Decreased Mortality Associated With the Use of Metformin Compared With Sulfonylurea Monotherapy in Type 2 Diabetes

Jeffrey A. Johnson, PhD1,2
Sumit R. Majumdar, MD, MPH, FRCP.2,3
Scot H. Simpson, PharmD2
Ellen L. Toth, MD, FRCP.2,3

OBJECTIVE — The aim of this study was to examine the relationship between use of metformin and sulfonylurea and mortality in new users of these agents.

RESEARCH DESIGN AND METHODS — Saskatchewan Health databases were used to examine population-based mortality rates for new users of oral antidiabetic agents. Individuals with prescriptions for sulfonylurea or metformin in 1991–1996 and no use in the year prior were identified as new users. Prescription records were prospectively followed for 1–9 years; subjects with any insulin use were excluded. Causes of death were identified based on ICD-9 codes in an electronic vital statistics database. Multivariate logistic regression and survival analyses were used to assess the differences in mortality between drug cohorts, after adjusting for potential confounding variables.

RESULTS — The total study sample comprised 12,272 new users of oral antidiabetic agents; the average length of follow-up was 5.1 (SD 2.2) years. Subjects with at least 1 year of drug exposure and no insulin use, mortality rates were 750/3,033 (24.7%) for those receiving sulfonylurea monotherapy, 159/1,150 (13.8%) for those receiving metformin monotherapy, and 635/4,683 (13.6%) for those receiving combination therapy over an average 5.1 (SD 2.2) years of follow-up. The adjusted odds ratio (OR) for all-cause mortality for metformin monotherapy was 0.60 (95% CI 0.49–0.74) compared with sulfonylurea monotherapy. Sulfonylurea plus metformin combination therapy was also associated with reduced all-cause mortality (OR 0.66, 95% CI 0.58–0.75). Reduced cardiovascular-related mortality rates were also observed in metformin users compared with sulfonylurea monotherapy users.

CONCLUSIONS — Metformin therapy, alone or in combination with sulfonylurea, was associated with reduced all-cause and cardiovascular mortality compared with sulfonylurea monotherapy among new users of these agents.

Diabetes Care 25:2244–2248, 2002

The U.K. Prospective Diabetes Study (UKPDS) clearly demonstrated the benefit of an intensive treatment policy aimed at “tight” glycemic control, particularly with respect to the microvascular complications of diabetes (1,2). In obese patients with type 2 diabetes, metformin monotherapy reduced all-cause mortality and any diabetes-related end point compared with conventional therapy as well as other intensive therapies (2). Furthermore, early addition of metformin in patients with suboptimal control while on maximum sulfonylurea therapy resulted in improved glycemic control (3). However, this early addition of metformin to sulfonylurea therapy was also associated with an increase in diabetes-related mortality compared with continued sulfonylurea alone (2). Two recent observational studies also reported significantly increased mortality associated with metformin use, suggesting caution in the use of metformin for type 2 diabetes (4,5). These discrepancies have left some question regarding the overall benefit of metformin therapy, alone or in combination with sulfonylureas (6).

Metformin has been available in Canada since 1980 and on the provincial formulary in Saskatchewan since 1981. The computerized administrative records of Saskatchewan Health (7) provide a unique opportunity in North America for continuous follow-up and identification of clinical outcomes associated with metformin use on a population basis. This investigation used a retrospective cohort design to test the hypotheses that new users of metformin or sulfonylurea/metformin combination therapy have no increased risk of mortality compared with new users of sulfonylurea.
Table 1—Study cohort characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sulfonylurea</th>
<th>Metformin</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>3,033</td>
<td>1,150</td>
<td>4,683</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.2 ± 12.9*</td>
<td>63.8 ± 12.7</td>
<td>62.1 ± 12.7</td>
</tr>
<tr>
<td>Men (%)</td>
<td>1,789 (59.0%)</td>
<td>621 (54.0%)</td>
<td>2,543 (53.4%)</td>
</tr>
<tr>
<td>Nitrate use (%)</td>
<td>799 (26.3%)</td>
<td>236 (20.5%)</td>
<td>1,313 (28.0%)</td>
</tr>
<tr>
<td>Duration of follow-up (years)</td>
<td>4.98 ± 1.9</td>
<td>4.74 ± 1.6</td>
<td>5.71 ± 1.8*</td>
</tr>
<tr>
<td>CDS</td>
<td>8.24 ± 4.0</td>
<td>8.04 ± 4.0</td>
<td>8.75 ± 4.1*</td>
</tr>
<tr>
<td>Median</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Data are means ± SD, n (%), and %. *P < 0.001 for ANOVA; †P < 0.001 for χ² test.

Individuals included in the cohort were those registered beneficiaries of Saskatchewan Health eligible for prescription drug benefits aged ≥30 years on the index date (i.e., the date of the first claim for cohort drug in index period) and having had continuous coverage in the provincial health plan for at least 1 year before the index date. New users were identified as those eligible beneficiaries with a prescription claim for a sulfonylurea or metformin (see Appendix A) in the index period of 1 January 1991 to 31 December 1996 and having no prescription claims for any antidiabetic agent for 1 year before the index date.

New users of antidiabetic agents were initially classified into one of two cohorts based on the initial prescription recorded (i.e., sulfonylurea or metformin). The prescription records for cohort members were then followed prospectively from the index date until death, study exit, or 31 December 1999, providing a maximum follow-up period of 9 years. Duration of therapy was determined by subtracting the index prescription date from the date of the last prescription during the follow-up period.

A total of 12,272 subjects met the inclusion criteria, being identified as new users of oral antidiabetic drugs from 1991 to 1996. The mean age at index date was 64.0 (SD 13.6) years, and 55% of subjects were men. The full cohort of study subjects had a mean follow-up of 5.1 (SD 2.2) years. Of subjects identified as monotherapy users throughout the full follow-up period, 4,423 (36.0%) were sulfonylurea monotherapy users and 1,546 (12.6%) were metformin monotherapy users. Approximately 40% of study subjects had records of combination therapy; 3,180 (25.9%) had sulfonylurea first and then metformin added and 1,680 (13.7%) had sulfonylurea added to metformin. Similar mortality rates were observed in both groups, and for purposes of analysis, we grouped all of these subjects together as users of combination therapy.

Excluded from the study cohorts were new users of oral antidiabetic drugs who had less than a 1-year supply of drug therapy dispensed. With this criterion, we excluded 1,390 (31.4%) new users of sulfonylurea, 396 (25.6%) new users of metformin monotherapy, and 177 (3.6%) combination users. Also excluded were 1,443 (11.7%) subjects who had insulin dispensed during the follow-up period.

The primary outcome measures in these analyses were all-cause and cardiovascular-related mortality. Cause of death was ascertained through the computerized vital statistics file of Saskatchewan Health. The electronically recorded underlying cause of death is the result of a trained coder evaluating the medical certificate of death and applying World Health Organization (WHO) standardized decision rules to determine the underlying cause of death. Specific ICD-9 codes for cardiovascular-related causes were identified (see Appendix B).

Crude odds ratios (ORs) or relative risks (RRs) and 95% CIs were calculated to assess the relationship between drug cohorts and mortality. Multivariate logistic regression and Cox proportional hazards regressions were conducted to estimate OR and RR, respectively, while simultaneously controlling for multiple confounding factors. The sulfonylurea monotherapy cohort served as the comparison group for all ORs and RRs reported.

In the multivariate models, the following potential confounding variables were included: age, sex, nitrate use, and a modified Chronic Disease Score (CDS). Use of nitrates at any time during the follow-up period was included as a marker for established coronary disease (8). The CDS provides an indication of burden of concurrent comorbidities by identifying specific drug therapies during the follow-up period; we included a modified CDS by simply updating the list of marker drugs previously identified (9). The CDS is a sum of the chronic diseases identified by drug therapies over the full follow-up period. For example, all study subjects had a minimum CDS of 2.0 by virtue of receiving any oral antidiabetic therapy. Interaction terms between each risk factor variable in the model and oral antidiabetic use group were also examined. None of the interaction terms attained statistical significance (P > 0.05) for all terms examined; therefore, all interaction terms were excluded from our final models.

RESULTS — The study cohorts for this analysis included 3,033 and 1,150 new users of sulfonylurea and metformin monotherapy, respectively, and 4,683 subjects on combination therapy (Table 1). The mean (SD) age for all subjects was 64.1 (13.0), and 55.9% were men. The mean duration of follow-up was 5.1 (SD 2.2) years. The mean CDS for the cohorts was 8.5 (4.1); the median CDS was 8.0. Nitrates were dispensed for 2,348 (26.5%) subjects during the follow-up period. The sulfonylurea monotherapy group was older, on average, and included more men (Table 1). The metformin monotherapy cohort had fewer nitrate users, whereas the combination therapy cohort had more comorbidity and a longer duration of therapy during the follow-up period (Table 1).

There were 159 (13.8%) deaths in the metformin monotherapy group and 635 (13.6%) in the combination therapy group, compared with 750 (24.7%) deaths in the sulfonylurea monotherapy group (Fig. 1). The numbers of cardiovascular-related deaths were 80 (7.0%) in the metformin monotherapy group, 299 (6.4%) in the combination group, and 351 (11.6%) in the sulfonylurea monotherapy group. The crude OR (95% CI) for all-cause mortality was 0.49 (0.41–0.59) for new users of metformin monotherapy and 0.48 (0.43–0.54) for users of combination therapy, compared with new users of sulfonylurea monotherapy. The crude ORs for cardiovascular-related...
mortality for the metformin and combination groups were 0.53 (0.41–0.68) and 0.48 (0.41–0.57), respectively.

In multivariate logistic regression analyses, metformin monotherapy was associated with reduced mortality for all causes compared with sulfonylurea monotherapy, after controlling for age, sex, CDS, and nitrate use (Table 2). Adjusted ORs for metformin in these multivariate models were 0.60 (0.49–0.74) for all-cause mortality and 0.64 (0.49–0.84) for cardiovascular-related mortality. For combination therapy compared with sulfonylurea monotherapy, the adjusted ORs were 0.66 (0.58–0.75) for all-cause mortality and 0.64 (0.54–0.77) for cardiovascular-related mortality.

The results were essentially the same with the multivariate survival analysis, although some risk estimates were of borderline significance. The adjusted RRs for metformin monotherapy compared with sulfonylurea monotherapy were 0.78 (0.65–0.92) and 0.84 (0.66–1.07) for all-cause and cardiovascular-related mortality, respectively. Combination therapy was also associated with a reduced risk of mortality compared with sulfonylurea monotherapy; the adjusted RRs were 0.63 (0.57–0.71) for all-cause mortality and 0.63 (0.54–0.74) for cardiovascular-related mortality.

**CONCLUSIONS**—Treatment of diabetes is aimed at normalizing blood glucose levels to minimize the short-term effects of hyperglycemia and hypoglycemia while preventing development of long-term complications of diabetes (10,11). Sulfonylureas have been the cornerstone of drug therapy for type 2 diabetes, either alone or in combination with metformin, for a quarter of a century (10). Pharmacologic therapy for type 2 diabetes has proven benefits in terms of reducing elevated blood glucose levels and reducing microvascular complications (1). The impact of antidiabetic therapy on macrovascular complications and cardiovascular mortality is less clear, however (12–14).

The reduced risk of mortality associated with metformin observed in this study contradicts other recently reported epidemiologic studies. In previous studies, increased mortality attributed to metformin was observed when it was used in combination with sulfonylurea therapy (4,5). Neither previous study had sufficient numbers of subjects or events to evaluate mortality in metformin monotherapy users alone. In the UKPDS, increased mortality risk was noted in the subgroup of patients in which metformin was added to sulfonylurea (2), although statistical chance and an unexpectedly low number of deaths in sulfonylurea users may account for this difference (6).

Unlike the previous studies (4,5), our analysis was population-based and controlled, to some extent, for cardiovascular

**Table 2**—Adjusted OR (95% CI) from multivariate logistic regression models

<table>
<thead>
<tr>
<th></th>
<th>All-cause deaths</th>
<th>Cardiovascular deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea*</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Metformin</td>
<td>0.60 (0.49–0.74)</td>
<td>0.64 (0.49–0.84)</td>
</tr>
<tr>
<td>Combination</td>
<td>0.66 (0.58–0.75)</td>
<td>0.64 (0.54–0.77)</td>
</tr>
<tr>
<td>Age (1-year increments)</td>
<td>1.11 (1.10–1.11)</td>
<td>1.11 (1.10–1.12)</td>
</tr>
<tr>
<td>Men</td>
<td>1.74 (1.54–1.98)</td>
<td>1.65 (1.40–1.95)</td>
</tr>
<tr>
<td>CDS</td>
<td>1.07 (1.05–1.09)</td>
<td>1.07 (1.04–1.09)</td>
</tr>
<tr>
<td>Nitrate use</td>
<td>1.06 (0.92–1.21)</td>
<td>1.56 (1.31–1.87)</td>
</tr>
</tbody>
</table>

*Sulfonylurea monotherapy cohort is the reference group.
risk. The inclusion criteria were chosen to identify newly treated patients; that is, native to oral antidiabetic therapy and presumably with relatively new onset of hyperglycemia. Although the duration of monotherapy was statistically different between the cohorts, the difference between sulfonylurea and metformin monotherapy cohorts was ~4 months and was unlikely to account for such a large difference in mortality. Furthermore, the combination therapy group had longer duration of follow-up but had a lower death rate than sulfonylurea monotherapy. Use of nitrates at any time during the follow-up period served as a marker for ischemic heart disease and in our analysis would control, to some extent, for both new and established coronary disease.

Other than a possible therapeutic advantage related directly to metformin use, there are at least three alternate explanations for our findings. First, the subjects in the metformin monotherapy cohort may have had a lower risk of all-cause mortality and, in particular, cardiovascular mortality. Because our analysis was based entirely on administrative databases and it is limited by a lack of direct clinical information, we could not control for level of glycemic control (e.g., fasting blood glucose or HbA1c), BMI, or other modifiable cardiovascular risk factors (e.g., smoking). However, we controlled for age, sex, comorbidity, and presence of coronary disease. Furthermore, metformin is likely to be used preferentially in obese patients (2,3), who have an increased risk of death. If this were the case, we would have expected an increased mortality in the metformin group.

Second, the observed differences in mortality risk may be related to exposure to hyperglycemia (14,15). Although metformin and sulfonylurea are equipotent as hypoglycemic agents (16), it may be that metformin was chosen as initial monotherapy in subjects with perceived ‘milder’ disease than subjects in the sulfonylurea cohort. If this was the case, subjects in the sulfonylurea cohort would have had greater exposure to hyperglycemia, with its attendant increased risk of morbidity and mortality. If this explanation was true, we would have expected an increased mortality rate in the combination cohort, because the addition of a second drug would imply greater exposure to hyperglycemia. The adjusted all-cause and cardiovascular-related mortality rates observed in the combination group compared with the sulfonylurea group would tend to refute this.

Third, it may be that sulfonylurea monotherapy, relative to any oral antidiabetic regimen that contains metformin, is associated with increased risk. This could be mediated by the well-documented increase in BMI associated with sulfonylurea therapy (10) or may possibly be due to the cardiovascular toxicity of this class of agents (17–19). Since the publication of the excess number of cardiovascular deaths in the tolbutamide treatment arm of the University Group Diabetes Program, controversy has surrounded the use of sulfonylurea in patients with type 2 diabetes (18,19). Although sulfonylurea therapy has a long record of safety and microvascular efficacy, our analyses cannot exclude the possibility that sulfonylurea may be associated with adverse macrovascular outcomes.

As with other studies based solely on administrative databases, several limitations must be recognized. Chief among these limitations is that administrative data of drug dispensations do not ensure the exact level of drug consumption and, therefore, exposure. However, the databases of Saskatchewan Health have been used in numerous epidemiologic studies of drug use outcomes (20–23) and are recognized for their comprehensiveness and quality (7). Furthermore, we believe our eligibility criteria and our ability to follow prescription refill patterns provided a reasonable level of confidence in the exposure status.

The association between insulin resistance, hyperinsulinemia, dyslipidemia, and cardiovascular morbidity and mortality has been recognized for some time (24,25). Cardiovascular-related mortality is the leading cause of death in individuals with type 2 diabetes (13). Pharmacologic therapy that increases insulin sensitivity should, therefore, have a beneficial effect on cardiovascular-related mortality outcomes in type 2 diabetes. If metformin acts to improve insulin sensitivity (26), then this relationship is borne out in the observed mortality rates in this analysis. At the least, our results refute previous epidemiologic studies suggesting that metformin is associated with increased mortality in type 2 diabetes. Furthermore, our results suggest that the combination of sulfonylurea and metformin is safe.

APPENDIX A

Antidiabetic agents
- Sulfonylureas
  - Acetohexamide
  - Chlorpropamide
  - Gliburide
  - Tolbutamide
  - Tolazamide

Metformin
Insulin

APPENDIX B

International Classification of Diseases, 9th Revision (ICD-9) codes for underlying cardiovascular cause of death

Rheumatic disease: 390–398
Hypertension: 401–404
Myocardial infarction: 410
Other ischemic heart diseases: 411–414
Diseases of pulmonary circulation: 415–417
Congestive heart failure: 428
Other forms of heart disease: 420–427, 429
Hemorrhagic stroke: 430–432
Ischemic stroke: 433–434
Transient ischemic attacks: 435
Other forms of stroke: 436–438
Atherosclerosis: 440
Other diseases of arteries, arterioles, and capillaries: 441–444, 446–448
Diseases of veins, lymphatics, and other diseases of circulatory system: 451–459

Acknowledgments—This study was funded, in part, by grants from the Alberta Heritage Foundation for Medical Research (AHFMR) and the Institute of Health Economics.

We thank MaryRose Stang, PhD, of Saskatchewan Health, for her help in compiling the datasets. We also thank Dr. Stang and William Ghali, MD, MPH, of the Department of Medicine, University of Calgary, for their comments on a draft of the manuscript.

Dr. Johnson holds a Canada Research Chair in Diabetes Health Outcomes. Drs. Johnson and Majumdar hold Population Health Investigator Awards through the Alberta Heritage Foundation for Medical Research.

References
1. UK Prospective Diabetes Study Group: Intensive blood-glucose control with