The Risk of Overall Mortality in Patients with Type 2 Diabetes Receiving Glipizide, Glyburide, or Glimepiride Monotherapy: A Retrospective Analysis

Short Running Title: Mortality Risk with Sulfonylurea Monotherapy

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Objective: Sulfonylureas have historically been analyzed as a medication class, which may be inappropriate given the differences in properties inherent to the individual sulfonylureas: hypoglycemic risk, sulfonylurea receptor selectivity and effects on myocardial ischemic preconditioning. The purpose of this study was to assess the relationship of individual sulfonylureas and the risk of overall mortality in a large cohort of patients with type 2 diabetes.

Research Design and Methods: A retrospective cohort study was conducted using an academic health center enterprise-wide electronic health record (EHR) system to identify 11,141 patients with type 2 diabetes (4,279 initiators of monotherapy with glyburide, 4,325 initiators of monotherapy with glipizide, and 2,537 initiators of monotherapy with glimepiride), ≥ 18 years of age, with and without a history of coronary artery disease (CAD), and not on insulin or a non-insulin injectable at baseline. The patients were followed for mortality by documentation in the EHR and Social Security Death Index. Multivariable Cox models were used to compare cohorts.

Results: No statistically significant difference in the risk of overall mortality was observed among these agents in the entire cohort, but we did find evidence of a trend towards an increased overall mortality risk with glyburide vs. glimepiride (HR 1.36; CI 0.96-1.91) and glipizide vs. glimepiride (HR 1.39; 95% CI 0.99-1.96), in those with documented CAD.

Conclusions: Our results did not identify an increased mortality risk among the individual sulfonylureas but did suggest that glimepiride may be the preferred sulfonylurea in those with underlying CAD.
The University Group Diabetes Project (UGDP) raised concern that the administration of tolbutamide, a first generation sulfonylurea, may increase the risk of cardiovascular death (1). It was largely this uncertainty surrounding sulfonylureas that prompted the United Kingdom Prospective Diabetes Study (UKPDS), which itself did not support the suggestion by the UGDP that sulfonylurea therapy increased the risk of cardiovascular mortality (2).

The proposed increased risk of cardiovascular death largely went unexplained until reports surfaced suggesting deleterious effects of some sulfonylureas (glyburide), specifically on the ischemic myocardium (impairment of ischemic preconditioning and/or increased infarct size) (3, 4). Interestingly, this has not been observed to be a class effect of the sulfonylureas, but an important difference among individual sulfonylureas based largely on their affinity for the three isoforms of the sulfonylurea receptor (SUR1, SUR2A and SUR2B). SUR1 is largely found in the adenosine 5'-triphosphate (ATP) dependent K⁺ (KATP) channels of β-cells, whereas SUR2A and SUR2B are largely found in the KATP channels of cardiac and vascular smooth muscle (5, 6). Sulfonylureas specific for SUR1, so called pancreatic-specific sulfonylureas (tolbutamide, chlorpropamide, gliclazide and glipizide), are specific for the pancreatic β-cells, and thus their effect is largely on potentiating insulin secretion (5, 7). Non-pancreatic-specific sulfonylureas (glibenclamide [glyburide] and glimepiride) in addition to potentiating insulin secretion via the β-cells, also exhibit their effects on cardiovascular and vascular smooth muscle (7, 8).

Although both glibenclamide [glyburide] and glimepiride have affinity for the SUR 2 receptor (non-pancreatic-specific), as determined by receptor interaction studies, glimepiride was found not to impair ischemic preconditioning in rats, or in human experiments, whereas glibenclamide [glyburide] has been shown to prevent ischemic preconditioning in humans (9-11). A recent cohort analysis by Evans JM et al. (12) found no difference in mortality between users of pancreatic and non-pancreatic-specific sulfonylureas; however, grouping non-pancreatic-specific sulfonylureas (glimepiride and glibenclamide [glyburide]) together into the same cohort, given their differing effects on ischemic preconditioning, as well as their differing risk of hypoglycemia, may be inappropriate (13).

We have previously reported an increased risk of overall mortality with sulfonylurea monotherapy (14); however, sulfonylureas were analyzed as a class (as they have been historically). It is possible that meaningful clinical differences could exist between the different specific sulfonylureas given their differences in pharmacologic characteristics. Through our enterprise-wide electronic health record (EHR), we were able to identify users of a pancreatic-specific sulfonylurea, glipizide, and two non-pancreatic-specific sulfonylureas with different effects on the ischemic myocardium (as well as differing risks of hypoglycemia), glimepiride and glyburide [glibenclamide], to determine if differences in overall mortality risk are present, as this would have important implications when picking a sulfonylurea agent to control glycemia in patients with type 2 diabetes, especially those with documented coronary artery disease (CAD).

**RESEARCH DESIGN AND METHODS**

The methods of data collection and analysis utilized in this study are similar to those used in our previously published analysis investigating adverse cardiovascular
outcomes and overall mortality risk with oral anti-diabetic monotherapy (14).

**Source population:** The source population was obtained from an electronic health record (EHR) derived clinical data repository at the Cleveland Clinic. This study was approved by the Institutional Review Board.

**Study Groups:** For the period 10/24/1998 to 10/12/2006 we identified all newly and previously diagnosed patients with type 2 diabetes using documented International Classification of Diseases version 9 codes (ICD-9) and by identifying patients with at least two encounters for diabetes after visiting the Cleveland Clinic main campus or family health centers and who had a prescription for glyburide, glipizide, and glimepiride entered into the EHR. Patients were stratified into three medication cohorts according to the initial prescription entered in the EHR at baseline. All patients were ≥ 18 years of age and had no history of dialysis at baseline. Patients prescribed insulin or other injectable diabetes medications (as monotherapy or in conjunction with oral agents), and those on multiple oral agents at baseline, were excluded.

**Follow-up:** Follow-up began on the day after the first prescription of the qualifying study drug was entered in the EHR. Patients entered the cohort in a staggered fashion at any time point between 10/24/1998 to 10/12/2006, and from that time were followed until the date of mortality or censoring. Patients with no observed mortality were censored on the last clinic encounter or the date of extraction of vital status from the Social Security Death Index (SSDI) minus a 6 month lag, whichever came last.

**Multivariable Analysis:** A multivariable analysis was utilized to compare patients in each cohort, which allowed us to adjust for differences in baseline characteristics. Variables were chosen and derived based on prior considerations of their clinical relevance with respect to the risk of mortality. The baseline medical history variables chosen for the overall mortality model were as follows: age, sex, race (Caucasian vs. noncaucasian), MDRD estimated glomerular filtration rate (GFR), hemoglobin A1C (HbA1C), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglycerides (TG), smoking status, angiotensin converting enzyme therapy (ACE) or angiotensin receptor blocker therapy (ARB), aspirin therapy (ASA), clopidogrel therapy, cholesterol lowering medication, new diabetes, CAD, congestive heart failure (CHF), and median household income.

We were unable to use family history or alcohol use as predictor variables due to inconsistent documentation in the EHR. The baseline variables were derived from the EHR on the date closest to the date of the first sulfonylurea prescription up to 21 days after baseline. Missing baseline values were imputed by chained equations (mice) package version 1.16 for R, without regard to the outcomes, using regression techniques that included all patients and all baseline values to predict the missing value.

**Outcomes:** Mortality was defined by documentation of death in the EHR or by being listed as deceased in the SSDI, which allowed us to identify those deceased individuals who were lost to follow-up in the EHR.

**Analysis:** Analyses were performed using the statistical package R for Windows version 2.8.1 (R Development Core Team 2008). Survival curves for mortality were estimated with the Kaplan-Meier procedure. Multivariable Cox proportional hazards models were used to derive hazard ratios for the three baseline medication group
comparisons. Restricted cubic splines were used to relax linearity assumptions for the continuous variables. After adjustments were made for the baseline covariates, the following comparisons were made in all patients and restricted to patients with a history of CAD:

- Glipizide versus Glyburide
- Glipizide versus Glimepiride
- Glyburide versus Glimepiride

RESULTS

Using the EHR we were able to identify 4,279 initiators of monotherapy with glyburide, 4,325 initiators of monotherapy with glipizide, and 2,537 initiators of monotherapy with glimepiride, with and without a history of CAD, ≥ 18 years of age, and not on insulin or a non-insulin injectable at baseline. Table 1 shows the distribution of the baseline categorical variables for the entire cohort as well as the subgroup of patients with a history of CAD. The baseline continuous variables for both groups are displayed in Table 2.

The cohorts contained a total of 1,921 mortality events in the entire cohort (N=11,141), and 322 in the subgroup with a history of documented CAD (N=1,505). The survival curves for mortality, for both the entire cohort and for the subgroup with a documented history of CAD, can be seen in Figure 1. There were 1,753 patients lost to follow-up in the EHR, but with vital status from the SSDI. The median follow-up was 2.4 years. The hazard ratios with 95% confidence intervals for the sulfonylurea monotherapy comparisons for mortality in the entire cohort, and the subgroup with documented CAD, can be seen in Table 3, after adjusting for baseline variables.

For the period 10/24/1998 to 10/12/2006 no difference in overall mortality risk was found with glipizide vs. glyburide (HR 1.04; 95% CI 0.94-1.15), glipizide vs. glimepiride (HR 1.05; CI 0.92-1.19), or with glyburide vs. glimepiride (HR 1.00; 95% CI 0.89-1.14). The subanalysis on patients with documented CAD revealed a trend towards an increased overall mortality risk with glyburide vs. glimepiride (HR 1.36; 95% CI 0.96-1.91) and glipizide vs. glimepiride (HR 1.39; 95% CI 0.99-1.96). No difference (or trend) in overall mortality within the subgroup was appreciated with glipizide vs. glyburide (HR 1.03; 95% CI 0.80-1.31).

Discussion: The present study did not find a statistically significant difference in the risk of overall mortality among the various treatment options; suggesting overall mortality is not substantially influenced by the choice of sulfonylurea. However, in the subanalysis of patients with documented CAD, a trend towards an increased overall mortality risk with glyburide vs. glimepiride (HR 1.36; 95% CI 0.96-1.91), and surprisingly a trend towards an increased risk of mortality with the SUR1 specific sulfonylurea glipizide vs. glimepiride (HR 1.39; 95% CI 0.99-1.96), were observed, suggesting that glimepiride may be the preferred sulfonylurea in those with underlying CAD.

Although the study did not find any obvious difference in mortality risk between patients treated with specific sulfonylureas, it is still possible that some differences in mortality may truly exist. There were significantly fewer patients in the CAD subanalysis and the results showed a strong trend towards a reduced risk with glimepiride. It is quite possible that a larger sample size would have detected a significant difference. However, it would not be appropriate to perform a post-hoc power calculation since non-significant p values will tend to be associated with low power even if the sample size was adequate (15). A clinically meaningful difference in mortality would seem unlikely in the main analysis of all patients given the large sample size. The point estimates (HRs) were all very close to 1.
Substantial multicollinearity in a regression model can cause erroneous conclusions about the association between individual variables (e.g. sulfonylurea type) and the outcome of interest. We calculated the variance inflation factors (VIFs) for the sulfonylurea comparisons. The VIFs ranged from 1.93-1.95 in the entire cohort and 2.35-2.40 in the subset of patients with documented CAD, which according to Snee suggests substantial multicollinearity is unlikely to be present (16).

There is a discrepancy within the literature regarding the risk of mortality (overall or cardiovascular mortality) with specific sulfonylureas. A recent report found no substantial (statistically significant) differences in either 30-day or 1-year mortality in users of various sulfonylureas after myocardial infarction (although use of gliclazide monotherapy showed a trend towards lower mortality [HR 0.70; 95% CI 0.48 to 1.0]) suggesting mortality is not substantially influenced by the choice of sulfonylurea (17). However, Khalangot et al. found total mortality was lower for gliclazide and glimepiride, vs. glibenclamide [glyburide] treatment (HR 0.33; 95% CI 0.26-0.41, p<0.001), (HR 0.605; 95% CI 0.41-0.89, p<0.01), respectively, as well as a reduced cardiovascular mortality with gliclazide vs. glibenclamide [glyburide] (HR 0.29; 95% CI 0.21-0.38, p<0.001) (18). The point estimates (HRs) differ greatly between the analyses conducted by Horsdal et al. and ourselves when compared to the analysis by Khalangot et al., likely because Khalangot and colleagues adjusted for few variables, many of which may have caused confounding.

There are a variety of proposed mechanisms for an increased mortality risk with specific sulfonylureas. Despite the differing effects regarding the risk of hypoglycemia, independent of their SUR binding characteristics, which may be influencing mortality (13). Among the sulfonylureas studied in our analysis, glyburide is the most common agent associated with documented hypoglycemia (19). Glyburide has been shown to continue to stimulate insulin secretion in the setting of profound hypoglycemia to a greater extent when compared to glimepiride (20), in part because glyburide accumulates within the beta-cell (21), unlike other sulfonylureas, prolonging insulin secretion. Thus, hypoglycemia could be playing a dominant role in increasing the risk of mortality (more so than differing selectivity and effects on the SUR receptors and ischemic preconditioning, respectively) which has previously been reported with sulfonylureas, specifically when compared to metformin (14, 22-24). Other than the increased risk of hypoglycemia documented with glyburide (and the differences in other pharmacologic properties inherent to the individual sulfonylureas: SUR specificity, and effects on ischemic myocardium), glipizide, glimepiride, and glyburide generally have very similar side effect profiles.

The current study has limitations inherent to most retrospective studies. The analysis was based on exposure to a medication based on the initial prescription entered in the EHR; however, there is no documentation of compliance with the prescribed medication.

The prescribed medication at baseline defined which medication group the patient belonged; however, the medication exposure times after baseline are unknown. Current clinical practice procedures suggest it is more likely for additional agents to be added to a baseline medication than to switch from one class of medication to another, or from one sulfonylurea to another. Approximately 70% of the cohort remained on a single drug
(baseline medication) throughout their time in the cohort.

The medication groups in our study were not balanced with respect to baseline variables and risk factors; however, the multivariable analysis adjusted for the differences in baseline variables and risk factors that had the most relevance with respect to the risk of mortality. Although some covariates may have changed over time, we would not anticipate these changes to favor one specific sulfonylurea versus another (besides the inherent characteristics of the individual agents). Nonetheless, we could not adjust for differences in unmeasured variables or characteristics.

Sulfonylurea monotherapy was not randomized in the present study so selection bias may be present. It is possible that one sulfonylurea may have been chosen over another because of cost (the FDA did not approve first-time generic formulations of glimepiride until November 2005), patient age, reduced GFR, risk of hypoglycemia, or perceived differing effects on myocardial ischemic preconditioning. However, although age and renal insufficiency are associated with an increased risk of death, the multivariable analysis adjusted for differences in baseline age and renal function, so this should not explain the results. To take into account the fact that generic glimepiride was not available throughout the entire duration of our study, we adjusted for socioeconomic status by including the median household income estimated from zip code data from the 2000 census in the multivariable analysis.

The strengths of the study include a large cohort of patients followed up to 8 years and real world effect of the medications in a diverse patient population. In addition, we adjusted for many baseline variables (accurately captured by the EHR) which have substantial effects on mortality. Furthermore, linking our outcome to the SSDI allowed us to capture mortality in those patients lost to follow-up in the EHR.

CONCLUSIONS

Our results did not identify an increased mortality risk among the individual sulfonylureas: glyburide, glipizide or glimepiride in the entire cohort, but did find evidence of a trend towards an overall mortality reduction with glimepiride in those with documented CAD, suggesting that glimepiride may be the preferred sulfonylurea in those with underlying CAD. The literature contains conflicting results regarding whether an increased overall mortality (or cardiovascular mortality) risk accompanies the various sulfonylureas (12, 17, 18). This discrepancy would support prospective studies to determine if the difference in pharmacologic properties inherent to individual sulfonylureas translates into differences in the risk of adverse cardiovascular outcomes and overall mortality, especially in patients with preexisting CAD.

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Table 1. Baseline characteristics of the entire cohort and the subgroup of patients with coronary artery disease (CAD): categorical variables

| Variable                        | Entire Cohort | Patients with CAD |
|---------------------------------|---------------|-------------------|
| | Glimepiride (N=2,537) | Glipizide (N=4,325) | Glyburide (N=4,279) | Glimepiride (N=341) | Glipizide (N=584) | Glyburide (N=580) |
| Male (%) | 1370 (54.0%) | 2422 (56.0%) | 2408 (56.3%) | 233 (68.3%) | 400 (68.5%) | 419 (72.2%) |
| Caucasian (%) | 2644 (80.6%) | 3237 (74.8%) | 3207 (74.9%) | 285 (83.6%) | 488 (83.6%) | 477 (82.2%) |
| Missing (%) | 86 (3.4%) | 129 (3.0%) | 131 (3.1%) | 10 (2.9%) | 10 (2.5%) | 11 (2.5%) |
| Current Smoker (%) | 254 (10.0%) | 459 (10.6%) | 425 (9.9%) | 34 (10.0%) | 49 (8.4%) | 50 (8.6%) |
| Never (%) | 836 (33.0%) | 1329 (30.7%) | 1326 (31.0%) | 97 (28.4%) | 145 (24.8%) | 147 (25.3%) |
| Passive (%) | 4 (0.2%) | 10 (0.2%) | 9 (0.2%) | 0 (0.0%) | 2 (0.3%) | 0 (0.0%) |
| Quit (%) | 739 (29.1%) | 1241 (28.7%) | 1209 (28.3%) | 157 (46.0%) | 272 (46.6%) | 240 (41.4%) |
| Missing (%) | 704 (27.7%) | 1286 (29.7%) | 1310 (30.6%) | 53 (15.5%) | 116 (19.9%) | 143 (24.7%) |
| ACE/ARB inhibitors (%) | 1344 (53.0%) | 2213 (51.2%) | 2220 (51.9%) | 245 (71.8%) | 378 (64.7%) | 382 (65.9%) |
| Cholesterol Medication (%) | 1158 (45.6%) | 1922 (44.4%) | 1787 (41.8%) | 264 (77.4%) | 422 (72.3%) | 401 (69.1%) |
| Plavix (%) | 221 (8.7%) | 333 (7.7%) | 322 (7.5%) | 90 (26.4%) | 101 (17.3%) | 113 (19.5%) |
| Aspirin (%) | 669 (26.4%) | 1029 (23.8%) | 1017 (23.8%) | 178 (52.2%) | 277 (47.4%) | 263 (45.3%) |
| CAD (%) | 341 (13.4%) | 584 (13.5%) | 580 (13.6%) | 341 (100%) | 584 (100%) | 580 (100%) |
| Heart Failure (%) | 197 (7.8%) | 319 (7.4%) | 326 (7.6%) | 82 (24.0%) | 141 (24.1%) | 150 (25.9%) |
| New Diabetes (%) | 249 (9.8%) | 411 (9.5%) | 280 (6.3%) | 47 (13.8%) | 71 (12.2%) | 43 (7.4%) |
Table 2. Baseline characteristics of the entire cohort and the subgroup of patients with coronary artery disease (CAD): continuous variables

| Characteristic          | Entire Cohort |          |          |          |          | Patients with CAD |          |          |          |          |
|-------------------------|---------------|----------|----------|----------|----------|------------------|----------|----------|----------|----------|
|                         | Glimepiride   | Glipizide| Glyburide| Missing  |          | Glimepiride      | Glipizide| Glyburide| Missing  |          |
|                         | Mean | SD   | Mean | SD   | Mean | SD   | Mean | SD   | Mean | SD  | Mean | SD   | %      | Mean | SD   | Mean | SD   | Mean | SD  | %     | Mean | SD   | Mean | SD   |
| Age (years)             | 65.6 | 13.1 | 66.1 | 13.3 | 67.8 | 13.1 | 0.0% |      |      |      |      |      |      |      |      |      |      |      |      |
| BMI (kg/m²)             | 31.1 | 6.5  | 30.8 | 6.8  | 30.8 | 6.7  | 49.7% |      |      |      |      |      |      |      |      |      |      |      |      |
| BP Systolic (mmHg)      | 134.8| 20.8 | 135.1| 21.8 | 135.9| 22.1 | 24.5% |      |      |      |      |      |      |      |      |      |      |      |      |
| BP Diastolic (mmHg)     | 75.8 | 11.6 | 75.4 | 11.8 | 74.9 | 11.8 | 24.5% |      |      |      |      |      |      |      |      |      |      |      |      |
| HDL (mg/dL)             | 45.4 | 14.4 | 45.6 | 14.2 | 45.9 | 15.4 | 56.0% |      |      |      |      |      |      |      |      |      |      |      |      |
| LDL (mg/dL)             | 105.3| 36.4 | 107.0| 39.5 | 106.7| 39.4 | 57.5% |      |      |      |      |      |      |      |      |      |      |      |      |
| Triglycerides (mg/dL)   | 205.8| 225.1| 204.4| 193.5| 192.0| 170.9| 56.5% |      |      |      |      |      |      |      |      |      |      |      |      |
| HDL (%)                 | 7.5  | 1.8  | 7.7  | 1.9  | 7.6  | 1.8  | 54.5% |      |      |      |      |      |      |      |      |      |      |      |      |
| MDRD eGFR               | 71.2 | 20.1 | 70.5 | 20.9 | 69.8 | 20.3 | 32.1% |      |      |      |      |      |      |      |      |      |      |      |      |
| Zip median income($)    | 46216.0| 14888.5| 43786.1| 14737.8| 43477.7| 14583.6| 0.1% |      |      |      |      |      |      |      |      |      |      |      |      |

Table 3. Hazard ratios with 95% confidence intervals for the sulfonylurea monotherapy comparisons for mortality in the entire cohort and the subgroup with documented coronary artery disease (CAD)

| Entire Cohort Contrast | HR   | 95% CI   | P-value |
|------------------------|------|----------|---------|
| Glyburide vs. Glimepiride | 1.00 | 0.89 | 1.14 | 0.952 |
| Glipizide vs. Glyburide | 1.04 | 0.94 | 1.15 | 0.430 |
| Glipizide vs. Glimepiride | 1.05 | 0.92 | 1.19 | 0.499 |

| CAD Subgroup Contrast | HR   | 95% CI   | P-value |
|-----------------------|------|----------|---------|
| Glyburide vs. Glimepiride | 1.36 | 0.96 | 1.91 | 0.081 |
| Glipizide vs. Glyburide | 1.03 | 0.80 | 1.31 | 0.838 |
| Glipizide vs. Glimepiride | 1.39 | 0.99 | 1.96 | 0.059 |

Mortality model adjusted for baseline covariates: age, sex, race (Caucasian vs. noncaucasian), MDRD estimated glomerular filtration rate (GFR), hemoglobin A1C (HbA1C), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglycerides (TG), smoking status, angiotensin converting enzyme therapy (ACE) or angiotensin receptor blocker therapy (ARB), aspirin therapy (ASA), clopidogrel therapy, cholesterol lowering medication, new diabetes, coronary artery disease, congestive heart failure, and median household income.
**Figure Legend**

**Figure 1**: Overall Mortality in the entire cohort (A), and subgroup with a documented history of CAD (B), treated with sulfonylurea monotherapy. The decreasing numbers of patients at risk for mortality are secondary to the staggered entry of the study subjects, not loss to follow-up. The final status of all patients was ascertained via the Social Security Death Index.

**Figure 1a**

| Drugs       | 0 Months | 12 Months | 24 Months | 36 Months | 48 Months | 60 Months | 72 Months |
|-------------|----------|-----------|-----------|-----------|-----------|-----------|-----------|
| GLIMEPIRIDE | 2537     | 1961      | 1262      | 875       | 532       | 136       | 68        |
| GLIPIZIDE   | 4325     | 3253      | 2470      | 1774      | 1063      | 389       | 217       |
| GLYBURIDE   | 4279     | 3335      | 2586      | 1855      | 1209      | 461       | 260       |
Figure 1b

B)