

Sulfonylurea Drugs Increase Early Mortality in Patients With Diabetes Mellitus After Direct Angioplasty for Acute Myocardial Infarction

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Objectives. The purpose of this study was to examine the impact of sulfonylurea drug use on outcome in diabetic patients undergoing direct coronary angioplasty for acute myocardial infarction.

Background. Sulfonylurea drugs impair ischemic preconditioning. Whether sulfonylurea drugs affect outcome adversely in diabetic patients undergoing direct angioplasty for acute myocardial infarction is unknown.

Methods. Clinical outcomes after direct balloon angioplasty for acute myocardial infarction were evaluated in 67 diabetic patients taking oral sulfonylurea drugs and 118 diabetic patients not taking these drugs.

Results. Hospital mortality was significantly higher among diabetics treated with sulfonylurea drugs at the time of myocardial infarction (24% vs. 11%). Univariate analysis identified sulfonylurea drug, age, ventricular function, ejection fraction less than 40%, prior bypass surgery and congestive heart failure as correlates of increased in-hospital mortality. Logistic regression

found sulfonylurea drug use (odds ratio 2.77, $p = 0.017$) to be independently associated with early mortality. Congestive heart failure, but not sulfonylurea drug use, was associated with an increased incidence of in-hospital ventricular arrhythmias. Congestive heart failure, prior bypass surgery and female gender, but not sulfonylurea drug use, were associated with late adverse events.

Conclusions. Sulfonylurea drug use is associated with an increased risk of in-hospital mortality among diabetic patients undergoing coronary angioplasty for acute myocardial infarction. This early risk is not explained by an increase in ventricular arrhythmias, but may reflect deleterious effects of sulfonylurea drugs on myocardial tolerance for ischemia and reperfusion. For surviving patients sulfonylurea drug use is not associated with an increased risk of serious late adverse events.

(J Am Coll Cardiol 1999;33:119-24)

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Patients with diabetes mellitus account for a large proportion of patients admitted with acute myocardial infarction (MI) and as a whole have a poorer prognosis when compared to nondiabetic patients (1-3). Moreover, diabetic patients with ischemic heart disease have a substantially worse outcome following coronary interventional procedures despite similar rates of procedural success when compared to patients without diabetes (4,5). The basis for these differences in outcome remains unresolved.

Among possible contributing factors, use of sulfonylurea hypoglycemic agents has been reported to increase cardiovascular mortality in patients with non-insulin dependent (type II) diabetes mellitus (6,7). The mechanism of action and the controversy surrounding the clinical use of sulfonylurea drugs has recently been reviewed in detail (8). Sulfonylureas, while

promoting release of insulin (9-11) through blockade of metabolism regulated adenosine triphosphate-sensitive potassium channel (K_{ATP}) channels present in pancreatic β -cell membranes (12,13), also block K_{ATP} channels present in cardiac cells and coronary vasculature (14-17). This action impairs ischemic preconditioning (18-20) and prevents coronary vasodilation in response to ischemia (21-23). Since ischemic preconditioning and coronary vasodilation act to protect the heart against ischemic insults (24), sulfonylurea drug action within the myocardium may increase its vulnerability to ischemia (25). Furthermore, sulfonylureas impair ischemic preconditioning during coronary angioplasty, leading to increased clinical manifestations of ischemia (26). However, there have been no clinical reports of increased mortality in patients with ischemic heart disease treated with glibenclamide, a sulfonylurea with known high affinity for myocardial K_{ATP} channels (15,16), and no data are available that address specifically outcomes in diabetic patients with MI undergoing direct coronary angioplasty while taking sulfonylurea drugs.

To address this, we examined mortality and other adverse events among diabetic patients undergoing direct balloon angioplasty for acute MI, and assessed the effects of oral sulfonylurea hypoglycemic drug use on clinical outcome.

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Manuscript received February 19, 1998; revised manuscript received August 10, 1998, accepted September 10, 1998.

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Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
CI	= 95% confidence interval
HgbA1C	= glycosylated hemoglobin
K _{ATP}	= adenosine triphosphate-sensitive potassium channel
LVEF	= left ventricular ejection fraction
MI	= myocardial infarction
OR	= odds ratio

Methods

Patient population. Patients with preexisting diabetes mellitus undergoing direct coronary angioplasty for treatment of acute MI between January 1985 and December 1994 were identified retrospectively from the Mayo Clinic coronary intervention database. This cutoff date was selected to assure against inclusion of patients using metformin, a nonsulfonylurea oral hypoglycemic agent available commercially in North America after December 29, 1994. Initial data for each patient were entered into the database prospectively, and follow-up data were obtained through review of medical records for all hospital and outpatient visits at Mayo Clinic and affiliated hospitals, and from a standardized questionnaire completed at 6 and 12 months following intervention, and annually thereafter. Adverse events were corroborated through review of medical records and death notices. In accordance with Minnesota law, only patients who consented to the use of their clinical records for research purposes were included in this study; the number of eligible patients not included for this reason was zero. This study was approved by the Mayo Clinic Institutional Review Board.

Medical treatment. Patients were divided into two groups on the basis of their use of diabetic medications. Group 1 consisted of diabetic patients with acute MI taking an oral sulfonylurea drug at the time of angioplasty, and group 2 consisted of diabetic patients with acute MI not taking a sulfonylurea drug. All patients were treated with conventional doses of heparin, aspirin, beta-adrenergic blocking drugs and nitroglycerin according to established protocols for the care of patients with acute MI.

Coronary angiography and revascularization. Coronary angiography was performed in patients immediately upon presentation with acute MI. All patients were treated with direct balloon angioplasty employing standard technique; non-balloon coronary intervention devices (atherectomy devices, lasers or stents) were not evaluated in this study. Multivessel disease was considered present when angiographic narrowing of $\geq 70\%$ involving at least one major coronary artery was accompanied by a narrowing of $\geq 50\%$ in at least one other artery. Procedural success was defined as improvement of $>40\%$ luminal diameter in all lesions treated. Abrupt closure was defined as reduction of anterograde coronary blood flow to Thrombolysis in Myocardial Infarction trial grade 0-1 after angioplasty. Circulatory shock was defined as systolic blood

pressure <90 mm Hg or cardiac output <2.5 liters/min. Clinical success was defined as procedural success without death, Q wave MI or urgent coronary artery bypass graft surgery (CABG).

End points. In-hospital adverse events assessed included death, serious ventricular arrhythmias (fibrillation or sustained tachycardia), procedural success and complications, recurrent Q wave MI, need for CABG or repeat angioplasty procedures and postprocedural renal insufficiency (defined as an elevation of creatinine to >2.5 mg/dl). Late events assessed included death, postdischarge MI (Q wave and non-Q wave), need for additional angioplasty procedures or CABG and presence of recurrent severe angina. Correlates of in-hospital mortality, in-hospital ventricular arrhythmias, late death and a combined late end point of death, repeat MI, recurrent severe angina, CABG or repeat target vessel angioplasty were sought.

Statistical analysis. Demographic characteristics and in-hospital adverse events in the two patient groups were compared using chi-square and student *t* test as appropriate. Stepwise logistic regression was used to model correlates of in-hospital adverse events. Variables included in the model were age, presence of congestive heart failure, left ventricular ejection fraction (LVEF), LVEF $<40\%$ (as a separate discrete variable), family history of atherosclerotic heart disease, gender, glycosylated hemoglobin (HgbA1C), HgbA1C $>8.5\%$ (as a separate discrete variable), hypercholesterolemia (defined as total serum cholesterol ≥ 250 mg/dl), hypertension (defined as diastolic blood pressure >90 mm Hg and/or systolic blood pressure >140 mm Hg), multivessel coronary disease, prior CABG and sulfonylurea drug use. Cox proportional hazard modeling was used to develop models for late mortality, MI, severe angina and a composite of these three end points.

Results

Baseline characteristics. One hundred and eighty-eight diabetic patients were identified who presented with acute MI and who were treated with direct balloon angioplasty during the study period. The use of sulfonylurea agents was uncertain in three patients, so they were excluded from analysis. Of the remainder, 67 were taking oral sulfonylurea hypoglycemic agents at the time of treatment (group 1), and 118 were not (group 2); 70 group 2 patients were using insulin, and 38 were controlled without either insulin or oral hypoglycemic agents. Clinical and angiographic characteristics of both groups are summarized in Table 1. Patients in group 1 were significantly older, and had a significantly lower mean LVEF when compared with group 2 (Table 1). Other factors known to affect mortality, such as extent of disease, incidence of congestive heart failure and infarct location, were similar in the two groups.

Procedural characteristics and success. In group 1, procedural success was achieved in 50 (74.6%) patients, which included 73 (85.9%) lesions. In group 2, procedural success was achieved in 95 (80.5%) patients, and 122 (84.1%) lesions. Overall rates of procedural success were not significantly

Table 1. Patient Characteristics

Clinical Characteristic	Group 1 (n = 67)	Group 2 (n = 118)	p Value
Men, n (%)	40 (59.7%)	73 (61.9%)	NS
Mean age (yr ± SD)	68.4 ± 10.5	63.2 ± 11.7	0.003
Current smoker, n (%)	7 (10.4%)	20 (16.9%)	NS
Hypertension, n (%)	41 (61.2%)	80 (67.8%)	NS
Hypercholesterolemia, n (%)	20 (29.9%)	37 (31.4%)	NS
Prior CABG, n (%)	6 (9%)	13 (11%)	NS
Mean LVEF, % ± SD	47.3 ± 14.7 (n = 29)	55.3 ± 14 (n = 51)	0.019
Congestive heart failure, n (%)	14 (20.9%)	24 (20.3%)	NS
Multivessel disease, n (%)	39 (61.2%)	70 (6.7%)	NS
Anterior MI, n (%)	31 (46%)	50 (42%)	NS

gb = coronary artery bypass graft surgery; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

different between the two groups. Although the incidence of circulatory shock was not significantly different, patients in group 1 required insertion of an intra-aortic balloon pump more frequently than patients in group 2 (p = 0.046) (Table 2).

In-hospital events. Despite similar rates of procedural success, in-hospital mortality was higher in patients from group 1 than group 2 (24% vs. 11%, p = 0.02). All early deaths were caused primarily by pump dysfunction with cardiogenic shock except for five arrhythmic deaths (two bradyarrhythmic events, three ventricular tachycardic or fibrillation events). Two patients died following emergency CABG. Logistic regression analysis found use of oral sulfonylurea agents to be associated with an increased risk of death (Table 3). Other variables associated independently with an increased risk of early mortality included LVEF, LVEF <40%, prior CABG, age and congestive heart failure. Multivariate analysis found oral sulfonylurea drug use to be independently associated with increased early mortality (Fig. 1).

Ventricular tachycardia or fibrillation occurred in 27% of group 1 and 22% of group 2 patients (p = NS). The presence of congestive heart failure (odds ratio [OR] = 2.77, 95% confidence interval [CI] = 1.2 to 6.60, p = 0.03) and male gender (OR = 2.53, CI = 1.04 to 6.14, p = 0.04), but not sulfonylurea drug use, were associated multivariately with an increased frequency of in-hospital ventricular fibrillation.

Rates of other adverse events, including recurrent MI and the need for additional revascularization procedures, were similar in the two groups.

Late events. Follow-up was available for all hospital survivors. Mean follow-up was 3.8 ± 2.3 years (range: 0.1 to 9.9

years) for group 1, and 3.6 ± 2.4 years (range: <0.1 to 9.1 years) for group 2. Although repeat coronary angioplasty procedures were performed more frequently for group 2 patients during the follow-up period (17.8% vs. 46.7% within 5 years after treatment, p = 0.05), no difference in the frequency of subsequent MI (19.9% vs. 23.1% at 5 years, p = NS), need for CABG (23.3% vs. 31.7% at 5 years; p = NS) or late mortality was found between the two groups. Only congestive heart failure (relative risk = 3.10, CI = 1.47 to 6.51, p = 0.003) was associated with an increased relative risk of death during the follow-up period.

Multivariate modeling identified only prior CABG to be associated with the combined end point of late death, MI, severe angina, CABG or repeat target vessel angioplasty.

Discussion

This study finds that the risk of death for diabetic patients undergoing balloon angioplasty for acute MI is 2.77 times higher if they are using an oral sulfonylurea hypoglycemic agent at the time of treatment. The impact of sulfonylurea drug use on early mortality was similar to the impact of reduced LVEF or overt clinical heart failure. Thus, use of sulfonylurea drugs may represent an additional risk factor in patients undergoing coronary interventional procedures in the presence of MI.

Sulfonylureas and mortality. Prior indication that sulfonylurea drug use may have adverse consequences in diabetic patients with cardiac disease came from epidemiological studies that demonstrated increased cardiovascular mortality among patients taking these agents (7). Although this observation generated much controversy, a similar conclusion was reached in a subsequent study that found increased mortality following MI in diabetic patients treated with sulfonylureas when compared to diabetic patients treated with insulin (6). The present study is consistent with these observations, and suggests that sulfonylurea drug use may increase mortality specifically among diabetic patients with MI undergoing acute revascularization therapy through coronary angioplasty. This

Table 2. Procedural Success and Complications of Angioplasty

Parameter	Group 1	Group 2	p Value
Successful procedure, n (%)	50 (74.6%)	95 (80.5%)	NS
Coronary segments treated, n	85	145	—
Successful lesions, n (%)	73 (85.9%)	122 (84.1%)	NS
Complete revascularization, n (%)	30 (44.8%)	43 (36.4%)	NS
Abrupt closure, n (%)	10 (14.9%)	9 (7.6%)	NS
Shock, n (%)	4 (6%)	7 (5.9%)	NS
Intra-aortic balloon pump, n (%)	5 (7.5%)	2 (1.7%)	0.046
Postprocedure renal failure, n (%)	4 (6%)	0	0.007

Table 3. Logistic Model for In-Hospital Death

Variable	p Value	OR	95% Confidence Intervals	
			Lower	Upper
Oral sulfonylurea use	0.024	2.534	1.133	5.666
HgbA1C	0.628	0.954	0.789	1.154
HgbA1C >8.5%	0.655	0.780	0.262	2.322
LVEF	0.019	0.940	0.895	0.990
LVEF <40%	0.009	7.467	1.669	33.407
Congestive heart failure	0.059	2.305	0.970	5.477
Gender	0.113	2.203	0.847	4.859
Prior CABG	0.011	3.818	1.357	10.743
Hypertension	0.681	0.842	0.371	1.912
Hypercholesterolemia	0.641	1.221	0.528	2.823
Emergency procedure	0.380	1.439	0.638	3.240
Age	0.016	1.050	1.009	1.093
Age \geq 75 yr	0.024	2.676	1.142	6.272
Family history of coronary disease	0.068	0.150	0.020	1.147
Multivessel disease	0.224	2.186	0.620	7.700
Anterior MI	0.060	0.433	0.181	1.037

HgbA1C = glycosylated hemoglobin; OR = odds ratio; other abbreviations as in Table 1.

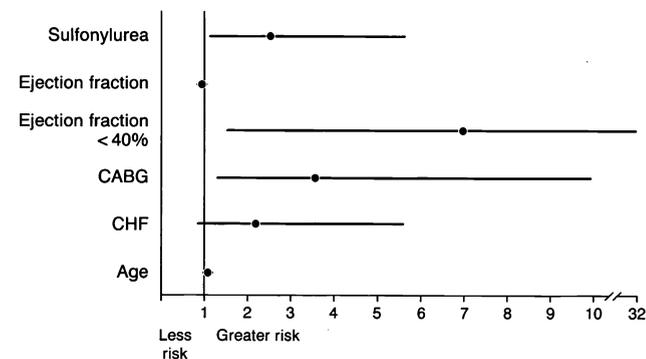
increased mortality could not be explained on the basis of differences in age, ventricular function, hyperglycemic control or procedural success between diabetic patients taking and not taking these drugs.

We did not find sulfonylurea drug use to be associated with an increased incidence of ventricular arrhythmias, suggesting that the observed increased mortality was not due to an increase in electrical instability in these patients. Thus, use of sulfonylurea drugs per se appears to be associated with worse early outcome in this patient population, but the mechanisms whereby sulfonylurea drugs may increase mortality have not been defined.

Potential explanations for increased mortality with sulfonylurea drugs. Experimentally, sulfonylureas increase infarct size and accelerate the death of hypoxic cardiomyocytes through blockade of K_{ATP} channels that mediate ischemic preconditioning in myocardium (8,27,28). Increased vulnerability of myocardium to ischemic insult in the presence of sulfonylurea drugs may have contributed to the increased mortality observed in this group of diabetic patients. Indeed, it has been demonstrated in isolated human myocardium (18) and in patients undergoing balloon angioplasty (26) that sulfonylurea drug treatment abolishes the cardioprotective efficacy of ischemic preconditioning. Although the extent of cell damage was not measured in the present study, increased ischemic myocardial injury should result in greater impairment of contractile function, which is an important known determinant of survival after acute MI (29,30). In this regard, our observations that the mean left ventricular ejection fraction was lower and requirement of intra-aortic balloon pump support was greater among patients taking sulfonylurea drugs are of interest.

Other mechanisms by which sulfonylureas may increase mortality in patients with MI include inhibition of the endogenous fibrinolytic system (31). This could be effected through

enhanced production of proinsulin, which is known to stimulate endothelial production of plasminogen activator inhibitor-1 (32-34). Elevated serum levels and activity of this inhibitor have been documented in animals and diabetic patients given sulfonylurea drugs (32,35-37), and resistance to tissue-type plasminogen activator has also been observed (38,39). This effect could also be mediated by lipoprotein(a) levels, which have been observed to correlate well with plasminogen activator inhibitor-1 activity and antigen levels (35,40) among diabetic patients using sulfonylurea drugs. When metformin, an antidiabetic biguanide compound, was substituted for sulfonylurea drugs in non-insulin dependent diabetic patients the abnormalities in plasminogen activator inhibitor-1 behavior improved without changes in lipoprotein(a) levels, suggesting a direct effect from sulfonylurea drugs, although the degree of individual improvement was related to the baseline lipoprotein(a) levels (40). These are important considerations, since refractory thrombosis is a recognized cause of failed angioplasty for acute MI (41-43).

Figure 1. Multivariate correlates of in-hospital mortality (odds ratios and 95% confidence intervals).

However, we observed no differences in the extent of refractory thrombosis but rather found similar overall procedural success rates during coronary intervention, suggesting that the principal mechanism by which sulfonylurea drugs increased mortality was not impaired endogenous fibrinolysis.

Sulfonylureas and late events. The finding that sulfonylurea drug use was not associated with an increased incidence of late events (other than the need for repeat balloon angioplasty) is consistent with our earlier observations (44). Unselected diabetic patients with MI treated with a variety of management strategies had similar late outcomes (2.7 ± 2.3 years) whether taking sulfonylurea drugs at the time of MI or not. This suggests either that the early mortality among diabetic patients using sulfonylurea drugs precluded the opportunity to observe late events in this group, or that the principal deleterious effects of sulfonylurea drug use are observed predominantly in the period of acute myocardial ischemia; the latter is consistent with previous studies, which indicate that the time of exposure to the drug and the state of the myocardium are important determinants of the consequences of sulfonylurea drug use (18,27,45,56).

Study limitations. The limitations of this study include the retrospective study design, and the limited number of patients with diabetes who underwent direct balloon angioplasty during the 10-year study period. Postulates regarding the potential role of K_{ATP} channels and other possible mediators of increased mortality are consistent with, but not supported directly by, the data presented. Patients not receiving sulfonylurea drugs were not analyzed further, so no conclusions may be made regarding the potential effects of other antidiabetic treatment strategies in the setting of acute MI (including the possible impact of oral biguanide therapy). Since only balloon angioplasty was studied, the impact of other catheter-based therapies, such as coronary stents, remains unknown.

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