–1.28)[d]
		Sulfonylureas vs. insulin	Myocardial infarction	1.09 (1.01–1.16)[d]
Pantalone et al. (42)	Cohort	Glipizide vs. metformin	All-cause mortality	1.64 (1.39–1.94)
		Glyburide vs. metformin	All-cause mortality	1.59 (1.35–1.88)
		Glimepiride vs. metformin	All-cause mortality	1.68 (1.37–2.06)
Currie et al. (45)	Cohort	Sulfonylureas vs. metformin	All-cause mortality	1.75 (1.64–1.86)
Ghotbi et al. (48)	Cohort	Sulfonylureas vs. insulin	MACE[g]	0.95 (0.73–1.22)
		Sulfonylureas vs. insulin	All-cause mortality	1.20 (0.90–1.60)
Selection bias				
Johnson et al. (14)	Cohort	Sulfonylureas vs. metformin	Nonfatal hospitalization, all-cause mortality	1.23 (1.03–1.47)[d]
McAlister et al. (22)	Cohort	Sulfonylureas vs. metformin	CHF	1.24 (1.01–1.54)

MACE, major adverse cardiovascular event; TZD, thiazolidinedione. [a]Relative risk is used as a generic term for rate ratio, HR, and odds ratio. [b]Estimated among women. [c]Estimated among men. [d]For consistency with the rest of the table, the relative risks and 95% CIs were inversed when sulfonylureas were the comparator group. [e]Analysis based on first-generation sulfonylureas. [f]Analysis based on second-generation sulfonylureas. [g]Included nonfatal myocardial infarction, nonfatal stroke, resuscitation after cardiac arrest, or cardiovascular death.

RCTs, the ITT approach assumes patients remain on the initial treatment throughout the follow-up period, regardless of treatment discontinuation and, in some cases, also regardless of treatment intensification or switching. Unlike in RCTs, however, this approach will not ensure that potential confounders are well balanced between the exposure groups, thus necessitating advanced study design and statistical methods to control for confounding. The appeal of using this approach within an observational setting is its simplicity of implementation, while minimizing potential biases related to censoring patients at the time of treatment discontinuation, particularly if the latter is related to the outcome of interest.

An example of this approach is one study using databases from the Italian region of Lombardy (36). In this well-conducted study, the authors identified a cohort of 70,437 patients who initiated metformin or a sulfonylurea in monotherapy between 2001 and 2003. Patients were followed from the date of the first prescription until the first hospitalization for macrovascular disease, death, emigration, or end of the study period (31 July 2007). Thus, patients were considered exposed to their initial treatment, either metformin or sulfonylureas, for up to 7 years after their first prescription, regardless of treatment termination or switch to another antidiabetic drug during this period. Overall, compared with metformin, the use of sulfonylureas was associated with an increased risk of hospitalization (hazard ratio [HR] 1.15 [95% CI 1.08–1.21]) and death from any cause (HR 1.37 [95% CI 1.26–1.49]). The ITT approach generally, and particularly in RCTs, leads to a nondifferential misclassification of exposure that results in biasing the risk estimates toward a null effect. However, there are certain situations, particularly in observational studies, where the opposite can occur. In the present example, the authors provided a useful analysis showing that sulfonylurea users were more likely to have switched to insulin during the follow-up period than metformin users (HR 1.55 [95% CI 1.43–1.68]). This may be related to the fact that sulfonylureas have a lower efficacy in lowering HbA_{1c} than metformin (52). It may also be related to the fact that sulfonylurea users had advanced disease when they initiated treatment and were thus more likely to progress to using the last-line treatment (i.e., insulin) than metformin users. As diabetes severity is likely associated with an increased risk of cardiovascular events, the ITT approach in this study

Table 2—Observational studies with no major biases assessing the cardiovascular safety of sulfonylureas

Author	Study design	Comparison	Outcome(s)	Relative risk[a] (95% CI)
Cardiovascular events				
McAfee et al. (21)	Cohort	Sulfonylureas vs. metformin	MI and coronary revascularization	1.30 (1.04–1.61)
Schramm et al. (38)	Cohort	Glimepiride vs. metformin	MACE	1.32 (1.24–1.40)
		Glyburide vs. metformin	MACE	1.19 (1.11–1.28)
		Glipizide vs. metformin	MACE	1.27 (1.17–1.38)
		Tolbutamide vs. metformin	MACE	1.28 (1.17–1.39)
Roumie et al. (43)	Cohort	Sulfonylureas vs. metformin	MACE	1.16 (1.08–1.25)
All-cause mortality				
Gulliford et al. (11)	Cohort	Sulfonylureas + metformin vs. metformin	All-cause mortality	0.95 (0.64–1.40)
Azoulay et al. (29)	Nested case-control	Sulfonylureas vs. metformin	All-cause mortality	1.43 (1.33–1.56)
Wheeler et al. (46)	Cohort	Glyburide vs. metformin	All-cause mortality	1.38 (1.27–1.50)
		Glipizide vs. metformin	All-cause mortality	1.55 (1.43–1.67)

MACE, major adverse cardiovascular event; MI, myocardial infarction. [a]Relative risk is used as a generic term for rate ratio, HR, and odds ratio.

likely led to an overestimation of the association. This potential bias could have been minimized by limiting follow-up to a shorter time period (e.g., 1 year) and/or using an as-treated exposure definition that would have limited the follow-up to the time while on treatment, or using a corresponding time-dependent analysis.

Time-Lag Bias

Time-lag bias arises when comparing treatments at different stages of the disease process (53). As duration of diabetes has been previously associated with cardiovascular outcomes (54), comparing drugs prescribed at different stages of the disease can introduce important bias (53). For example, in cohort studies, time-lag bias can be introduced when comparing a second- to third-line treatment (e.g., thiazolinedediones) to a first-line treatment (e.g., metformin). Such comparisons introduce confounding by disease severity that may be difficult to control for in the analysis (see Fig. 1 for a graphical representation of this bias). This bias can also be present in case-control studies if the duration of the disease is different between case and control subjects.

A number of observational studies investigating the cardiovascular effects of sulfonylureas were likely affected by time-lag bias (12,13,20,25,26,37,42,45,48). In one study using the U.K. General Practice Research Database (GPRD) (now known as the Clinical Practice Research Datalink [CPRD]), the authors conducted a nested case-control analysis to assess the association between different antidiabetic drugs and the risk of congestive heart failure (CHF) (13). The underlying cohort included 21,888 patients newly diagnosed with type 2 diabetes, of which 1,301 were diagnosed with CHF during follow-up (case subjects). These case subjects were then matched to 7,788 control subjects who were never diagnosed with CHF during follow-up on age, sex, and calendar year of the CHF diagnosis. Overall, compared with sulfonylurea monotherapy, the combination of metformin with sulfonylureas was associated with an increased risk of CHF (odds ratio 1.38 [95% CI 1.13–1.69]). It is important to note that calendar time was the underlying time axis used to match case and control subjects, and not duration of disease. As such, this may result in a differential duration of disease between case and control subjects. In this particular example, it is possible that case subjects were more likely to be using a combination therapy if their duration of disease was on average longer than in their matched control subjects. Conversely, because of the random selection of control subjects, it is also possible for control subjects to have a longer duration of disease compared with case subjects. As a result, failure to match on disease duration can produce spurious results that can go in either direction (i.e., increased risk as observed in this study or decreased risk).

In another study using the U.K. GPRD, the authors conducted a large cohort study among 91,521 patients to assess the association between different antidiabetic drugs and the risk of myocardial infarction, CHF, and all-cause mortality (25). The unit of analysis was the time interval on which a patient was using a specific antidiabetic drug. For example, a patient starting treatment with metformin monotherapy and then switching to a sulfonylurea would contribute two time intervals, one corresponding to metformin and another corresponding to sulfonylurea. As a result, the 91,521 patients included in the study generated 2,843,007 intervals of treatment with antidiabetic drugs. Using metformin monotherapy as the reference, the authors reported that monotherapy with sulfonylureas (either first or second generation) was associated with increased risks of all three outcomes. The methodology used in this study may hold well in settings where the time intervals are assumed to be interchangeable, i.e., where the risk of the outcome of interest is the same regardless of follow-up or disease duration. In the context of the progressive nature of type 2 diabetes, however, this assumption is unlikely to hold. As a result, comparing treatment intervals that are separated by several years may introduce time-lag bias, as it becomes difficult to separate the effects of the drug from the effects of the underlying disease progression. While one method for minimizing this potential bias can be to adjust the statistical models for duration of diabetes (as was done by the authors), the latter is at best a moderate proxy for diabetes severity. Alternatively, matching the treatment intervals on diabetes duration or defining exposure as a time-varying variable using duration of diabetes as the underlying time axis may be a more effective means of minimizing this source of confounding.

Choice of the Comparator

The choice of the comparator group is another major consideration in observational studies assessing the safety of second- to third-line antidiabetic drugs, which can affect the risk estimates

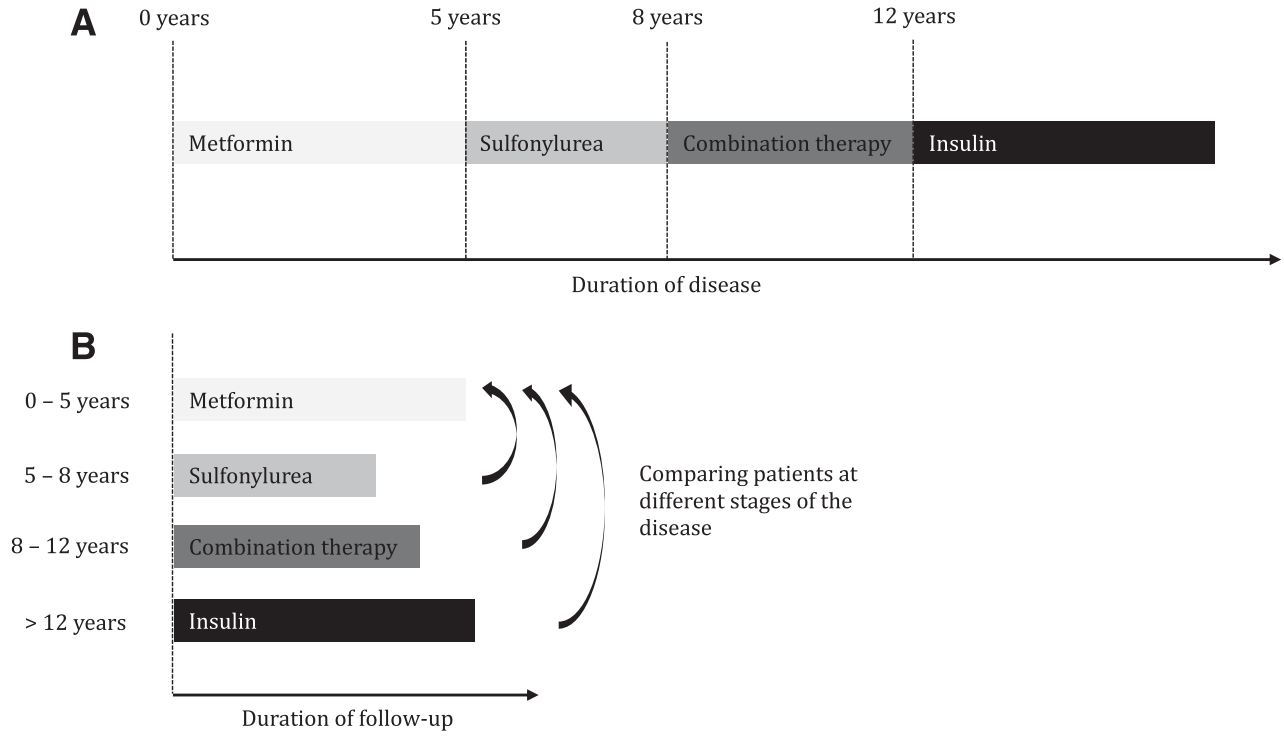

Figure 1—Time-lag bias introduced by comparing patients at different stages of the disease progression. *A*: Treatment trajectory of a hypothetical patient. *B*: Time-lag bias is introduced when comparing patients at different stages of the disease, in this case, the use of different antidiabetic drugs to metformin.

above and beyond the biases described above. For instance, using as comparator thiazolidinediones, which have been associated with an increased risk of cardiovascular events (55), could lead to an underestimation of the association. In contrast, another approach has been to compare the use of sulfonylureas with "no use," a comparator group consisting of patients not currently using any antidiabetic drug (13). As this comparator group may include patients with less severe disease not requiring pharmacological treatment, comparing an antidiabetic drug to this comparator may lead to an overestimation of the association. Indeed, in one study assessing the association between different antidiabetic drugs and the risk of CHF, sulfonylurea monotherapy was associated with a 19% increased risk (HR 1.19 [95% CI 1.02–1.39]) when compared with no use (13). Interestingly, a similar HR was observed with metformin monotherapy (HR 1.20 [95% CI 0.97–1.48]), a drug thought to have neutral effects on cardiovascular risk (13). Finally, a common approach has been to compare a specific antidiabetic drug with "any use" of other antidiabetic drugs. The latter may include a mix of patients using antidiabetic drugs in monotherapy, combination users, and insulin users. As such, this comparator group includes patients with different disease severities, rendering the findings difficult to interpret.

Selection Bias

Selection bias is an important threat to the validity of observational studies. Selection bias is a systematic error that occurs when the selection of patients into a study is influenced by their exposure and disease status. Some of the observational studies investigating the association between sulfonylureas and cardiovascular outcomes likely suffered from selection bias (14,22). For example, in one study using the Saskatchewan Health administrative databases, the authors conducted a cohort study among 5,702 patients to assess whether metformin monotherapy is associated with a lower risk of a composite end point of first nonfatal hospitalization for any cause or death, compared with sulfonylurea monotherapy (14). Overall, metformin monotherapy, compared with sulfonylureas, was associated with a decreased risk of the composite end point (HR 0.81 [95% CI 0.68–0.97]), which corresponds by numerical inversion to an increased risk with sulfonylureas (HR 1.23 [95% CI 1.03–1.47]), compared with metformin. Although this study had several strengths, a number of exclusions may have affected the findings. Specifically, out of the 12,188 patients prescribed oral antidiabetic drugs during the study period (1991–1999), 6,486 (53.2%) patients were excluded on the basis of future events occurring during the follow-up period (such as a dispensation of insulin [n = 1,443], $<$1 year of oral antidiabetic drug use [n = 2,009], and receiving less than the recommended average daily dose during one or more 6-month intervals [n = 3,034]). These exclusion criteria all involve immortal time, which implies that the patient necessarily had to be alive during part of the follow-up period to satisfy one of the criteria. For example, the 1,443 patients excluded because they received insulin some time during follow-up had to be alive at the time that they received the insulin; such exclusions will introduce immortal time bias (56). The magnitude of this bias will be particularly important if the time to insulin is longer in one group than the other, which we suspect to be the case

with metformin (longer time to starting insulin) and sulfonylureas (shorter time). Consequently, selection bias was likely introduced in an effort to create mutually exclusive groups of sulfonylurea and metformin monotherapy users during the entire follow-up period.

Studies With No Major Biases

All observational studies are prone to some degree of bias. However, certain design and analytical choices could minimize these biases. To date, six observational studies did not suffer from the major biases discussed above (11,21,29,38,43,46). For example, in the study by Roumie et al. (43), the authors used the Veterans Health Administration databases to assess whether sulfonylurea monotherapy (n = 98,665) was associated with an increased risk of a composite of acute myocardial infarction, stroke, or death, compared with metformin monotherapy (n = 155,025). In addition to its large sample size, this study restricted the cohort to patients newly treated with these drugs (defined as no prescription in the year before), thereby minimizing time-lag bias (53). It also used an as-treated exposure definition that followed patients until a switch or an addition of another antidiabetic drug, an outcome, or one of the study's censoring events, an approach that minimized exposure misclassification. In addition, the study minimized the potential for confounding bias, with the use of propensity score matching of the patients on sulfonylurea monotherapy with those on metformin monotherapy. Overall, the use of sulfonylureas was associated with a modest increased risk of the composite end point (HR 1.16 [95% CI 1.08–1.25]).

Meta-Regression Analysis

The results of the meta-regression log-linear model analysis are summarized in Table 3. Overall, the relative risk of an adverse event is higher by 13% when the comparator is metformin with an RRR of 1.13 (95% CI 1.01–1.27). Moreover, the relative risk is higher by 20% when death is the outcome (RRR 1.20 [95% CI 1.07–1.34]). Finally, for the studies with major bias as defined above, the relative risk was higher by 7% (RRR 1.07 [95% CI 0.95–1.20]). As a result of this model, the lowest PRR was for studies with no major bias, where the comparator was other than metformin and where the outcome was a nonfatal cardiovascular event (lowest PRR 1.06 [95% CI 0.92–1.23]). The highest PRR was for studies with major bias, where the comparator was metformin and where the outcome was mortality (highest PRR 1.53 [95% CI 1.43–1.65]).

Table 3—Crude and adjusted RRRs of adverse event associated with sulfonylurea use according to study design parameters from the meta-regression analysis of 36 estimates of relative risk from the observational studies listed in Tables 1 and 2

	Number of relative risk estimates	Mean relative risk	Crude RRR	Adjusted RRR* (95% CI)
Comparator				
Metformin	27	1.43	1.08	1.13 (1.01–1.27)
Other (reference)	9	1.32	1.00	1.00 (reference)
Outcome				
Death	24	1.50	1.24	1.20 (1.07–1.34)
Cardiovascular (reference)	12	1.21	1.00	1.00 (reference)
Major bias				
Yes	26	1.44	1.13	1.07 (0.95–1.20)
No (reference)	10	1.28	1.00	1.00 (reference)

*Adjusted for one another and weighted by the inverse of the variance.

CONCLUSIONS

Assessing the cardiovascular safety of second- to third-line antidiabetic drugs can be challenging. As discussed above, certain design and analytical decisions can help circumvent some of these challenges and the biases that ensue. First, given the progressive nature of type 2 diabetes, the primary exposure definition should be based on an as-treated approach or modeling exposure as a time-varying variable. An ITT exposure could also be used to complement the aforementioned exposure definitions but will need to be limited to a relatively short follow-up period (e.g., 1 year) to avoid the exposure misclassification issues described above. Second, it is important to compare drugs used at a similar stage of the disease to avoid time-lag bias (53). For example, comparing a combination of metformin and sulfonylurea (a second- to third-line treatment strategy) to metformin monotherapy (a first-line treatment strategy) will introduce important confounding by indication that may be difficult to adjust for in the statistical models. The alternative would be to compare a combination therapy with another combination used at a similar stage of the disease, or alternatively match the combination users with monotherapy users on diabetes duration. Third, inclusion of patients in a study should not be based on future events occurring during the follow-up period (such as excluding patients eventually exposed to a specific antidiabetic drug); such inclusion criteria could lead to important selection bias. Instead, such patients should be allowed to be included in the cohort, and other mechanisms such as censoring could be used to mitigate this issue (assuming the censoring is noninformative). Finally, rigorous adjustment of potential confounders is necessary; this can be achieved with the use of methods such as propensity scores or marginal structural models (57).

In addition to the methodological issues described above, it is important to recognize that there are differences in the pharmacodynamic and pharmacokinetic properties of the different sulfonylureas; these may have an impact on their association with cardiovascular outcomes (58). Indeed, some sulfonylureas are not selective for pancreatic β-cells and thus may increase the risk of cardiovascular outcomes by binding to receptors in other tissues, such as cardiomyocytes and vascular smooth muscle cells (59). As such, it will be necessary for future studies to assess the effects of sulfonylureas as a class, as well as the effects of each individual sulfonylurea.

Understanding the cardiovascular effects of sulfonylureas is also important because many RCTs of the newer antidiabetic drugs use sulfonylureas as the comparator drug or include them as part of the comparator regimen. Thus, the safety assessment of these newer drugs can inherently possibly conceal an increased cardiovascular risk if the comparator group includes a treatment that increases this risk. Likewise, it is possible that the benefits on cardiovascular and mortality outcomes observed in some of the recent trials may be due, at least in part, to the fact that a higher proportion of patients in the placebo

arms initiated sulfonylureas during the follow-up period (60–62). Thus, our present meta-regression analysis of the observational studies to data suggests that some caution be used in interpreting the data from such recent trials when sulfonylureas are involved in the comparator.

The cardiovascular safety of some of the newer antidiabetic agents, such as DPP-4 inhibitors, has also recently been the subject of some concern. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 trial, patients randomized to saxagliptin had a higher risk of hospitalization for CHF compared with placebo (HR 1.27 [95% CI 1.07–1.51]) (63). In contrast, this association was not observed in the vast majority of the observational studies conducted to date (64–72), with the exception of two studies (73,74). Although the absence of an association in most of these studies provides some reassurance with respect to CHF, the assessment of other cardiovascular outcomes will require careful attention to design-related decisions. As the newer antidiabetic drugs are intended to be used as second- to third-line treatments, it will be imperative that they are compared with drugs used at a similar stage of the disease, and using the appropriate exposure definitions. Failure to consider these important design-related decisions will likely introduce bias and, in the process, generate more uncertainty on the safety of these drugs.

In summary, the majority of the studies reporting on the association between sulfonylureas and cardiovascular risk had design-related biases, such as exposure misclassification, time-lag bias, and selection bias. However, the majority of studies with no major designed-related biases reported increased risks of cardiovascular events and mortality with sulfonylureas. Overall, the role of the comparator drug used had an important bearing on the risk estimates. Indeed, the lowest PRR was for studies with none of the major biases described above, where the comparator was not metformin, and where the event definition was based on a cardiovascular outcome. In contrast, the highest PRR was for studies with major biases, where metformin was the comparator, and where the outcome was mortality. This heterogeneity highlights the need to use appropriate methodological approaches to minimize bias when assessing the safety of second- to third-line antidiabetic drugs. This is highly relevant in this era of new antidiabetic drugs (such as DPP-4 inhibitors, GLP-1 analogs, and SGLT2 inhibitors), where there will be a need to assess their cardiovascular safety in the real-world setting.

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