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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Running Head: Sulfonylureas plus metformin and risk of mortality

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.
**Background:** 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.

**Objective:** To evaluate the effects of combination therapy of sulfonylureas and metformin on risk of all-cause mortality and cardiovascular disease among people with type 2 diabetes.

**Research Design and Methods:** A MEDLINE search (1966- July 2007) was conducted to identify observational studies that examined the association between combination therapy of sulfonylureas and metformin on risk of cardiovascular disease or all-cause mortality. From 299 relevant reports, nine were included in the meta-analysis. In these studies, combination therapy of metformin and sulfonylurea was assessed, the risk of cardiovascular disease and/or mortality was reported, adjusted relative risk or equivalent (hazard ratio, odds ratio), and corresponding variance or equivalent was reported.

**Results:** The pooled relative risks (95% confidence intervals) 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 cardiovascular disease mortality, and 1.43 (1.10-1.85) for a composite endpoint of cardiovascular disease hospitalizations or mortality (fatal or non-fatal events).

**Conclusions:** The combination therapy of metformin and sulfonylurea significantly increased the relative risk of the composite endpoint 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 cardiovascular disease mortality or all-cause mortality alone.
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 United Kingdom 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 FDA-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 meta-analysis of observational studies to examine the association between combination therapy of sulfonylureas and metformin and risk of CVD and all-cause mortality.

METHODS

Study Selection: 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; chlorpropamide; tolbutamide; tolazamide; glyburide; glipizide; biguanides; 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 or equivalent (i.e. hazard ratio, odds ratio) and corresponding variance or
equivalent reported; and (3) diagnosis of type 2 diabetes mellitus established using the standard criteria for the time of the study.

**Data Abstraction:** 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 gender, mean diabetes duration, mean HbA1c), type of reference group, and confounding factors controlled for. The relative risk of cardiovascular mortality/morbidity and/or all-cause or cause-specific mortality associated with combination therapy and their corresponding confidence intervals or standard errors were abstracted. The number of events for all-cause mortality and cardiovascular mortality/morbidity were abstracted.

**Statistical Analysis:** Relative risks were used as the measure of association between combination therapy of metformin and sulfonylurea and CVD and all-cause mortality. The relative risks of each study were weighted by the inverse of their variance. To stabilize the variances and to normalize the distributions, the relative risks and corresponding standard errors from each of the individual studies were transformed to their natural logarithms. When necessary, standard errors were derived from the confidence intervals 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, relative risk estimates and 95% confidence intervals 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 relative risk of CVD and all-cause mortality associated with combination therapy (9). Although both models yielded similar findings, results from random-effects model are presented herein owing to significant heterogeneity among the studies.

Cardiovascular disease was defined by each of the individual studies. We used cardiovascular mortality, all-cause mortality, as well as a composite endpoint of cardiovascular disease hospitalizations (the first cardiovascular event either fatal or nonfatal event) or mortality as our study outcomes. One study reported relative risks separately for coronary heart disease and stroke (10). For this study, we first weighted both of the relative risks by the inverse of their variance and then pooled the relative risks 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 standard error for each study, 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 Corp., College Station, TX).

**RESULTS**

Online Appendix Figure A1 (Appendix Figure A1 is available at http://care.diabetesjournals.org) depicts the
flow of studies in the meta-analysis. Among 25 studies which met the inclusion criteria, 16 were excluded from the meta-analysis. Eleven studies did not report CVD or mortality as an outcome, three studies represented duplicate 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 design of the 9 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, 2 were prospective cohort studies and 1 was a nested case-control study. Of the 9 studies, 1 was conducted in the United States, 2 in Canada, 1 in Israel, and 5 in European countries. The number of participants in these studies ranged from 910 in the study by Olsson (10) to 39,721 in the study by Kahler (7). Mean age ranged from 58.9 to 71.3 years. The mean follow-up time ranged from 2.1 years to 7.7 years. Among the 9 studies, 7 reported all-cause-mortality, 4 reported cardiovascular mortality, and 3 studies reported cardiovascular hospitalizations. Of the 101,733 participants included in these studies, 25,091 participants had received a combination therapy of metformin and sulfonylurea. Bruno (13) and Koro (16) did not specify the number of participants receiving combination therapy.

Figure 1 depicts the results from the random-effects models pooling the adjusted relative risks for all-cause mortality, CVD mortality and CVD hospitalizations or mortality. Pooled relative risk 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 analysis, 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 sulfonylureas (relative risk, 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), participants of the reference group were used more than once in computing of 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:** Relative risk 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 relative risks were greater than 1.0 in all subgroups except for the association...
between all-cause mortality and combination therapy compared with sulfonylurea.

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

**DISCUSSION**

In the current meta-analysis, combination therapy of metformin and sulfonylurea significantly increased the relative risk 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 have 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 not only may be important to reduce blood glucose, but the choice of agent used to make such a reduction may also be very important. A recent meta-analysis has created much controversy about some of the newer medications used to reduce blood glucose, 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 relative risk of adverse cardiovascular outcomes, compared to 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...
Sulfonylureas plus metformin and risk of mortality coronary artery disease, as part of the Bezafibrate Infarction Prevention Study. The patients were followed for over seven 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 taking 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 of a relatively greater association with fatal and non-fatal 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 ACCORD study (22) in which intensive treatment with multiple combinations of diabetes therapies was associated with decreased non-fatal CVD events but increased fatal events. It is impossible to determine the reason for this discrepancy, though it is possible that patients in the observational studies included in our analysis did not have a level of glycemia as low as attempted in the ACCORD trial.

Several hypothetical considerations may explain the increased risk associated with such a combination. Firstly, 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. Secondly, 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 in order 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 has to balance the risks and benefits of medications used while making treatment decisions.

We wish to emphasize that this metaanalysis 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 not only to assess the association of combination therapy of metformin and sulfonylurea with all-cause and/or cardiovascular mortality, but also to understand the potential mechanism of its deleterious effects.

ACKNOWLEDGEMENTS

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REFERENCES

22. NHLBI Press Release. [Internet]. ; [1]
<table>
<thead>
<tr>
<th>Author and Publication Year</th>
<th>Country Period of Study</th>
<th>Sample Size</th>
<th>Age (Yrs)</th>
<th>Diabetes Duration (Yrs)</th>
<th>HbA1c (%)</th>
<th>Male (%)</th>
<th>Variables Controlled For</th>
<th>Duration of Follow-Up (Yrs) and Follow-Up Process</th>
<th>Combination therapy vs Control group</th>
<th>Outcome and Diagnostic Criteria</th>
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<tr>
<td>Bruno (13) 1999</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>77 Town demographical files; death certificates</td>
<td>Sulfonylurea plus Biguanides vs Diet group</td>
<td>Stroke, IHD, CVD, and all-cause mortality IHD: ICD-9 (410-414) Stroke: ICD-9 (430-438)</td>
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<td>Fisman (14) 2001</td>
<td>Israel 2001</td>
<td>2,275</td>
<td>60.1</td>
<td>--</td>
<td>--</td>
<td>74.5</td>
<td>Age, sex, FBG, smoking, BMI, hypertension, use of beta-blockers and antiplatelet drugs, PVD previous CVA, anginal syndrome, CHF</td>
<td>7.7* --</td>
<td>Sulfonylurea plus Metformin vs Diet group</td>
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<td>Johnson (8) 2002</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, and modified chronic disease score</td>
<td>5.1* Saskatchewan Health computerized vital statistics</td>
<td>Sulfonylurea plus Metformin vs Sulfonylurea monotherapy</td>
<td>CVD and all-cause mortality CVD: ICD-9 (390-459)</td>
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<td>Gulliford (6) 2004</td>
<td>United Kingdom 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>A. Sulfonylurea first, added Metformin vs Sulfonylurea monotherapy B. Metformin first, added Sulfonylurea vs Metformin monotherapy</td>
<td>All cause mortality</td>
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<td>4,142</td>
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<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 plus Metformin vs Sulfonylurea monotherapy</td>
<td>CVD hospitalizations and CVD mortality CVD: ICD-9</td>
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<tr>
<td>Author and Publication Year</td>
<td>Country Period of Study</td>
<td>Sample Size</td>
<td>Age (Yrs)</td>
<td>Diabetes Duration (Yrs)</td>
<td>HbA1c (%)</td>
<td>Male (%)</td>
<td>Variables Controlled For</td>
<td>Duration of Follow-Up (Yrs) and Follow-Up Process</td>
<td>Combination Therapy vs Control Group</td>
<td>Outcome and Diagnostic Criteria</td>
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<td>Koro (16) 2005</td>
<td>United Kingdom 1987-2001</td>
<td>9,089</td>
<td>71.3</td>
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<td>52.3</td>
<td>Age, sex, hypertension, duration of diabetes, CHF, angina, MI, IHD, PVD, retinopathy, nephropathy, neuropathy, foot ulcers and gangrene, ESRD, valvular disease</td>
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<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, HbA1c, previous hospital admission, treatment with cardiovascular medication</td>
<td>8‡ Death certificates from the Registrar General</td>
<td>A. Sulfonylurea first, added Metformin vs Metformin monotherapy B. Metformin first, added Sulfonylurea vs Metformin monotherapy C. Sulfonylurea plus Metformin vs Metformin monotherapy</td>
<td>CVD hospitalizations and CVD and all-cause mortality CVD: ICD-9 and ICD-10</td>
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<td>Kahler (7) 2007</td>
<td>United States 1998-2001</td>
<td>39,721</td>
<td>66.9</td>
<td>--</td>
<td>7.4</td>
<td>98</td>
<td>Age, duration of diabetes HbA1c, propensity score, creatinine, diabetes-related physician visits, use of lipid lowering and hypertensive medications</td>
<td>3‡ Veterans Health Administration mortality database</td>
<td>Metformin plus Sulfonylurea vs Sulfonylurea monotherapy</td>
<td>All-cause mortality</td>
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Yrs = years; FBG = fasting blood glucose; BMI = body mass index; PVD = peripheral vascular disease; CVA = cerebrovascular accident; CHF = congestive heart failure; IHD = ischemic heart disease; CVD = cardiovascular disease; CAD = coronary artery disease; MI = myocardial infarction; ESRD = end stage renal disease

* Mean follow-up length  
† Median follow-up length  
‡ Maximum follow-up length
Table 2. Pooled Relative Risk (95% Confidence Interval) of All-Cause Mortality, CVD Mortality and the Composite Endpoint of CVD Hospitalizations or CVD Mortality According to Different Exclusion Criteria

<table>
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<tr>
<th>Studies described</th>
<th>All-Cause Mortality</th>
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<th>CVD Mortality</th>
<th></th>
<th>CVD Hospitalizations or CVD Mortality</th>
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<tr>
<td></td>
<td>No. of Studies</td>
<td></td>
<td>RR (95% CI)</td>
<td></td>
<td>No. of Studies</td>
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<td>All Studies</td>
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<td>1.19</td>
<td></td>
<td>6</td>
<td>1.29</td>
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<td></td>
<td>(0.88, 1.62)</td>
<td></td>
<td>(0.73, 2.27)</td>
<td></td>
<td>(1.10, 1.85)</td>
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<td>Studies that controlled for important confounding factors *</td>
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<td>1.36</td>
<td></td>
<td>5</td>
<td>1.63</td>
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<tr>
<td></td>
<td>(0.93, 2.04)</td>
<td></td>
<td>(1.11, 2.39)</td>
<td></td>
<td>(1.28, 1.87)</td>
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<td>Studies that controlled for important confounding factors †</td>
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<td>1.34</td>
<td></td>
<td>3</td>
<td>1.72</td>
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<td>(0.73, 2.47)</td>
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<td>(0.93, 3.20)</td>
<td></td>
<td>(1.25, 1.78)</td>
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</table>

CVD=Cardiovascular disease; RR=relative risk; CI=confidence interval

* Studies that did not control for duration of diabetes were excluded. For all-cause mortality, excluded the studies by Gulliford (12), Johnson (14), and Fisman (21). For CVD mortality and the composite endpoint of CVD hospitalizations or CVD mortality, excluded the study by Johnson (23).

† Studies that did not control of duration of diabetes or previous CVD were excluded. For all-cause mortality, excluded the studies by Gulliford (12), Johnson (14), Olsson (16), Bruno (20) and Fisman (21). For CVD mortality and the composite endpoint of CVD hospitalizations or CVD mortality, excluded the studies by Olsson (16), Johnson (23) and Bruno (20).
Figure 1. Relative risk estimates and 95% confidence intervals for all-cause mortality, cardiovascular disease mortality and composite endpoint of cardiovascular disease hospitalizations or cardiovascular disease mortality associated with combination therapy of metformin and sulfonylurea by study and pooled along with proportion of events for each outcome.
Relative Risk (95% CI) | No. of Events/Total
--- | --- | --- | ---
Bruno (1999) | 1.04 (0.62, 1.75) | Not specified | Not specified
Olsson (2000) | 1.86 (1.33, 2.61) | Not specified | Not specified
Johnson (2005) | 0.56 (0.09, 0.07) | 11/125 | 12/134
Evans (2006) (A) | 2.43 (1.61, 3.66) | 72/1252 | 382286
Evans (2006) (B) | 2.29 (1.45, 3.63) | 42/985 | 362286
Evans (2006) (C) | 0.62 (0.25, 1.53) | 6/113 | 362286
Overall | 1.29 (0.73, 2.37) | | |

Relative Risk (95% CI) | No. of Events/Total
--- | --- | --- | ---
Bruno (1999) | 1.04 (0.62, 1.75) | Not specified | Not specified
Olsson (2000) | 1.86 (1.33, 2.61) | Not specified | Not specified
Johnson (2005) | 0.56 (0.09, 0.07) | 264/1081 | 541/1238
Koo (2005) | 1.38 (1.13, 1.69) | Not specified | Not specified
Evans (2006) (A) | 2.24 (1.26, 3.99) | 133/1252 | 229/2286
Evans (2006) (B) | 1.86 (1.03, 3.35) | 92/985 | 229/2286
Evans (2006) (C) | 1.52 (0.84, 2.76) | 12/113 | 229/2286
Overall | 1.43 (1.10, 1.88) | | |