Is the Combination of Sulfonylureas and Metformin Associated With an Increased Risk of Cardiovascular Disease or All-Cause Mortality?

A meta-analysis of observational studies

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OBJECTIVE — Observational studies assessing the association of combination therapy of metformin and sulfonylurea on all-cause and/or cardiovascular mortality in type 2 diabetes have shown conflicting results. We therefore evaluated the effects of combination therapy of sulfonylureas and metformin on the risk of all-cause mortality and cardiovascular disease (CVD) among people with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A MEDLINE search (January 1966–July 2007) was conducted to identify observational studies that examined the association between combination therapy of sulfonylureas and metformin on risk of CVD or all-cause mortality. From 299 relevant reports, 9 were included in the meta-analysis. In these studies, combination therapy of metformin and sulfonylurea was assessed, the risk of CVD and/or mortality was reported, and adjusted relative risk (RR) or equivalent (hazard ratio and odds ratio) and corresponding variance or equivalent was reported.

RESULTS — The pooled RRs (95% CIs) of outcomes for individuals with type 2 diabetes prescribed combination therapy of sulfonylureas and metformin were 1.19 (0.88–1.62) for all-cause mortality, 1.29 (0.73–2.27) for CVD mortality, and 1.43 (1.10–1.85) for a composite end point of CVD hospitalizations or mortality (fatal or nonfatal events).

CONCLUSIONS — The combination therapy of metformin and sulfonylurea significantly increased the RR of the composite end point of cardiovascular hospitalization or mortality (fatal and nonfatal events) irrespective of the reference group (diet therapy, metformin monotherapy, or sulfonylurea monotherapy); however, there were no significant effects of this combination therapy on either CVD mortality or all-cause mortality alone.

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Type 2 diabetes is associated with increased risk of all-cause mortality and cardiovascular disease (CVD). However, clinical trials to date have not demonstrated that achieving normal glucose levels can reduce the risk for cardiovascular events.

In the UK Prospective Diabetes Study (UKPDS), intensive blood glucose reduction was achieved using metformin therapy in diet-treated overweight patients, resulting in a decreased risk of myocardial infarction and all-cause mortality. However, when a combination of metformin and sulfonylurea was prescribed in the same trial for glycemic control, there was a significant increased risk of diabetes-related death and all-cause mortality rather than a beneficial effect, a finding attributed by the investigators to be due to chance (1). In the UKPDS, sulfonylureas themselves were not associated with the risk of diabetes-related death or myocardial infarction (2), but in previous studies such as the University Group Diabetes Program (UGDP) some increased risk was seen (3), and a warning about increased risk of CVD is included in the Federal Drug Administration–approved label for this class of drugs.

A recent systematic review of clinical trials of diabetes therapies noted that data on long-term outcomes were not available in most clinical trials (4). Observational studies investigating the association between combination therapy of metformin and sulfonylureas and risk of CVD and mortality have reported conflicting results. Some studies have reported that the use of this combination therapy increases the risk of all-cause and CVD mortality (5), while others have reported no association (6,7) or a decreased risk of mortality from all causes and CVD (8). Since these are likely the most commonly prescribed medications for type 2 diabetes, the possible increase in risk of all-cause mortality and cardiovascular events is troubling (1).

Given these inconsistencies in the literature and the lack of clinical trials assessing the long-term effects of combination therapy of sulfonylureas and metformin, we conducted a meta-analysis of observational studies to examine the association between combination therapy of sulfonylureas and metformin and risk of CVD and all-cause mortality.

RESEARCH DESIGN AND METHODS

A literature search of the MEDLINE database (from January 1966 through July 2007) was conducted using the medical subject headings "diabetes mellitus, type 2;" "drug therapy, combination;" "drug combinations;" "sulfonylurea compounds;" "acetohexamide;" "chlorprop-

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amide;" "tolbutamide;" "tolazamide;" "glyburide;" "glipizide;" "biguanides;" and "metformin" and keyword "glimepiride." The search was restricted to include studies conducted only in human subjects. Studies were also identified through a search of references cited in the original published studies and relevant review articles.

The contents of 299 abstracts or full-text manuscripts identified during the literature search were reviewed independently by two investigators in duplicate to determine whether they met the criteria for inclusion. When there were discrepancies between investigators for inclusion or exclusion, a third investigator conducted additional evaluation of the study and the discrepancies were resolved in conference. The following inclusion criteria were used for study selection: *1*) observational study that investigated the relationship between combination therapy with metformin (biguanides) plus sulfonylureas and risk of CVD and/or mortality, *2*) adjusted relative risk (RR) or equivalent (i.e., hazard ratio, odds ratio) and corresponding variance or equivalent reported, and *3*) diagnosis of type 2 diabetes established using the standard criteria for the time of the study.

All data were independently abstracted in duplicate. Differences in data extraction were resolved in conference and by referencing the original publication. No authors were contacted to request additional information. A standardized abstraction form was used to record the following information: study title, first author's name, year of publication, study country, study years, name of cohort, study design (prospective or retrospective cohort study or case-control study), duration of follow-up, characteristics of the study population (sample size, distribution of age, race, and sex, mean diabetes duration, mean A1C), type of reference group, and confounding factors controlled for. The RR of cardiovascular mortality/morbidity and/or all-cause or cause-specific mortality associated with combination therapy and their corresponding CIs or SEs were abstracted. The number of events for all-cause mortality and cardiovascular mortality/morbidity were abstracted.

Statistical analysis

RRs were used as the measure of association between combination therapy of metformin and sulfonylurea and CVD and all-cause mortality. The RRs of each study were weighted by the inverse of their variance. To stabilize the variances and to normalize the distributions, the RRs and corresponding SEs from each of the individual studies were transformed to their natural logarithms. When necessary, SEs were derived from the CIs provided in each original study.

The primary data for time to event analyses were not available for the combined cohort. Therefore, for the overall analysis, RR estimates and 95% CIs for all-cause mortality and CVD associated with combination therapy were pooled irrespective of the reference group used. Subgroup analyses were conducted by reference group (diet, sulfonylurea monotherapy, or metformin monotherapy).

Both fixed-effects and DerSimonian and Laird random-effects models were used to calculate the pooled RR of CVD and all-cause mortality associated with combination therapy (9). Although both models yielded similar findings, results from the random-effects model are presented herein owing to significant heterogeneity among the studies.

CVD was defined by each of the individual studies. We used cardiovascular mortality and all-cause mortality, as well as a composite end point of CVD hospitalizations (the first cardiovascular event either fatal or nonfatal event), or mortality as our study outcomes. One study reported RRs separately for coronary heart disease and stroke (10). For this study, we first weighted both of the RRs by the inverse of their variance and then pooled the RRs by using a fixed-effects model to obtain an overall estimate for the study.

Begg's rank correlation test was used to examine the association between effect estimates and their variances, and Egger's linear regression test, which regresses *Z* statistics on the reciprocal of the SE for each study, was used to detect publication bias (11,12). Additionally, each study was omitted one at a time to evaluate the influence of that study on the pooled estimate. All analyses were performed using STATA version 8.2 (STATA, College Station, TX).

RESULTS — Online appendix Figure A1 (available at http://dx.doi.org/10.2337/dc08-0167) depicts the flow of studies in the meta-analysis. Among 25 studies that met the inclusion criteria, 16 were excluded from the meta-analysis. Eleven studies did not report CVD or mortality as an outcome, three studies were duplicated, and two involved multiple drug combinations. Two studies examined the association between combination therapy of metformin and sulfonylurea in different groups of individuals according to which drug was given first, and these groups were treated as separate studies in the meta-analysis.

The characteristics of the study participants and the design of the nine observational studies included in the meta-analysis are presented in Table 1 (5–8,10,13–16). Six of the studies were retrospective cohort studies, two were prospective cohort studies, and one was a nested case-control study. Of the nine studies, one was conducted in the U.S., two in Canada, one in Israel, and five in European countries. The number of participants in these studies ranged from 910 in the study by Olsson et al. (10) to 39,721 in the study by Kahler et al. (7). Mean age ranged from 58.9 to 71.3 years. The mean follow-up time ranged from 2.1 to 7.7 years. Among the nine studies, seven reported all-cause mortality, four reported cardiovascular mortality, and three reported cardiovascular hospitalizations. Of the 101,733 participants included in these studies, 25,091 participants received a combination therapy of metformin and sulfonylurea. Bruno et al. (13) and Koro et al. (16) did not specify the number of participants receiving combination therapy.

Figure 1 depicts the results from the random-effects models pooling the adjusted RRs for all-cause mortality, CVD mortality, and CVD hospitalizations or mortality, respectively, associated with combination therapy of metformin and sulfonylurea. In addition, it shows the number of events associated with combination therapy in comparison with the control group for all-cause mortality, CVD mortality, and CVD hospitalizations or mortality. Pooled RR estimates were not statistically significant for all-cause mortality or CVD mortality, while the use of combination therapy was significantly associated with an increased risk of cardiovascular hospitalizations or mortality.

In sensitivity analyses, significant heterogeneity was present for studies reporting all-cause mortality ($P < 0.001$). However, exclusion of any study did not change the pooled estimate. For studies reporting CVD mortality, significant heterogeneity was present ($P < 0.001$), and exclusion of the study by Johnson et al. (15) led to a significant increased risk of CVD mortality associated with combination therapy of metformin and sulfonyl-

Table 1—*Characteristics of observational studies of combination therapy with metformin and sulfonylurea associated with risk of CVD and mortality*

Author, publication year (ref.)	Country, period of study	Sample size	Age (Years)	Diabetes duration (years)	A1C (%)	Male (%)	Variables controlled for	Duration of follow-up (years) and follow-up process	Combination therapy vs. control group	Outcome and diagnostic criteria
Bruno, 1999 (13)	Italy, 1988–1995	1,967	58.9	8.5	—	42.6	Age, sex, FBG, smoking, BMI, hypertension, duration of diabetes, calendar period, referring physician	7, town demographical files, death certificates‡	Sulfonylurea + biguanides vs. diet group	Stroke, IHD, CVD, and all-cause mortality; IHD: ICD-9 (410–414); Stroke: ICD-9 (430–438)
Olsson, 2000 (10)	Sweden, 1984–1996	910	—	—	7.5	—	Age, sex, FBG, duration of diabetes, study area, year of inclusion	6.1, Swedish mortality register*	Sulfonylurea + metformin vs. sulfonylurea monotherapy	Stroke, IHD, and all-cause mortality; IHD: ICD-8 (410–414); Stroke: ICD-8 (430–438)
Fisman, 2001 (14)	Israel	2,275	60.1	—	—	74.5	Age, sex, FBG, smoking, BMI, hypertension, use of beta-blockers and antiplatelet drugs, PVD previous CVA, anginal syndrome, CHF	7.7*	Sulfonylurea + metformin vs. diet group	All-cause mortality
Johnson, 2002 (8)	Canada, 1991–1996	8,866	64.1	—	—	55.9	Age, sex, nitrate use, modified chronic disease score	5.1, Saskatchewan Health computerized vital statistics*	Sulfonylurea + metformin vs. sulfonylurea monotherapy	CVD and all-cause mortality; CVD: ICD-9 (390–459)
Gulliford, 2004 (6)	U.K., 1992–1998	11,587	64.2	—	—	52.6	Age, sex, year of treatment, CHD, cardiovascular drugs	2.1, general practice research database †	A. Sulfonylurea first, added metformin vs. sulfonylurea monotherapy; B. metformin first, added sulfonylurea vs. metformin monotherapy	All-cause mortality
Johnson, 2005 (15)	Canada, 1991–1999	4,142	65.6	—	—	56.0	Age, sex, nitrate use, chronic disease score	9, Saskatchewan Health computerized vital statistics‡	Sulfonylurea + metformin vs. sulfonylurea monotherapy	CVD hospitalizations and CVD mortality; CVD: ICD-9
Koro, 2005 (16)	U.K., 1987–2001	9,089	71.3	—	—	52.3	Age, sex, hypertension, duration of diabetes, CHF, angina, MI, IHD, PVD, retinopathy, nephropathy, neuropathy foot ulcers and gangrene, ESRD, valvular disease	3.4, general practice research database *	Sulfonylurea + metformin vs. sulfonylurea monotherapy	Incident CHF (mortality or hospitalizations) defined as an Oxford Medical Information System code or Read medical code
Evans, 2006 (5)	Scotland, 1994–2001	5,730	63.6	3.9	—	54.1	Age, sex, smoking, duration of diabetes, blood pressure, cholesterol, A1C previous hospital admission, treatment with cardiovascular medication	8, death certificates from the Registrar General‡	A. Sulfonylurea first, added metformin vs. metformin monotherapy; B. metformin first, added sulfonylurea vs. metformin monotherapy; C. Sulfonylurea + metformin vs. metformin monotherapy	CVD hospitalizations and CVD and all-cause mortality; CVD: ICD-9 and ICD-10
Kahler, 2007 (7)	U.S., 1998–2001	39,721	66.9	—	7.4	98	Age, duration of diabetes, A1C, propensity score, creatinine, diabetes-related physician visits, use of lipid lowering and hypertensive medications	3, Veterans Health Administration mortality database‡	Metformin + sulfonylurea vs. sulfonylurea monotherapy	All-cause mortality

CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; ESRD, end-stage renal disease; FBG, fasting blood glucose; IHD, ischemic heart disease; MI, myocardial infarction; PVD, peripheral vascular disease. *Mean follow-up length. †Median follow-up length. ‡Maximum follow-up length.

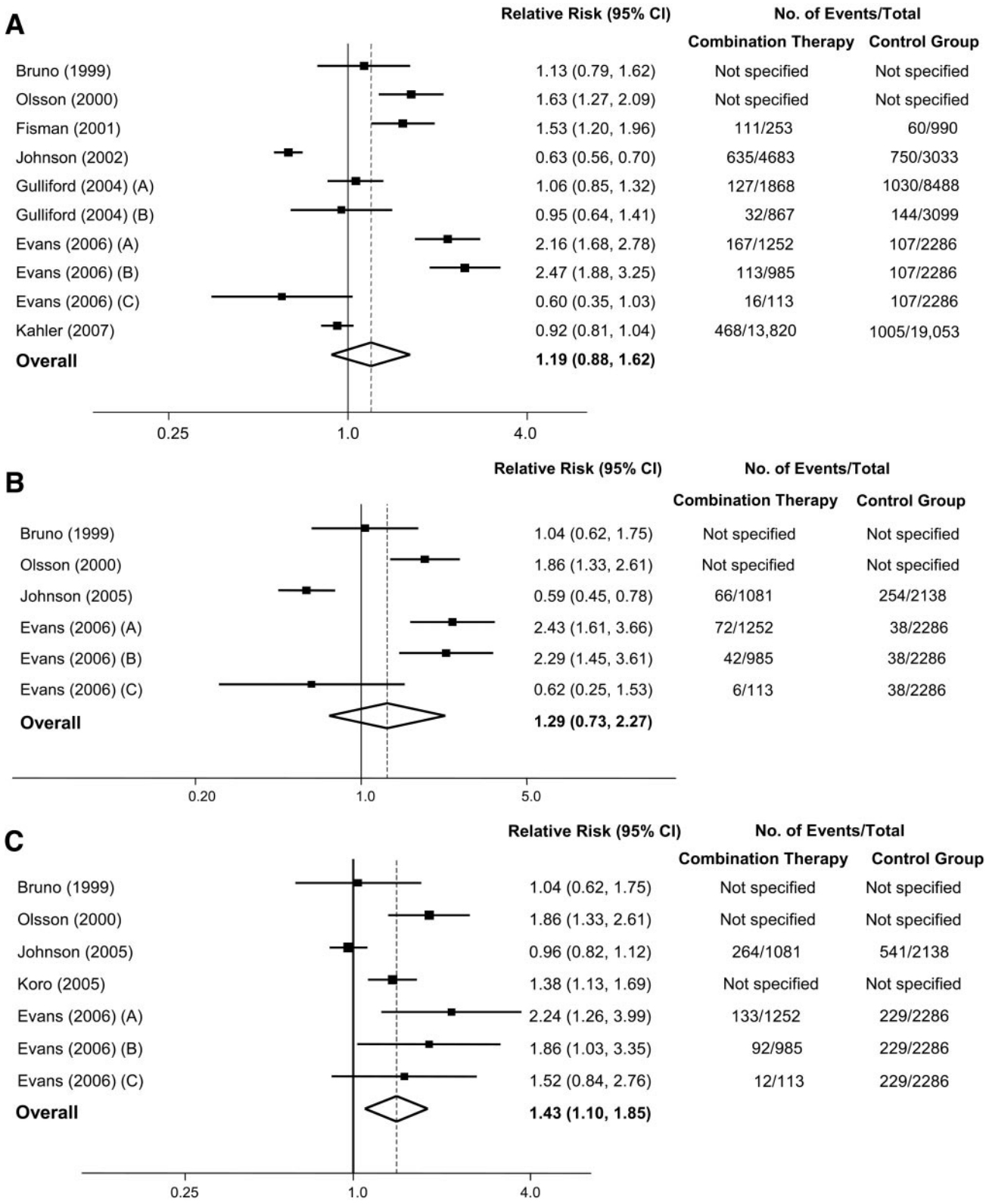

Figure 1—*RR estimates and 95% CIs for all-cause mortality (*A*), CVD mortality (*B*), and composite end point of CVD hospitalizations or CVD mortality (C) associated with combination therapy of metformin and sulfonylurea by study and pooled along with proportion of events for each outcome.*

ureas (RR 1.63 [95% CI 1.11–2.39]). Significant heterogeneity was also present for studies that reported cardiovascular hospitalizations or mortality ($P = 0.001$), and the exclusion of any study did not alter the pooled estimate. There was no evidence of publication bias by rank correlation or regression testing ($P > 0.10$ for all). In the study by Evans et al. (5), par-

Table 2—*Pooled RR (95% CI) of all-cause mortality, CVD mortality, and composite end point of CVD hospitalizations or CVD mortality according to different exclusion criteria*

	All-cause mortality		CVD mortality		CVD hospitalizations or CVD mortality	
	No. of studies	RR (95% CI)	No. of studies	RR (95% CI)	No. of studies	RR (95% CI)
All studies	10	1.19 (0.88–1.62)	6	1.29 (0.73–2.27)	7	1.43 (1.10–1.85)
Studies that controlled for important confounding factors*	6	1.36 (0.93–2.04)	5	1.63 (1.11–2.39)	6	1.55 (1.28–1.87)
Studies that controlled for important confounding factors†	4	1.34 (0.73–2.47)	3	1.72 (0.93–3.20)	4	1.50 (1.25–1.78)

*Studies that did not control for duration of diabetes excluded. For all-cause mortality, excluding the studies by Gulliford (12), Johnson (14), and Fisman (21). For CVD mortality and the composite end point of CVD hospitalizations or CVD mortality, excluding the study by Johnson (23). †Studies that did not control of duration of diabetes or previous CVD excluded. For all-cause mortality, excluding the studies by Gulliford (12), Johnson (14), Olsson (16), Bruno (20), and Fisman (21). For CVD mortality and the composite end point of CVD hospitalizations or CVD mortality, excluding the studies by Olsson (16), Johnson (23), and Bruno (20).

ticipants of the reference group were used more than once in computing the pooled estimate. Analyses were repeated omitting various combinations of this study, and no substantive changes in results were noted. Furthermore, we conducted a sensitivity analysis in which those studies that did not adjust for duration of diabetes or previous CVD were excluded (6,8,13,14,17). This information is included in Table 2.

Subgroup analysis

RR estimates of all-cause mortality, CVD mortality, and CVD hospitalizations or mortality associated with combination therapy of metformin and sulfonylurea for subgroups defined according to the comparator treatment are presented in online appendix Table A1. The estimated RRs were >1.0 in all subgroups except for the association between all-cause mortality and combination therapy compared with sulfonylurea.

Compared with diet therapy, combination therapy significantly increased the RR of all-cause mortality, and combination therapy compared with metformin monotherapy significantly increased the RR of CVD hospitalizations or mortality.

CONCLUSIONS — In the current meta-analysis, combination therapy of metformin and sulfonylurea significantly increased the RR of cardiovascular hospitalization or mortality (fatal and nonfatal events) irrespective of the reference group (diet therapy, metformin monotherapy, or sulfonylurea monotherapy) used. However, there were no statistically significant effects of combination therapy of sulfonylurea and metformin on CVD mortality or all-cause mortality. These results may help clarify the conflicting findings of several large observational studies that examined the effect of combination therapy with metformin and sulfonylureas on the risk of CVD events among patients with type 2 diabetes, while the association of this combination with all-cause and cardiovascular mortality remains obscure.

Due to the progressive nature of type 2 diabetes, many patients are put on combinations of oral antihyperglycemic agents in order to meet glycemic goals. For instance, in the recommended algorithm, the combination of sulfonylurea and metformin is the second step in the management of patients with type 2 diabetes (18). It is likely that patients on combination therapy are likely to have either a more rapidly progressive form of the disease or a longer duration of diabetes, perhaps both. The reduction of blood glucose in high-risk obese patients with type 2 diabetes on metformin therapy alone in the UKPDS was associated with a decrease in adverse cardiovascular events (2). However, when a combination of metformin and sulfonylurea was prescribed, there was an increased risk, which is in contrast with some of the observational studies. This discrepancy may be due to differences in the population between these studies.

It may not only be important to reduce blood glucose, but also to consider the choice of agent used to make such a reduction. A recent meta-analysis has created much controversy about some of the newer medications used to reduce blood glucose by suggesting that rosiglitazone may be associated with an increased risk of myocardial infarction and possibly death (19). It is noteworthy that much of this increased risk with rosiglitazone was seen in combination therapies (20). However, the interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial has shown inconclusive results (21). Our meta-analysis is important in the context of that study, as the combination of metformin and sulfonylurea is the comparator group to the rosiglitazone combinations.

Several observational studies have examined the association between combination therapy and risk of CVD and all-cause mortality. Evans et al. (5) carried out an analysis of a database of 400,000 people in Scotland and identified 5,730 patients who were prescribed oral hypoglycemia agents between 1994 and 2001. Patients treated with sulfonylureas alone or in combination with metformin appeared to have an increased RR of adverse cardiovascular outcomes compared with those treated with metformin alone. It was particularly disturbing to note that the combination of sulfonylurea with metformin seemed to abrogate the potential benefit of metformin on CVD outcome, as seen in the UKPDS (2). A study by Fisman et al. (14) was carried out among 2,275 patients with type 2 diabetes and coronary artery disease, as part of the Bezafibrate Infarction Prevention Study. The patients were followed for over 7 years, and the authors demonstrated that cardiovascular events and mortality were the same whether glyburide, a sulfonylurea, or metformin was used for treatment. However, there was a significant time-related increased mortality when the combination therapy was used. Olsson et al. (10) analyzed mortality in a small cohort of patients taking sulfonylureas alone or in combination with metformin and demonstrated a higher cardiovascular mortality in patients tak-

ing the combination than those taking sulfonylurea alone.

In our meta-analysis, exclusion of the study by Johnson et al. (15) led to a significant increased risk of CVD mortality associated with combination therapy of metformin and sulfonylurea. The study by Johnson et al. (15) reported a reduced risk of CVD mortality associated with combination therapy of metformin and sulfonylurea when compared with sulfonylurea monotherapy, but the study had many limitations. A large number of patients were excluded because of short-term insulin use. Patients prescribed the combination therapy were 2.3 years younger than those prescribed metformin monotherapy and 5.8 years younger than those prescribed sulfonylurea monotherapy, a discrepancy that is difficult to explain. Patients with more severe disease or intercurrent illnesses including hospitalization for cardiovascular events may have required insulin use and were therefore excluded from the study.

In our analysis, we found a relatively greater association with fatal and nonfatal CVD events than in fatal events alone, suggesting that the incidence of CVD events may be increased with combination therapy, but there may have been a lower case-fatality rate. This contrasts with the recent data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (22) in which intensive treatment with multiple combinations of diabetes therapies was associated with decreased nonfatal CVD events but increased fatal events. It is impossible to determine the reason for this discrepancy, although it is possible that patients in the observational studies included in our analysis did not have a level of glycemia as low as that attempted in the ACCORD trial.

Several hypothetical considerations may explain the increased risk associated with such a combination. First, it is possible that patients needing such a combination have a more aggressive form of the disease and therefore more rapid deterioration in glycemic control over time. Second, sulfonylureas are associated with weight gain, whereas metformin is associated with weight loss, as well as some improvement in a variety of cardiovascular risk factors. Any weight gain induced by the combination may negate some of these beneficial effects and increase risks.

Other possible explanations include the known propensity of sulfonylureas to cause hypoglycemia. When used in combination with a drug like metformin, which may decrease hepatic glucose production, recovery from hypoglycemia may be impaired. Hypoglycemia may increase the risk of cardiovascular abnormalities, including ischemia and a propensity to cause arrhythmias (23,24). There is also considerable controversy about the impact of sulfonylureas on ischemic preconditioning (25), but nothing is known about the effects of combination therapy.

Although a meta-analysis is not the best way to test the efficacy and safety of such a combination of treatments, it is highly unlikely that a large-scale clinical trial to test this hypothesis will be carried out. Thus, we must rely on data from observational studies to arrive at conclusions and make appropriate recommendations. It is also unclear to what extent certain biases and methodological limitations, such as residual confounding, might exist in the studies included in this meta-analysis, since the majority of these studies were retrospective database analyses. In addition, the reference group varied among the studies. For instance, some studies used diet as the reference group, while others used sulfonylureas or metformin monotherapy as the reference group. Finally, we observed substantial quantitative heterogeneity across the studies, but the small number of studies limited our ability to explore possible sources of this variability. Additionally, findings from the subgroup analyses should be interpreted cautiously, as the number of studies examined was small.

Overall, our results provide a mix of reassurance and concern to prescribers of diabetes medications who use combination therapies to achieve good glycemic control. Since sulfonylurea and metformin are likely the most widely used combination, it is possible that such use leads to early improvement in glycemic control, which, in itself, may lead to better microvascular outcomes. Although diet alone is associated with lower mortality risk, in the UKPDS, diet alone was associated with increased microvascular complications (2). Therefore, one must balance the risks and benefits of medications used while making treatment decisions.

We emphasize that this meta-analysis has limitations and serves to examine published data to generate hypotheses. Such analysis should not be used as a basis for clinical decisions. We hope that our analysis will prompt the planning of future clinical trials to determine not only the value of good glycemic control, but also the safest and most cost effective way to achieve glycemic goals. Clearly, we need further studies to assess the association of combination therapy of metformin and sulfonylurea with all-cause and/or cardiovascular mortality as well as to understand the potential mechanism of its deleterious effects.

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