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.

Diabetes Care 31:1672–1678, 2008

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.

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-
mortality, sulfonylureas and risk of CVD and/or 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 or mortality (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/dci08-0167) 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 Kahl er 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>
<thead>
<tr>
<th>Author, publication year (ref.)</th>
<th>Country, period of study</th>
<th>Sample size</th>
<th>Age (Years)</th>
<th>Diabetes duration (years)</th>
<th>A1C (%)</th>
<th>Male (%)</th>
<th>Variables controlled for</th>
<th>Duration of follow-up (years) and follow-up process</th>
<th>Combination therapy vs. control group</th>
<th>Outcome and diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruno, 1999 (13)</td>
<td>Italy, 1988–1995</td>
<td>1,967</td>
<td>58.9</td>
<td>8.5</td>
<td>—</td>
<td>42.6</td>
<td>Age, sex, FBG, smoking, BMI, hypertension, duration of diabetes, calendar period, referring physician</td>
<td>7, town demographical files, death certificates ‡</td>
<td>Sulfonylurea + biguanides vs. diet group</td>
<td>Stroke, IHD, CVD, and all-cause mortality; IHD: ICD-9 (410–414); Stroke: ICD-9 (430–438)</td>
</tr>
<tr>
<td>Fisman, 2001 (14)</td>
<td>Israel</td>
<td>2,275</td>
<td>60.1</td>
<td>—</td>
<td>—</td>
<td>74.5</td>
<td>Age, sex, smoking, BMI, hypertension, use of beta-blockers and antiplatelet drugs, PVD previous CVA, anginal syndrome, CHF</td>
<td>7.7*</td>
<td>Sulfonylurea + metformin vs. diet group</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Johnson, 2002 (8)</td>
<td>Canada, 1991–1996</td>
<td>8,866</td>
<td>64.1</td>
<td>—</td>
<td>—</td>
<td>55.9</td>
<td>Age, sex, nitrate use, modified chronic disease score</td>
<td>5.1, Saskatchewan Health computerized vital statistics*</td>
<td>Sulfonylurea + metformin vs. sulfonylurea monotherapy</td>
<td>CVD and all-cause mortality; CVD: ICD-9 (380–459)</td>
</tr>
<tr>
<td>Gulliford, 2004 (6)</td>
<td>U.K., 1992–1998</td>
<td>11,587</td>
<td>64.2</td>
<td>—</td>
<td>—</td>
<td>52.6</td>
<td>Age, sex, year of treatment, CHD, cardiovascular drugs</td>
<td>2.1, general practice research database †</td>
<td>Sulfonylurea first, added metformin vs. sulfonylurea monotherapy; B. metformin first, added sulfonylurea vs. metformin monotherapy</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Johnson, 2005 (15)</td>
<td>Canada, 1991–1999</td>
<td>4,142</td>
<td>65.6</td>
<td>—</td>
<td>—</td>
<td>56.0</td>
<td>Age, sex, nitrate use, chronic disease score</td>
<td>9, Saskatchewan Health computerized vital statistics†</td>
<td>Sulfonylurea + metformin vs. sulfonylurea monotherapy</td>
<td>CVD hospitalizations and CVD mortality; CVD: ICD-9</td>
</tr>
<tr>
<td>Koro, 2005 (16)</td>
<td>U.K., 1987–2001</td>
<td>9,089</td>
<td>71.3</td>
<td>—</td>
<td>—</td>
<td>52.3</td>
<td>Age, sex, hypertension, duration of diabetes, CHF, angina, MI, IHD, PVD, retinopathy, nephropathy, neuropathy, lost ulcers, and gangrene, ESRD, valvular disease</td>
<td>3.4, general practice research database *</td>
<td>Sulfonylurea + metformin vs. sulfonylurea monotherapy</td>
<td>Incident CHF (mortality or hospitalizations) defined as an Oxford Medical Information System code or Read medical code</td>
</tr>
<tr>
<td>Evans, 2006 (5)</td>
<td>Scotland, 1994–2001</td>
<td>5,730</td>
<td>63.6</td>
<td>3.9</td>
<td>—</td>
<td>54.1</td>
<td>Age, sex, smoking, duration of diabetes, blood pressure, cholesterol, A1C previous hospital admission, treatment with cardiovascular medication</td>
<td>8, death certificates from the Registrar General†</td>
<td>Sulfonylurea first, added metformin vs. sulfonylurea monotherapy; B. metformin first, added sulfonylurea vs. metformin monotherapy; C. Sulfonylurea + metformin vs. metformin monotherapy</td>
<td>CVD hospitalizations and CVD and all-cause mortality; CVD: ICD-9 and ICD-10</td>
</tr>
</tbody>
</table>

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.
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-
CONCLUSIONS—In the current RR of CVD hospitalizations or mortality.

monotherapy significantly increased the

tion therapy compared with metformin

combination therapy significantly increased the

the association between all-cause mortality,

ments of several large observational studies

that examined the effect of combination

therapy with metformin and sulfonyl-

ureas on the risk of CVD events among

patients with type 2 diabetes, while the

association of this combination with all-

cause and cardiovascular mortality re-

mains obscure.

Due to the progressive nature of type 2 diabetes, many patients are put on com-

binations of oral antihyperglycemic agents in order to meet glycemic goals.

For instance, in the recommended algo-

rithm, the combination of sulfonylurea and metformin is the second step in the

management of patients with type 2 dia-

betes (18). It is likely that patients on combination therapy are likely to have ei-

ther a more rapidly progressive form of the disease or a longer duration of diabe-

tes, 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 pre-

scribed, there was an increased risk,

which is in contrast with some of the ob-

servational studies. This discrepancy

can be due to differences in the population

between these studies.

It may not only be important to re-

duce blood glucose, but also to consider

the choice of agent used to make such a

reduction. A recent meta-analysis has cre-

ated 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). How-
ever, the interim analysis of the Rosiglita-

zone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes

(RECORD) trial has shown inconclusive

results (21). Our meta-analysis is impor-
tant in the context of that study, as the

combination of metformin and sulfonyl-

urea is the comparator group to the ros-

iglitazone combinations.

Several observational studies have ex-

amined the association between combina-

tion 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 hypo-


Patients treated with sulfonylureas alone

or in combination with metformin ap-

peared 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 poten-
tial benefit of metformin on CVD out-

come, as seen in the UKPDS (2). A study

by Fisman et al. (14) was carried out

among 2,275 patients with type 2 dia-

betes and coronary artery disease, as part

of the Bezafibrate Infarction Prevention

Study. The patients were followed for

over 7 years, and the authors demon-

strated that cardiovascular events and

mortality were the same whether gly-

buride, a sulfonylurea, or metformin was

used for treatment. However, there was a

significant time-related increased mortal-

ity when the combination therapy was

used. Olsson et al. (10) analyzed mortality

in a small cohort of patients taking sulfo-

nylureas 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 of treatments, it is highly unlikely 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.

Acknowledgments—This study was not funded. K.R. was partially supported by grant P20-RR17659 from the National Center for Research Resources (National Institutes of Health [NIH]). Diabetes research and education at Tulane University Health Sciences Center is supported in part by the Tullis-Tulane Alumni Chair in Diabetes and the Earl Madison Ellis fund. V.F. is supported in part by the American Diabetes Association (ADA) and the NIH (ACCORD and TINDAL T2D trials). V.F. has also received research support (to Tulane) from Glaxo Smith Kline, Novartis, Takeda, Asta-Zeneca, Pfizer, sanofi-aventis, Eli Lilly, NIH, and ADA, and honoraria from Glaxo Smith Kline, Novartis, Takeda, Pfizer, sanofi-aventis, and Eli Lilly.

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