

Impact of Type of Preadmission Sulfonylureas on Mortality and Cardiovascular Outcomes in Diabetic Patients with Acute Myocardial Infarction

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Background: The impact of antidiabetic medications on clinical outcomes in patients developing acute myocardial infarction (MI) is controversial. We sought to determine whether in-hospital outcomes in patients who were on sulfonylureas (SUs) when they developed their MIs differed from that of diabetic patients not receiving SUs and whether clinical outcomes were related to the pancreatic cells specificity of SUs.

Methods and Results: We analyzed the outcomes of the 1310 diabetic patients included in the nationwide French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction in 2005. Medications used before the acute episode were recorded. In-hospital complications were analyzed according to prior antidiabetic treatment. Mortality was lower in patients previously treated with SUs (3.9%) vs. those on other oral medications (6.4%), insulin (9.4%), or no medication (8.4%) ($P = 0.014$). Among SU-treated patients, in-hospital mortality was lower in patients receiving pancreatic cells-specific SUs (gliclazide or glimepiride) (2.7%), compared with glibenclamide (7.5%) ($P = 0.019$). Arrhythmias and ischemic complications were also less frequent in patients receiving gliclazide/glimepiride. The lower risk in patients receiving gliclazide/glimepiride vs. glibenclamide persisted after multivariate adjustment (odds ratio 0.15; 95% confidence interval 0.04–0.56) and in propensity score-matched cohorts.

Conclusion: In this nationwide registry of patients hospitalized for acute MI, no hazard was associated with the use of SUs before the acute episode. In addition, patients previously receiving gliclazide/glimepiride had improved in-hospital outcomes, compared with those on glibenclamide. (*J Clin Endocrinol Metab* 95: 4993–5002, 2010)

The cardiovascular safety of antidiabetic medications has received much attention in the recent past. Among antidiabetic medications, it has been suggested that sulfonylureas (SUs) might exert a deleterious role on cardiovascular events because of their potential impact on myocardial ischemic preconditioning (1–3). Experimentally it has been shown that some SUs such as glibenclamide (glyburide), which bind on myocardial as well as

pancreatic ATP-sensitive potassium channel (K_{ATP}) channels are able to block myocardial preconditioning mechanisms (4, 5). In contrast, newer SUs, such as gliclazide or glimepiride, are quite exclusively pancreatic β -cells specific and might therefore offer advantages over older agents in case of acute myocardial ischemia (5–8).

In the clinical setting, however, only very limited data on the impact of SUs on cardiovascular outcomes are avail-

ISSN Print 0021-972X ISSN Online 1945-7197

Printed in U.S.A.

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doi: 10.1210/jc.2010-0449 Received February 23, 2010. Accepted July 8, 2010.

First Published Online August 11, 2010

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Abbreviations: ADM, Antidiabetic medication; CI, confidence interval; FAST-MI, French registry on Acute ST-elevation and non ST-elevation Myocardial Infarction; GRACE, Global Registry of Acute Coronary Event; HbA1c, glycosylated hemoglobin; K_{ATP} , ATP-sensitive potassium channel; MI, myocardial infarction; NSTEMI, non-ST-segment-elevation MI; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI; SU, sulfonylurea.

able, and the results reported from different observational studies are conflicting (1, 9–21). In particular, it is not known whether the lack of interference with myocardial preconditioning translates into clinically evident benefits.

The French registry on Acute ST-elevation and non ST-elevation Myocardial Infarction (FAST-MI) was designed to describe the therapeutic management and outcomes of patients admitted to intensive care units with acute myocardial infarction (MI) at the end of 2005. One of the strengths of the registry was that all medications used before the acute episode, at the acute stage, and at discharge were prospectively recorded, allowing the comprehensive analysis of their potential impact on outcomes. The present study sought to assess the impact of chronic use of SUs, either as monotherapy or in combination with other antidiabetic medications and their type on the in-hospital outcomes in diabetic patients admitted for acute MI.

Patients and Methods

Population

The population and methods of the FAST-MI registry have been described in detail elsewhere (22). Briefly, the objective of the study was to collect comprehensive data on the management and outcome of consecutive patients admitted to intensive care units for definite acute MI over a 1-month period in France, irrespective of the type of institution to which the patients were admitted (*i.e.* university hospitals, public hospitals, or private clinics, with or without on-site catheterization facilities). Because of the rising concern with diabetes in coronary artery disease patients, recruitment was extended over 2 months for diabetic patients. Of the 374 centers that treated patients with acute MI at that time in France, 223 participated in the study (60%). One physician responsible for the study was recruited in each center and provided a complete list of all patients meeting the inclusion criteria and admitted to the intensive care unit during the study recruitment period; the physicians in charge of the patients cared for them according to their usual practice, independent of the study.

Patient selection

All consecutive adult (≥ 18 yr of age) diabetic patients admitted to the participating centers for a 2-month period beginning on October 1, 2005, were included in the registry if they had the following: 1) elevated serum markers of myocardial necrosis more than twice the upper limit of normal for creatine kinase, creatine kinase-MB, or elevated troponins and (2) either symptoms compatible with acute MI and/or electrocardiographic

changes on at least two contiguous leads with pathological Q waves (at least 0.04 sec) and/or persisting ST elevation or depression 0.1 mV or greater. The time from the beginning of symptoms to admission to the intensive care unit had to be 48 h or less. Patients with iatrogenic MIs were not included.

For the present analysis, patients with either ST-segment elevation (STEMI) or non-ST-segment-elevation (NSTEMI) MIs were included when they had a history of diabetes mellitus and/or received antidiabetic medications (ADM) at the time of admission.

Patients gave informed consent for participation in the survey and late follow-up. The protocol was reviewed by the Committee for the Protection of Human Subjects in Biomedical Research of Saint Antoine University Hospital.

Data collection

Standardized data were recorded on computerized case record forms by dedicated research technicians who visited each site at least once per week. An audit was performed in three of the 21 administrative regions and found complete concordance for more than 90% of the data collected. Cardiovascular history, current medication, risk factors, and clinical and biological data were collected on admission. In-hospital clinical course (including maximal Killip class and initial diagnostic and therapeutic management) were also recorded. Medications used during the first 48 h were also recorded, including type of medication and dose. When known, duration of diabetes mellitus was recorded. The Global Registry of Acute Coronary Event (GRACE) risk score (23) was calculated for each patient with admission variables including age, heart rate, serum creatinine, systolic blood pressure, Killip class, cardiac arrest, ST-segment deviation, and cardiac markers. Recurrent MI was defined as recurrent symptoms with a new rise in cardiac markers. Isolated troponin re-elevation after percutaneous coronary intervention (PCI) was not considered recurrent MI in the absence of recurrent symptoms. Left ventricular ejection fraction was available in 81% of the patients, with 65% determined by echocardiography and 35% by left ventricular angiography.

In the present work, corresponding to prespecified analysis, we sought to assess the impact of the type of SUs on the in-hospital outcomes in diabetic patients. Hence, the medications, including all the antidiabetic medications, used either chronically before the acute episode or acutely during the hospital phase or at discharge, were prospectively recorded for each patient. Such a prospective design allows the comprehensive analysis of their potential impact on outcomes. Antidiabetic treatment before hospital admission was categorized into the following groups: no ADM, insulin without SU, other ADM without SU, and SU. SU therapy was further categorized into glibenclamide and pancreatic β -cell-specific SUs (gliclazide or glimepiride). Of note, none of the patients received other SUs.

Statistical analysis

All continuous variables are described as mean \pm SD or median and interquartile range. Categorical variables are described with absolute and relative frequency distributions and were compared by χ^2 or Fisher's exact tests. For continuous variables, comparisons between the three groups used one-way ANOVA or Kruskal-Wallis one-way ANOVA by rank and comparisons between two groups used unpaired Student's *t* tests or Mann-Whitney *U* tests. A backward logistic regression multivariate analysis was used to assess independent correlates of mortality or complications. A first model was built by backward logistic regression analysis for the prediction of mortality, which was used either in the whole study population ($n = 1310$), or in the SU-treated patients ($n = 459$) or in stratified analysis (men or women; age <65 or ≥ 65 yr; STEMI or NSTEMI; insulin or no insulin before; metformin or no metformin before). The model was built on the basis of the univariate association between the variable and mortality with a $P = 0.05$ and an elimination $P = 0.20$. All the variables listed in Table 1 were tested for their univariate relationship with mortality. At last, the propensity score for receiving glibenclamide was added to this model as a covariate. To avoid an untoward effect of order of entry, we tested different procedures of model building (forward, backward, and stepwise), which provided similar results. A similar multivariate model by backward logistic regression was also built to predict the in-hospital complications, following the same procedures.

The third multivariate model was built in the SU-treated population ($n = 459$) to predict the chronic use of glibenclamide and to calculate a propensity score for the use of glibenclamide (*vs.* other SU). All the variables listed in the Table 1 were tested for their univariate relationship with glibenclamide use and were included in the model on the basis of $P < 0.05$.

Then two cohorts were built, with one patient on glibenclamide matched with one or, when possible, two patients on either gliclazide or glimepiride, based on the propensity score. No adjustment for multiplicity were made as the results are to be considered exploratory. For all tests, $P < 0.05$ was considered significant.

Results

Sulfonylureas *vs.* other types of antidiabetic medications

Of the 1310 patients with a history of diabetes, 459 (35%) received SUs, 341 (26%) insulin, 295 (23%) other oral ADMs, and 215 (16%) were not treated. There were major differences between the population according to the use and type of ADMs (Table 1). Briefly, patients on insulin were older and had a longer duration of diabetes, more frequent previous cardiovascular disease and more comorbidities; they had a higher GRACE score and high admission blood glucose and glycosylated hemoglobin (HbA1c) levels. In contrast, patients without antidiabetic treatment had a shorter duration of diabetes and lower admission blood glucose levels. Patients on SUs had high admission blood glucose levels, had a higher proportion of STEMI compared with insulin-treated patients, and more

frequently received more than one ADM. Early in-hospital management also differed according to previous ADMs; in particular, insulin-treated patients with STEMI less frequently had reperfusion therapy (Table 1).

In-hospital complications according to prehospital antidiabetic regimen are listed in Table 2: in-hospital death was 9.4% in insulin-treated patients, 8.4% in patients without ADMs, 6.4% in patients on oral, non-SU treatment, and 3.9% in SU-treated patients ($P = 0.014$).

By multivariate logistic regression analysis, patients on SU had a lower risk of in-hospital mortality, compared with patients without sulfonylurea therapy before admission [odds ratio (OR) (95% confidence interval [CI]) 0.50 (0.27–0.94), $P = 0.03$]. The other variables significantly associated with mortality were: GRACE risk score [OR (95% CI) 1.04 (1.03–1.05), $P < 0.001$], medications at the acute stage [low molecular weight heparin: OR (95% CI) 0.43 (0.25–0.75), $P = 0.003$ and β -blocker: OR (95% CI) 0.57 (0.33–0.97), $P = 0.04$].

Type of sulfonylureas

Baseline characteristics and management

Among patients treated with SUs ($n = 459$), 207 (45%) were on gliclazide, 132 (29%) were on glimepiride, and 120 (26%) were on glibenclamide (including two patients also receiving glimepiride and one receiving gliclazide). Of the 205 patients initially on gliclazide, 143 received a sustained-release presentation (69%), 41 received an immediate-release presentation (20%) and the type of presentation was not available in 21 patients. Patients under glibenclamide were slightly older, with higher levels of creatinine, and more frequently associated with other ADMs than patients under gliclazide/glimepiride (Table 3). The other characteristics were similar for the two groups.

Complications

Glimepiride *vs.* gliclazide

In-hospital complications were similar in patients treated with gliclazide or glimepiride, for either arrhythmias (occurrence of atrial fibrillation, ventricular fibrillation, sustained ventricular tachycardia, or atrioventricular block: gliclazide, 6.3% *vs.* glimepiride, 9.7%, $P = 0.30$) or ischemic complications (reinfarction or stroke: gliclazide, 3.4% *vs.* glimepiride, 5.2%, $P = 0.41$), or mortality (gliclazide, 3.8% *vs.* glimepiride, 1.5%, $P = 0.33$), or any of the above complications (gliclazide, 12.0% *vs.* glimepiride, 14.9%, $P = 0.51$).

Glibenclamide *vs.* glimepiride/gliclazide

In contrast, in-hospital complications, including hospital mortality, significantly differed for patients on pan-

TABLE 1. Baseline characteristics, chronic medications used before acute MI, and admission data

Variable	No ADM (n = 215)	Insulin (n = 341)	Non-SU oral ADM (n = 295)	SU (n = 459)	P value
Risk factors					
Age (yr)	69 ± 12	72 ± 11	68 ± 11	69 ± 11	<0.001
Women	63 (29)	159 (47)	80 (27)	139 (30)	<0.001
BMI (kg/m ²)	28.2 ± 4.8	28.3 ± 5.1	29.4 ± 5.6	28.7 ± 5.2	0.071
Hypertension	142 (66)	268 (79)	221 (75)	345 (75)	0.011
Hyperlipidemia	99 (46)	209 (61)	183 (62)	250 (54)	0.001
Current smoking	63 (29)	49 (14)	64 (22)	98 (21)	<0.001
Medical history					
CHF	19 (9)	50 (15)	12 (4)	21 (5)	<0.001
MI	50 (23)	124 (36)	57 (19)	93 (20)	<0.001
Chronic renal failure	17 (8)	64 (19)	21 (7)	19 (4)	<0.001
COPD	14 (7)	29 (8)	20 (7)	21 (5)	0.164
Diabetes					
Duration of diabetes >5 yr (n = 731)	40 (48)	190 (81)	97 (56)	162 (68)	<0.001
HbA1c (n = 657)					<0.001
≤6.5%	48 (48)	16 (10)	48 (31)	62 (25)	
6.51–8.0%	35 (35)	77 (49)	76 (50)	106 (43)	
>8.0%	16 (16)	63 (40)	29 (19)	81 (32)	
Antidiabetic medications					
Insulin	0	341 (100)	0	50 (11)	<0.001
Metformin	0	41 (12)	216 (73)	199 (43)	<0.001
Glitazone	0	2 (1)	28 (9)	21 (5)	<0.001
Acarbose	0	7 (2)	24 (8)	53 (12)	<0.001
>One ADM	0	52 (15)	25 (8)	183 (40)	<0.001
Other chronic medications					
Antiplatelet agents	60 (28)	200 (59)	118 (40)	189 (41)	<0.001
Statins	48 (22)	156 (46)	117 (40)	169 (37)	<0.001
ACE-I or ARB	70 (33)	215 (63)	154 (52)	231 (50)	<0.001
β-Blockers	39 (18)	136 (40)	97 (33)	146 (32)	<0.001
Loop diuretic	40 (19)	125 (37)	46 (16)	68 (15)	<0.001
Time delay and clinical data on admission					
Time to admission ≤180 min	131 (62)	199 (58)	166 (56)	259 (56)	0.600
STEMI	108 (50)	118 (35)	121 (41)	217 (47)	<0.001
Anterior MI STEMI (%)	56 (52)	50 (42)	47 (39)	89 (41)	0.197
Cardiac arrest	6 (3)	3 (1)	3 (1)	3 (1)	0.136
GRACE score	152 ± 38	163 ± 35	147 ± 36	149 ± 35	<0.001
Killip class ≥2	60 (28)	151 (44)	83 (28)	116 (25)	<0.001
SBP ≥120 mm Hg	175 (81)	275 (81)	248 (84)	382 (83)	0.701
Heart rate ≥90 bpm	67 (31)	136 (40)	107 (36)	155 (34)	0.193
Biological data on admission					
Creatinine (mg/dl)	113 ± 81	134 ± 105	106 ± 70	102 ± 61	<0.001
Glycemia (mg/dl)	191 ± 95	223 ± 107	184 ± 74	221 ± 104	<0.001
Acute treatments					
β-Blockers	135 (63)	197 (58)	201 (68)	334 (73)	<0.001
Statins	141 (66)	230 (67)	218 (74)	360 (78)	<0.001
ACE-I	100 (47)	170 (50)	138 (47)	232 (51)	0.650
Loop diuretic	75 (35)	193 (57)	97 (33)	164 (36)	<0.001
Clopidogrel	171 (80)	271 (79)	263 (89)	412 (90)	<0.001
LMWH	130 (60.5)	174 (51)	187 (63)	279 (61)	0.007
Amiodarone	32 (15)	48 (14)	25 (8)	34 (7)	0.002
Digoxin	8 (4)	12 (3)	6 (2)	4 (1)	0.037
Insulin	76 (35)	302 (89)	146 (49)	281 (61)	<0.001
Metformin	3 (1)	9 (3)	58 (20)	38 (8)	<0.001
Sulfonylureas	11 (5)	6 (2)	11 (4)	191 (42)	<0.001
Reperfusion Rx in STEMI (n = 564)	60 (56)	50 (42)	76 (63)	128 (59)	0.008
Any PCI during stay	136 (63)	158 (46)	188 (64)	301 (66)	<0.001

BMI, Body mass index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SBP, systolic blood pressure; LMWH, low-molecular-weight heparin; Rx, medication.

creatic cell-specific SUs, compared with those on glibenclamide (Fig. 1A). Rhythm or ischemic complications were less frequent in patients previously receiving gliclazide or

glimepiride, compared with those receiving glibenclamide (10.9 vs. 18.3%, $P = 0.037$). The in-hospital death rate was also lower in the patients on gliclazide/glimepiride

TABLE 2. In-hospital complications

	No ADM (n = 215)	Insulin (n = 341)	Oral non-SU ADM (n = 295)	SU (n = 459)	P value
Death	18 (8.4)	32 (9.4)	19 (6.4)	18 (3.9)	0.014
Reinfarction	5 (2.3)	8 (2.3)	6 (2.0)	15 (3.3)	0.721
Stroke	3 (1.4)	5 (1.5)	2 (0.7)	3 (0.7)	0.579
Atrial fibrillation	13 (6.0)	27 (7.9)	14 (4.7)	26 (5.7)	0.382
Ventricular fibrillation	7 (3.3)	5 (1.5)	6 (2.0)	6 (1.3)	0.328
AV block	5 (2.3)	5 (1.5)	7 (2.4)	4 (0.9)	0.332
Sustained VT	10 (4.7)	8 (2.3)	5 (1.7)	12 (2.6)	0.215
Any of the above	45 (20.9)	73 (21.4)	46 (15.6)	70 (15.3)	0.058

AV, Atrioventricular; VT, ventricular tachycardia.

(2.7%) *vs.* those on glibenclamide (7.5%) ($P = 0.019$). Overall, fewer patients on gliclazide/glimepiride experienced in-hospital death or complications (12.7 *vs.* 22.5%, $P = 0.01$).

Multivariate analyses and propensity-score-matched cohorts

The use of gliclazide/glimepiride, compared with glibenclamide, was associated with a significantly decreased risk of in-hospital mortality (OR 0.15; 95% CI 0.04–0.56, $P = 0.005$) and overall in-hospital complications (OR 0.39; 95% CI 0.21–0.72; $P = 0.003$).

Multivariate analyses to predict the use of glibenclamide included demographic characteristics, risk factors, previous cardiovascular history, duration of diabetes, comorbidities, type of MI, GRACE risk score, and cardiovascular and antidiabetic medications used before the index episode as well as glycemia on admission and acute treatments including reperfusion therapy (in STEMI patients), clopidogrel, glycoprotein IIb/IIIa inhibitors, low-molecular-weight heparin, β -blockers, statins, loop diuretics, and insulin.

The lower risk of mortality associated with gliclazide/glimepiride was further confirmed when the propensity score for receiving glibenclamide was introduced into the model (in-hospital mortality: OR 0.13; 95% CI 0.03–0.53; $P = 0.004$); overall complications: OR 0.26; 95% CI 0.13–0.53; $P < 0.001$). Likewise, stratified analyses showed that mortality was lower in patients on gliclazide or glimepiride, whatever the subgroups considered (men or women; age <65 or ≥ 65 yr; STEMI or NSTEMI; insulin or no insulin before; metformin or no metformin before) (Fig. 2).

To further limit the potential imbalances between patients receiving gliclazide or glimepiride *vs.* glibenclamide, two cohorts matched on the propensity score for glibenclamide use were built. Both cohorts had similar baseline characteristics (Table 4). When comparing in-hospital outcomes in the two cohorts, in-hospital rhythm/ischemic complication and death rates were lower in patients with

prior use of gliclazide or glimepiride (10.6 *vs.* 20.4%, $P = 0.028$ and 2.4 *vs.* 7.5%, $P = 0.045$, respectively) (Fig. 1B). Overall, 12.4 *vs.* 25.8% died or had in-hospital complications ($P = 0.006$).

Discussion

The effects of SUs in patients with MI have been subject to debate. Our real-world data show that patients chronically treated with SUs who suffer an acute MI have an in-hospital mortality that compares favorably with that of diabetic patients who did not receive SUs. More specifically, patients who were on gliclazide or glimepiride therapy had fewer arrhythmias or ischemic complications and a lower early mortality than those treated with glibenclamide. These results were further supported by multivariate adjustments including the GRACE risk score, risk factors, cardiovascular history, comorbidities, and concomitant medications and confirmed by the comparison of two cohorts of patients matched on a propensity analysis score for glibenclamide use. They strongly suggest that, in the clinical setting, treatment with glibenclamide is associated with a poorer in-hospital outcome, which might be related to blockade of myocardial preconditioning.

Cardiovascular safety of sulfonylureas

Older studies, beginning in the 1970s with the University Group Diabetes Program trial have suggested that diabetic patients receiving SU were at increased cardiovascular risk compared with diabetic patients who did not receive such medications (12, 19). In diabetic patients with acute MI, the first Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction randomized trial (15) documented improved outcomes in patients who received insulin, when compared with controls who were probably mostly treated with SUs. In contrast, in the United Kingdom Prospective Diabetes Study (9), treatment with SU was not associated with higher rates of cardiovascular complications. Much more recently, the Ac-

TABLE 3. Baseline characteristics and early in-hospital management of sulfonylurea-treated patients, according to the medication used

Variable	Glibenclamide (n = 120)	Gliclazide/ glimepiride (n = 339)	P value
Risk factors			
Age (yr)	71 ± 10	69 ± 11	0.05
Women	31 (26)	108 (32)	0.22
BMI (kg/m ²)	28.8 ± 5.2	28.7 ± 5.2	0.80
Hypertension	89 (74)	256 (75.5)	0.77
Duration of diabetes			
>5 yr (n = 731)	44 (71)	118 (67)	0.61
Hyperlipidemia	70 (58)	180 (53)	0.32
Current smoking	19 (16)	79 (23)	0.09
CV history			
CHF	5 (4)	16 (5)	0.80
MI	31 (26)	62 (18)	0.08
Chronic renal failure	8 (7)	11 (3)	0.11
COPD	8 (7)	13 (4)	0.20
Medications used before acute MI			
Aspirin	42 (35)	97 (29)	0.19
Statins	45 (37)	124 (37)	0.86
β-Blockers	45 (37)	101 (30)	0.12
ACE-I or ARB	57 (47)	174 (51)	0.47
Loop diuretic	21 (17)	47 (14)	0.34
Insulin	19 (16)	31 (9)	0.04
Metformin	63 (52)	136 (40)	0.02
Glitazone	3 (3)	18 (5)	0.21
Acarbose	17 (14)	36 (11)	0.30
Repaglinide	3 (3)	3 (1)	0.18
SU monotherapy	44 (37)	158 (47)	0.06
Number of ADMs	1.88 ± 0.80	1.68 ± 0.71	0.01
Data on admission			
Time to admission ≤180 min	73 (61)	186 (55)	0.23
STEMI	50 (42)	167 (49)	0.15
Anterior MI (STEMI, %)	23 (46)	66 (40)	0.41
Cardiac arrest	0	3 (1)	0.30
GRACE score	148 ± 33	149 ± 35	0.66
Killip class ≥2	30 (25)	86 (25)	0.92
Admission SBP (mm Hg)	151 ± 31	145 ± 29	0.04
Heart rate ≥90 bpm	33 (27.5)	122 (36)	0.09
Creatinine (mg/dl)	114 ± 101	98 ± 36	0.015
Glycemia (mg/dl)	234 ± 105	217 ± 103	0.12
HbA1c (n = 1201)			0.09
≤6.5%	10 (15)	52 (28)	
6.51–8.0%	30 (45)	76 (41.5)	
>8.0%	26 (39)	55 (30)	

(Continued)

TABLE 3. Continued

Variable	Glibenclamide (n = 120)	Gliclazide/ glimepiride (n = 339)	P value
Acute medications			
β-Blockers	83 (69)	251 (74)	0.30
Statins	98 (82)	262 (77)	0.32
ACE-I	64 (53)	168 (50)	0.48
Loop diuretic	44 (37)	120 (35)	0.80
Clopidogrel	106 (88)	303 (89)	0.75
Amiodarone	11 (9)	23 (7)	0.39
Digoxin	0 (0)	4 (1)	0.23
Insulin	78 (65)	203 (60)	0.32
Metformin	10 (8)	28 (8)	0.98
Repaglinide	3 (2.5)	1 (0.5)	0.03
Sulfonylureas	46 (38)	145 (43)	0.40
Reperfusion Rx in STEMI (n = 564)	30 (60)	98 (59)	0.97
Any PCI during stay	79 (66)	222 (65)	0.95

BMI, Body mass index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SBP, systolic blood pressure; ACE-I, angiotensin-converting enzyme inhibitor; LMWH, low-molecular-weight heparin; Rx, medication.

tion in Diabetes and Vascular Disease trial showed that gliclazide treatment used to achieve intensive glucose control was associated with a decreased rate of primary endpoints at 5 yr, combining major macrovascular and microvascular events (21). Likewise, reassuring results as to the safety of SUs were also reported in patients who survived an acute MI. In the population-based Olmsted County cohort (1), mortality was not statistically different in 46 patients receiving SU compared with 56 receiving insulin, during a mean follow-up of 2.7 yr after acute MI. More recently a *post hoc* analysis from the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction-2 trial showed that, contrary to patients on insulin, patients discharged on SUs had no increased risk of stroke or recurrent MI (24). Finally, in elderly diabetic patients with previous MI, an increased long-term risk, was reported when they were treated with SUs (25), whereas another report (26) found no association between SU therapy and adverse outcome. In the specific context of acute myocardial infarction, Garratt *et al.* (12) observed more adverse outcomes in 67 patients treated with primary balloon angioplasty who were on SUs, compared with 118 who were not. Most recent reports, however, have challenged these conclusions. Klamann *et al.* (27) found no increase in hospital mortality in 76 patients admitted for acute MI while on SUs, compared with 89 diabetic patients without SUs. In patients receiving thrombolysis from a multicenter trial, Halkin *et al.* (13) found that the 121 diabetic patients treated with SU had no in-

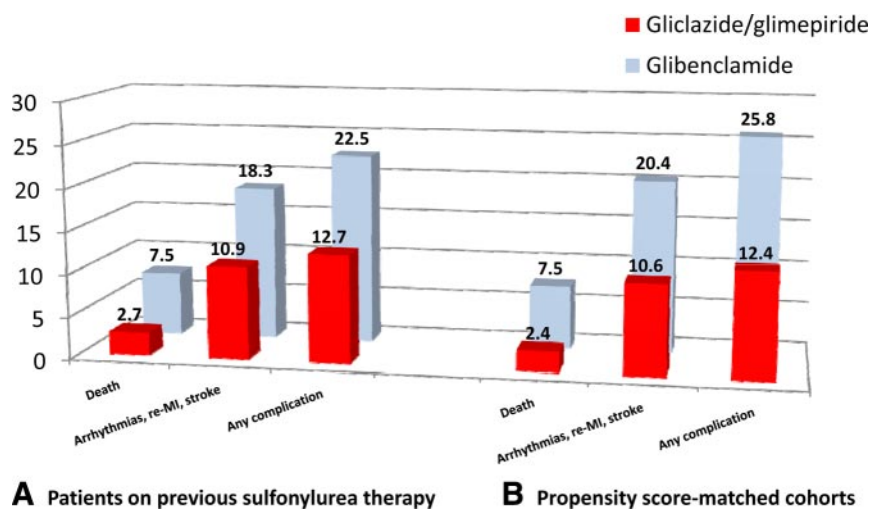


FIG. 1. In-hospital complications in patients on previous sulfonylurea therapy (n = 459) (A) and the cohort of patients matched on the propensity score for glibenclamide treatment (n = 263) (B).

creased in-hospital or 1-yr mortality; survival appeared lower in diabetic patients previously treated with insulin. In the previous French Unité de Soins Intensifs Cardiaques 2000 registry of MI (10), early mortality of the 215 patients treated with SUs was lower than that of the 272 diabetic patients not receiving these medications (10.2 vs. 16.9%). After multivariate analysis, the OR for in-hospital death was 0.44 in patients on SUs; in addition, there was a trend for a reduction in occurrence of ventricular fibrillation (2.3 vs. 5.9%, $P = 0.052$) in patients receiving SUs.

Sulfonylureas and adaptation to ischemia: differences between older and newer medications

SUs inhibit potassium efflux through the K_{ATP} membrane channel, which results in insulin release from the pancreatic β -cells. SUs may also bind the K_{ATP} channel that is present in cardiac myocytes and is involved in the mechanism of ischemic preconditioning. To date, two receptors to SUs (SUR1 and SUR2) have been identified in the human heart. All SUs do not have the same effect on the myocardium but the clinical relevance of these differences has not been fully elucidated. In a model of preconditioning using repeated balloon inflations during coronary angioplasty, Klepzig *et al.* (5) found that, contrary to glibenclamide, glimepiride did not affect ischemic preconditioning, a finding in keeping with the experimental results of Mocanu *et al.* (8), who showed that glimepiride did not abolish the effect of preconditioning in the isolated rat heart. Likewise, gliclazide is specific of the pancreatic SU receptors and does not interfere with the protective action of nicorandil on myocardial preconditioning in experimental conditions (6). However, in normal and poststenotic coronary arteries, Reffelmann *et al.* (28) found no change in coronary blood flow at rest, as well as coronary

flow reserve, after treatment with iv glibenclamide compared with baseline conditions, thereby challenging the importance of the concept of vascular smooth muscle cell K_{ATP} blockade in the clinical setting. Contradictory results have also been reported with regard to the impact of SUs on the risk of arrhythmias at the acute stage of MI. Studies on glibenclamide have shown either a neutral or a protective effect of the molecule (17, 29), whereas there have been no specific studies with newer SUs.

Observational studies in diabetic patients on chronic therapy have suggested that patients treated with either glimepiride or gliclazide had lower long-term mortality than patients receiving glibenclamide (30, 31). A case-control study from the large North Jutland County registry showed that, compared with non diabetic patients, subjects treated with older SUs (glibenclamide, tolbutamide, or glipizide) had a greater risk of MI than patients treated with newer SUs (gliclazide or glimepiride) [respectively, OR (95% CI) 2.07 (1.81–2.37) vs. 1.36 (1.01–1.84)] (32). In addition, the preadmission use of older SUs but not newer SUs was also associated with an increased risk of case fatality at the acute stage of MI, when compared with nondiabetic subjects [adjusted OR (95% CI) 1.29 (1.00–1.67) vs. 1.00 (0.53–1.90), respectively]. Our contemporary data, including a more extensive use of newer SU, extend the findings on the difference in risk between newer and older SU within the diabetic population, at least when they develop acute MI.

Strengths and limitations

The main strength of this study is the use of nationwide population-based registry, reflecting the daily clinical practice in France, with prospectively collected data including details of all cardiovascular and noncardiovascular medications. The adjustment for a wide range of possible confounding factors limits the risk of bias in our conclusions. This registry, however, suffers the usual limitations of observational, nonrandomized studies and therefore determines correlations, rather than causal relationships. The observation of an increased risk in patients on glibenclamide, compared with those on pancreatic-specific sulfonylureas, must therefore be interpreted with a fair amount of caution. However, to limit the influence of unknown confounding factors that could have impacted the prognosis, we have developed several ana-

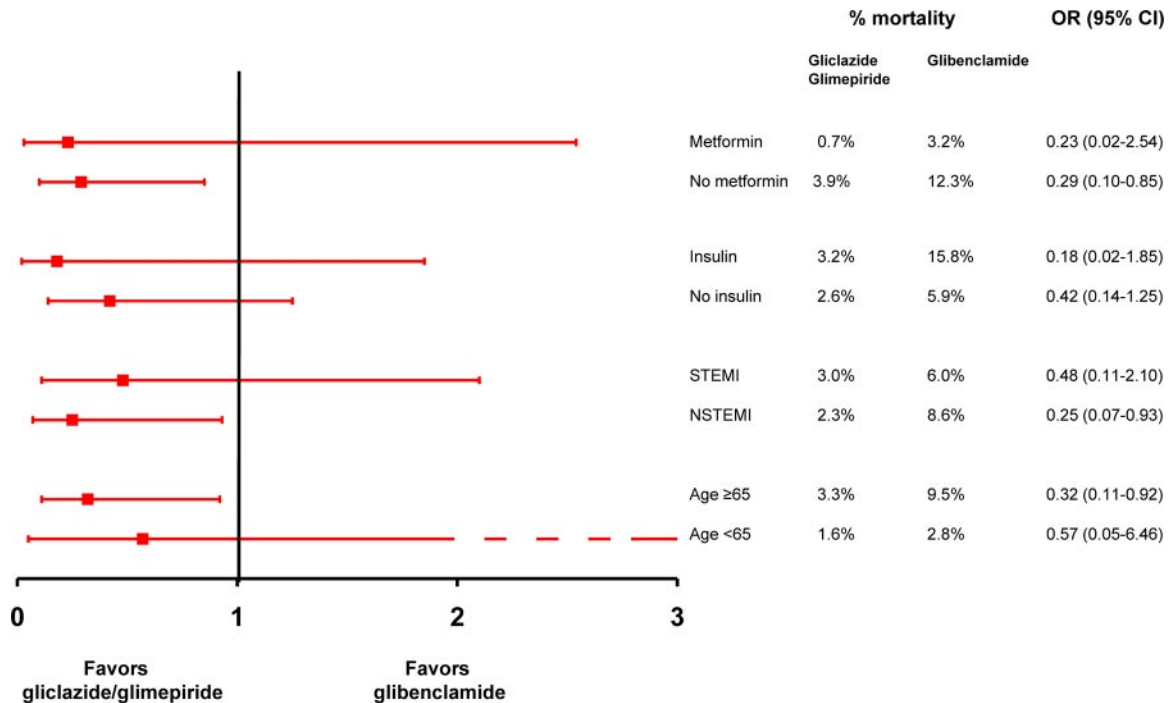


FIG. 2. In-hospital mortality in patients on sulfonylureas before admission (n = 459) according to the type of sulfonylureas and stratified by specific subgroups.

lytical strategies: 1) first, we have performed the analysis by adjusting for a very wide range of possible confounding factors, including demographics, cardiovascular risk factors and medical history, characteristics of the diabetic disease, insulin treatment, level of glycemic control, etc. that could limit the risk of bias in our conclusions; 2) second, a propensity score for the use of glibenclamide has been calculated, and a matching procedure, based on the propensity score, has been used to further limit the potential imbalances between patients receiving gliclazide/glimepiride vs. glibenclamide; and 3) moreover, the propensity score was also added as a covariate in the multivariate models. Hence, although we cannot exclude

the impact of other unmeasured confounding factors, we may think that the observed effects of SUs on the outcomes are robust and reliable. In the analysis, some variables, such as duration of diabetes, or HbA1c were treated as categorical variables, that may limit their statistical accuracy. They were treated as discrete because either there were rather numerous missing data (e.g. HbA1c) and we created a category with missing information on HbA1c to avoid missing patients in the multivariate analysis. Also, some data were collected as discrete (e.g. duration of diabetes, which was collected as less than 1 yr, 1–5 yr, more than 5–10 yr, and 10 yr or longer and used as such in the multivariate analysis). Rerunning the analyses with cate-

TABLE 4. Patient characteristics in the subgroup of patients on sulfonylureas and matched on propensity score for the use of glibenclamide

Variable	Propensity score-matched patients on glibenclamide (n = 93)	Propensity score-matched patients on gliclazide or glimepiride (n = 170)	P value
Age (yr)	71 ± 10	70 ± 11	0.80
Women	26 (28)	48 (28)	0.96
Hypertension	70 (75)	127 (75)	0.92
Hyperlipidemia	52 (56)	94 (55)	0.92
Duration of diabetes >5 yr (n = 138)	30 (65)	62 (67)	0.80
Admission HbA1c (%) (n = 151)	7.97 ± 1.62	7.75 ± 1.40	0.38
Admission glycemia (mg/dl)	229 ± 104	225 ± 112	0.78
Previous MI	22 (24)	37 (22)	0.72
STEMI	37 (40)	75 (44)	0.50
GRACE score	148 ± 34	150 ± 34	0.69
Insulin before	13 (14)	24 (14)	0.98
Metformin before	46 (49)	87 (51)	0.79
Glitazones before	3 (3)	9 (5)	0.44

gorization of HbA1c into deciles (approaching a continuous distribution) yielded similar results as the analysis reported here, both for in-hospital mortality and overall in-hospital complications, and both analyses remained highly significant. Finally, our study included only patients having developed acute MI; it is beyond its scope to determine whether the type of medications used in diabetic patients puts them at different risks of developing an MI initially. From this nationwide registry, we have also analyzed regional differences for the outcomes; however, there were no regional differences in mortality, even after multivariate adjustment (Danchin, N., M. Zeller, and T. Simon, unpublished data).

Conclusion

These data from a large nationwide registry of patients admitted for acute MI confirm that the in-hospital outcome of patients on chronic SU therapy is, if anything, better than that of patients without such treatment. Among patients on SUs, those on newer SUs have fewer early complications and lower mortality than those on glibenclamide, suggesting that the interference with cardiac K⁺ ATP channels may have clinically relevant deleterious consequences in the specific setting of acute myocardial ischemia. Our study strengthens the case that all SUs do not have the same impact on cardiac outcomes and should therefore not be considered a single pharmacologic entity (33). Further studies are needed to investigate whether ischemic preconditioning plays a truly relevant beneficial effect at the acute stage of MI, as our findings with an SU known to block preconditioning mechanisms might suggest.

Acknowledgments

The authors are deeply indebted to all physicians having taken care of the patients at the participating institutions as well as to Nadine Roumier (the International Clinical Trials Association contract research organization, Fontaine-lès-Dijon, France) and the devoted personnel of the Unité de Recherche Clinique Est (Assistance Publique des Hôpitaux de Paris and University Paris 6) and Institut National de la Santé et de la Recherche Médicale Unité 558 (Toulouse, France). Special thanks go to Vincent Bataille for his careful data management, Benoît Pace (Société Française de Cardiologie) for his invaluable assistance in designing the electronic case record form, and the personnel of the registry committee of the Société Française de Cardiologie. A complete list of participating centers and investigators can be found elsewhere (10).

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This work was supported by the FAST-MI registry, a registry of the French Society of Cardiology, and unrestricted grants from Pfizer and Servier. Additional support was obtained from a research grant from the French Caisse Nationale d'Assurance Maladie.

Disclosure Summary: D.S., A.V., L.L., Y.C., J.B., P.G., P.W., R.D., X.T., J.M., F.L., E.D., G.M., V.B., J.-P.C., J.F., and T.S. have no disclosures reported. N.D. has received consulting or speaking fees from Astra-Zeneca, BMS, Boehringer-Ingelheim, GSK, MSD-Schering Plough, Pfizer, Sanofi-Aventis, Servier, and Takeda. M.Z. has received speaking fees from Servier, MSD-Schering Plough, and BMS.

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