Effect of Second-Generation Sulfonylureas on Survival in Patients With Diabetes Mellitus After Myocardial Infarction

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OBJECTIVE: To examine possible adverse effects of sulfonylureas on survival among patients with diabetes mellitus (DM) who experience a myocardial infarction (MI).

PATIENTS AND METHODS: Residents of Olmsted County, Minnesota, with an MI that met standardized criteria from January 1, 1985, through December 31, 2002, were followed up for mortality.

RESULTS: Among 2189 patients with MI (mean $\pm$ SD age, 68 $\pm$ 14 years; 1237 men [57%]), 409 (19%) had DM. The 23 patients treated with first-generation sulfonylureas, biguanides, or thiazolidinediones were excluded from analyses. Among the remaining 386 patients with DM, 120 (31%) were taking second-generation sulfonylureas, 180 (47%) were taking insulin, and 86 (22%) were receiving nonpharmacological treatment. Patients with DM treated with second-generation sulfonylureas were more likely to be men and have higher creatinine clearance than those treated with insulin. After adjusting for age, sex, Killip class, duration of DM, creatinine clearance, and reperfusion therapy or revascularization, patients treated with second-generation sulfonylureas had a lower risk of death than did diabetic patients receiving insulin (hazard ratio, 0.41; 95% confidence interval, 0.21-0.80; $P=.009$).

CONCLUSION: These population-based data do not support the concern about an adverse effect of second-generation sulfonylureas on survival after MI and underscore the importance of population-based studies of surveillance of drug safety.

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CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; MI = myocardial infarction

Diabetes mellitus (DM) is associated with increased cardiac morbidity and mortality.¹ Although advances in cardiovascular care and revascularization techniques have been associated with improved outcomes in the population overall, the burden of cardiovascular disease remains substantial among patients with DM.² In particular, after myocardial infarction (MI), patients with DM experienced worse survival rates compared with those without DM, as shown by hospital and community studies.^{3,4} Furthermore, the prevalence of DM among patients with MI is increasing over time.⁴

Guidelines for treatment of DM recommend aggressive management of hyperglycemia, which involves lifestyle changes and use of medications.⁵ Sulfonylureas are effective oral hypoglycemic agents that have been widely used in clinical practice since the mid-1960s.⁶ The availability of first-generation sulfonylureas was followed by Food and Drug Administration approval of second-

generation sulfonylureas in the early 1980s.⁷ The hypoglycemic effect of all sulfonylureas occurs through inhibition of adenosine triphosphate-sensitive potassium channels in β cells of the pancreas.⁸ However, in the heart, inhibition of these channels impairs ischemic preconditioning^{9,10}; thus, protection of the myocardium against ischemia is reduced.^{6,11} This decreased protection could potentially result in larger areas of myocardial injury.⁶ Within this context, there is an ongoing controversy regarding the safety of sulfonylureas among patients with DM at the time of MI.^{12,13} Population-based studies have the potential to provide some insight into such outcomes in clinical practice.

The current study was undertaken to examine possible adverse effects of sulfonylureas on survival among patients with DM who experience an MI. We tested the hypothesis that diabetic patients taking sulfonylureas when they experienced an MI had increased mortality rates compared with diabetic patients receiving insulin.

PATIENTS AND METHODS

STUDY SETTING

All study participants were residents of Olmsted County, Minnesota, which is relatively isolated from other urban areas. Mayo Clinic, Olmsted Medical Center, and a handful of private practitioners are the only health care providers in the county. The Rochester Epidemiology Project¹⁴ enables the linkage of medical records from all sources of care used by the population of Olmsted County. This system enables complete capture of all health care-related events and

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FIGURE 1. Diabetic treatment by year of myocardial infarction. Other refers to biguanides and thiazolidinediones.

retrieval of all medical record data for epidemiological investigations.

ASSEMBLING THE MI INCIDENCE COHORT

Assembly of the cohort of patients hospitalized with MI followed standardized surveillance methods¹⁵ and has been previously reported.¹⁶ Lists of patients discharged from hospitals in Olmsted County from January 1, 1979, through December 31, 2002, who had diagnoses compatible with MI were obtained from the Rochester Epidemiology Project index of diagnoses and the Hospital Utilization Review Database. The target *International Classification of Diseases, Ninth Revision*, codes were 410 (acute MI), 411 (other acute and subacute forms of ischemic heart disease), 412 (old MI), 413 (angina pectoris), and 414 (other forms of ischemic heart disease). Abstractors determined incident status through review of the hospital and ambulatory records. Information on cardiac pain, biomarker values, and the date and time of the electrocardiograms was collected. The reliability of this method has been previously reported.¹⁶ Standard epidemiological criteria were applied to assign a diagnosis of confirmed MI on the basis of cardiac pain, biomarker values, and Minnesota coding of the electrocardiograms.¹⁶ All aspects of the current study were approved by Mayo Clinic and Olmsted Medical Center institutional review boards.

ASCERTAINMENT OF DM

Patients were identified as having DM according to the National Diabetes Data Group criteria.¹⁷ Diabetes mellitus

was defined by 2 consecutive fasting blood glucose levels of 140 mg/dL or higher or an oral glucose tolerance test result at 1 to 2 hours after oral ingestion of glucose of 200 mg/dL or higher. In the absence of 2 qualifying glucose values, patients taking any oral hypoglycemic agent for at least 2 consecutive weeks or until death also qualified as having DM. The date each patient first met criteria for DM was defined as *diabetes onset*. Hyperglycemia diagnosed at the time of the index MI was not considered. Patients whose first glucose value in the medical record met criteria and who had a prior clinical diagnosis of DM (ie, moved to the county with DM) were assigned diabetes onset as the date of diagnosis reported by the patient at the initial visit with a Rochester Epidemiology Project provider. Treatment of DM was categorized as nonpharmacological, insulin, or oral hypoglycemic agent used as part of the preadmission treatment before the index MI.

The use of second-generation sulfonylureas was approved by the Food and Drug Administration in 1984.⁷ Therefore, the study period was defined as January 1, 1985, through December 31, 2002. During that time, first-generation sulfonylureas were gradually replaced by second-generation drugs (Figure 1).

CLINICAL CHARACTERISTICS AND SURVIVAL

Both inpatient and outpatient medical records were reviewed for cardiovascular disease risk factors, including history of familial coronary disease, smoking status, hypertension, hyperlipidemia, and other comorbid conditions, based on clinical diagnosis. Height and weight measurements recorded at hospital admission for the MI

were used to calculate body mass index (weight in kilograms divided by height in meters squared).

ST-segment elevation and Q-waves were identified using the Minnesota coding of the electrocardiogram.¹⁸ Because of changes in normal values over time, peak creatine kinase ratio (maximum creatine kinase value divided by the upper limit of normal) was used. Indicators of MI severity, such as Killip class, ST-segment elevation, Q-wave MI, and peak creatine kinase ratio, were obtained as previously described.¹⁹ Killip class was categorized as 1 (no signs of heart failure), 2 (presence of rales, S3 gallop, and venous hypertension), 3 (presence of pulmonary edema), or 4 (presence of cardiogenic shock, defined as a systolic blood pressure <90 mm Hg in the absence of hypovolemia). Revascularization included the use of thrombolytic therapy, coronary angioplasty, or coronary artery bypass surgery within the same hospitalization. Time to presentation was defined as the time from symptom onset to the first electrocardiogram.

Ascertainment of death incorporated autopsy reports, obituary notices, death certificates filed in Olmsted County, and electronic files of death certificates obtained from the State of Minnesota Department of Vital and Health Statistics.

STATISTICAL ANALYSES

The data are presented as percentage or mean $\pm$ SD. Associations between clinical characteristics and DM status were examined with χ^2 tests for the categorical variables and rank sum tests for the continuous variables. Associations between clinical characteristics and treatment for DM were examined with χ^2 tests for the categorical variables and Kruskal-Wallis tests for the continuous variables. For 2-way comparisons of the treatments, the Bonferroni correction was used to determine the level of significance of .017. Survival analyses compared the 2 pharmacological therapies. Survival was analyzed with the Kaplan-Meier method. Proportional hazards regression was used to examine the association between death and DM status and between death and treatment of DM. In examining the association between death and treatment of DM, all baseline characteristic variables (body mass index, hypertension, hyperlipidemia, familial coronary disease, current smoker, Killip class, peak creatine kinase ratio, Q-wave MI, ST-segment elevation MI, time from DM diagnosis to MI, hours from onset of symptoms to presentation, peripheral or cerebrovascular disease, creatinine clearance, chronic pulmonary disease, peptic ulcer disease, malignancy, reperfusion, and year of MI) were included, one at a time, with age and sex in the model. The significant variables were included in the final multivariable model.

The proportional hazards assumption was tested using Schoenfeld residuals. Because the proportional hazards assumption was not met, follow-up was censored at 1 year in the proportional hazards regression models. Missing values did not exceed 5% for any variable used in the regression analyses. $P=.05$ was selected for the threshold of statistical significance. Analyses were performed using SAS statistical software, version 8 (SAS Institute, Cary, NC).

RESULTS

BASELINE CHARACTERISTICS

From January 1, 1985, through December 31, 2002, a total of 2189 residents of Olmsted County were hospitalized with MI. Among these, the mean $\pm$ SD age was 68 ± 14 years, 1237 (57%) were men, and 409 (19%) had DM. The clinical characteristics of patients with DM differed markedly from those without DM (Table 1). Patients with DM were older, more likely to be women, and more likely to have a higher body mass index. They had a greater prevalence of hypertension, hyperlipidemia, and peripheral or cerebrovascular disease but were less likely to be smokers and had lower creatinine clearance. Patients with DM sought treatment later after the onset of symptoms, were in a higher Killip class, and were less likely to be treated with thrombolytics, but they were more likely to undergo coronary artery bypass surgery than patients without DM. Other MI characteristics were similar for patients with and without DM.

Two patients were taking both insulin and second-generation sulfonylureas and were classified as being treated with insulin. A few patients were treated with first-generation sulfonylureas ($n=8$), biguanides ($n=9$), or thiazolidinediones ($n=6$) and were excluded from the analyses that examined treatments among patients with DM. Among the remaining 386 patients with DM, 86 (22%) were treated nonpharmacologically, 120 (31%) were treated with second-generation sulfonylureas, and 180 (47%) were treated with insulin. Among patients receiving second-generation sulfonylureas, 76 (63%) were treated with glyburide, 39 (33%) with glipizide, and 5 (4%) with glimepiride.

The clinical characteristics of diabetic patients differed according to treatment categories (Table 1). Compared with diabetic patients treated nonpharmacologically or with insulin, those taking sulfonylureas were more likely to be men and to have higher creatinine clearance. Patients taking insulin had a higher Killip class, had more peripheral and cerebrovascular disease, and were less likely to undergo reperfusion or revascularization during their hospitalization than diabetic patients treated with sulfonylureas. They also had longer duration of DM before MI compared with diabetic patients treated with sulfonylureas or nonpharmacologically.

TABLE 1. Clinical Characteristics at the Time of MI^a

Characteristic	Non-DM (n=1780)	DM (n=409)	P value ^b	Diet (n=86)	SU2 (n=120)	Insulin (n=180)	P value ^c	P value ^d		
								Diet vs SU2	Diet vs insulin	SU2 vs insulin
Age (y), mean ± SD	68±15	70±12	.003	73±11	70±12	70±12	.24	.13	.13	.86
Men (%)	58	49	<.001	40	58	44	.01	.008	.50	.01
BMI, mean ± SD	27±6	30±7	<.001	28±6	30±6	31±7	.08	.06	.03	.83
Cardiovascular risk factors (%)										
Hypertension	53	74	<.001	74	75	74	.98	.89	.97	.83
Hyperlipidemia	35	48	<.001	43	55	47	.20	.09	.51	.17
Familial coronary disease	20	24	.11	22	24	25	.85	.67	.58	.91
Current smoker	28	12	<.001	15	15	9	.24	.95	.16	.14
MI characteristics										
Killip class >1 (%)	32	42	<.001	40	32	50	.008	.22	.14	.002
Peak creatine kinase ratio (%)										
Tertile 1	32	38	.09	40	34	30	.47	.42	.18	.80
Tertile 2	33	33		26	35	37				
Tertile 3	34	29		35	32	34				
Q-wave MI (%)	54	57	.30	59	56	57	.95	.74	.82	.89
ST-segment elevation MI (%)	38	34	.15	40	34	29	.25	.43	.10	.38
Time from DM diagnosis to MI (y), mean ± SD	NA	12.9±10.2	NA	10.1±8.6	7.8±6.2	18.4±10.7	<.001	.17	<.001	<.001
Time from onset of symptoms to presentation (h), median (IQR)	1.7 (0.9-4.1)	2.2 (0.9-5.8)	.02	2.0 (0.8-5.8)	2.1 (1.1-6.9)	2.4 (0.8-5.9)	.83	.49	.73	.80
Comorbidities										
Peripheral or cerebrovascular disease (%)	22	39	<.001	34	32	48	.006	.76	.02	.004
Creatinine clearance (mL/min), mean ± SD	67±36	61±37	<.001	53±30	71±44	58±35	.002	.002	.47	.003
Chronic pulmonary disease (%)	13	11	.22	10	12	12	.95	.79	.77	>.99
Peptic ulcer disease (%)	15	16	.55	20	13	17	.45	.21	.61	.36
Malignancy (%)	15	16	.49	23	14	16	.19	.09	.13	.74
Reperfusion therapy or revascularization during hospitalization (%)	57	52	.09	53	60	46	.05	.35	.23	.01
Thrombolytics (%)	15	9	.002	14	10	6	.07	.38	.02	.15
PCI (%)	40	36	.08	30	40	35	.35	.15	.44	.38
CABG (%)	9	13	.03	17	16	9	.08	.76	.04	.07

^a BMI = body mass index; CABG = coronary artery bypass grafting; DM = diabetes mellitus; IQR = interquartile range; MI = myocardial infarction; NA = not applicable; PCI = percutaneous coronary interventions; SU2 = second-generation sulfonylurea.

^b From the χ^2 test for categorical variables and rank sum test for continuous variables.

^c From the χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables.

^d From the χ^2 test for categorical variables and rank sum test for continuous variables. The values in bold are significant using the Bonferroni-adjusted significance level of .017.

SURVIVAL AFTER MI

After a mean ± SD follow-up of 4.9±3.6 years, 943 patients died; 235 had DM, and 708 did not. Survival rates differed between those with and without DM ($P<.001$). At 1 year, the Kaplan-Meier survival estimate for diabetic patients was 75% (95% confidence interval [CI], 70%-79%) compared with 82% (95% CI, 80%-84%) among their nondiabetic counterparts. Patients with DM were 46% more likely to die within 1 year after MI than nondiabetic patients (hazard ratio [HR], 1.46; 95% CI, 1.17-1.81; $P<.001$). This association persisted after adjustment for age and sex (HR, 1.37; 95% CI, 1.10-1.71; $P=.01$).

Among the 300 patients with DM treated pharmacologically, 170 died. Of those 170 patients, 50 were treated

with second-generation sulfonylureas, and 120 were treated with insulin. Survival rates differed between the 2 groups (Figure 2). At 30 days, the Kaplan-Meier survival estimates were 95% (95% CI, 91%-99%) and 83% (95% CI, 78%-89%) for patients with DM treated with second-generation sulfonylureas and those treated with insulin, respectively. At 1 year, the survival estimates were 89% (95% CI, 84%-95%) and 65% (95% CI, 58%-72%) for patients with DM treated with second-generation sulfonylureas and those treated with insulin, respectively. Considering diabetic patients treated with insulin as the reference group, those taking second-generation sulfonylureas had a reduced risk of death within 1 year after MI (HR, 0.27; 95% CI, 0.15-0.49; $P<.001$). This

FIGURE 2. Survival after myocardial infarction (MI) for diabetic patients treated with second-generation sulfonylureas and those treated with insulin.

association was attenuated but remained significant after adjustment for age, sex, duration of DM before the MI, Killip class, creatinine clearance, and reperfusion or revascularization (Table 2).

In examining the cause of death, the proportions of cardiovascular deaths were similar between the 2 DM groups treated pharmacologically (68% vs 66% for diabetic patients treated with second-generation sulfonylureas and insulin, respectively; $P=.83$). In ancillary analyses, we examined the impact of relying on the American Diabetes Association criteria to ascertain DM.²⁰ This analysis yielded similar trends as the main analyses presented herein, thereby attesting to the robustness of our findings.

DISCUSSION

In this population-based study, patients with DM experienced greater mortality rates after MI compared with nondiabetic patients. Patients with DM treated with second-

TABLE 2. Hazard Ratios (95% CIs) for Death Within 1 Year After MI^a

	Hazard ratio (95% CI)	P value
Second-generation sulfonylureas ^b	0.41 (0.21-0.80)	.009
Age	1.02 (0.99-1.04)	.15
Men	1.06 (0.66-1.72)	.80
Killip class >1	2.14 (1.28-3.55)	.004
Years from DM diagnosis to MI	1.02 (0.99-1.04)	.21
Creatinine clearance	0.98 (0.97-0.99)	<.001
Reperfusion therapy or revascularization during hospitalization	0.60 (0.36-1.03)	.06

^a CI = confidence interval; DM = diabetes mellitus; MI = myocardial infarction.

^b The reference group is diabetic patients treated with insulin.

generation sulfonylureas at the time of index MI experienced better survival rates compared with the reference group of diabetic patients treated with insulin after adjustment for measurable clinic characteristics, including age, sex, Killip class, duration of DM diagnosis, creatinine clearance, and reperfusion therapy or revascularization.

Sulfonylurea agents have been used to achieve glycemic control in patients with DM. In the early 1970s, concern was raised that tolbutamide, a first-generation sulfonylurea, could be associated with excess mortality when used for patients with DM.²¹ Sulfonylureas act by inhibition of the adenosine triphosphate-sensitive potassium channels. In the pancreas, inhibition of these channels induces release of insulin.⁸ However, in the heart, inhibition of the adenosine triphosphate-sensitive potassium channels prevents ischemic preconditioning.^{9,10} This effect has been shown in various animal models.^{22,23} In the human heart, ischemic preconditioning has been shown using sequential balloon inflation during coronary angioplasty or intermittent aortic cross-clamping during coronary artery bypass surgery.²⁴⁻²⁶ However, not all studies have found evidence of ischemic preconditioning in the human heart, which could be related to the presence of numerous confounding variables in clinical practice.^{6,27-29} To this end, clinical studies that have examined this issue reported conflicting results with regard to the association of sulfonylureas with adverse events after MI. In a hospital-based case series of patients with DM, Garratt et al³⁰ reported a large increase in the risk of early death after MI among those treated with sulfonylureas. Similar concern was raised in a recent study of a large number of individuals from Denmark.³¹ However, other reports did not detect such an association.³²⁻³⁴ Differences in sample size and study design likely account for these discrepancies. However, none of these prior studies reported on the comprehensive experience of a community in a population-based framework, thereby avoiding many confounding effects of referral bias. Thus, the current results augment previous knowledge by indicating that, in this observational population-based cohort, the use of second-generation sulfonylureas as part of the preadmission treatment of patients presenting with MIs was not associated with excess mortality.

Potential limitations of the current study need to be considered when interpreting the data. Although Olmsted County is becoming more diverse, its racial and ethnic composition during the study period may limit the generalizability of these data to ethnic groups underrepresented in this population. Unmeasured confounders, an unavoidable issue in observational studies, likely explain the "protective" association detected between sulfonylureas and outcomes. However, the important point of the current study is the absence of an adverse effect of sulfonylureas

among patients with MI in a rigorously ascertained community cohort, which helps to dispel previous concerns. The National Diabetes Data Group criteria were used to ascertain DM.¹⁷ However, our sensitivity analyses using the more stringent American Diabetes Association diagnostic criteria for diabetes²⁰ yielded similar results.

This population-based study has several strengths. All cases were rigorously ascertained using standardized criteria for both DM and MI. Because all cases are incident infarctions, the data are not affected by incidence prevalence bias. The data represent the comprehensive experience of an entire community within a geographically defined population. All these aforementioned factors optimize the external validity of these data.

CONCLUSION

In this population-based study, patients with DM experienced greater mortality rates than did nondiabetic patients after MI. However, diabetic patients receiving second-generation sulfonylureas at the time of presentation did not experience greater mortality rates than diabetic patients treated with insulin.

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