Improved Clinical Outcomes Associated With Metformin in Patients With Diabetes and Heart Failure

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OBJECTIVE — Metformin is considered contraindicated in patients with heart failure because of concerns over lactic acidosis, despite increasing evidence of potential benefit. The aim of this study was to evaluate the association between metformin and clinical outcomes in patients with heart failure and type 2 diabetes.

RESEARCH DESIGN AND METHODS — Using the Saskatchewan Health databases, 12,272 new users of oral antidiabetic agents were identified between the years 1991 and 1996. Subjects with incident heart failure (n = 1,833) were identified through administrative records based on ICD-9 code 428 and grouped according to antidiabetic therapy: metformin monotherapy (n = 208), sulfonylurea monotherapy (n = 773), or combination therapy (n = 852). Multivariate Cox proportional hazards models were used to assess differences in all-cause mortality, all-cause hospitalization, and the combination (i.e., all-cause hospitalization or mortality).

RESULTS — Average age of subjects was 72 years, 57% were male, and average follow-up was 2.5 ± 2.0 (SD) years. Compared with sulfonylurea therapy, fewer deaths occurred in subjects receiving metformin: 404 (52%) for sulfonylurea monotherapy versus 69 (33%) for metformin monotherapy (hazard ratio [HR] 0.70 [95% CI 0.54–0.91]) and 263 (31%) for combination therapy (0.61 [0.52–0.72]). A reduction in deaths or hospitalizations was also observed: 658 (85%) for sulfonylurea monotherapy versus 160 (77%) for metformin monotherapy (0.83 [0.70–0.99]) and 681 (80%) for combination therapy (0.86 [0.77–0.96]). There was no difference in time to first hospitalization between study groups.

CONCLUSIONS — Metformin, alone or in combination, in subjects with heart failure and type 2 diabetes was associated with lower morbidity and mortality compared with sulfonylurea monotherapy.

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Heart failure is common in patients with type 2 diabetes, and diabetes portends poorer outcomes in individuals with heart failure (1–3). There is also evidence that chronic hyperglycemia is associated with an increased risk for cardiovascular morbidity and mortality (4,5). However, clinicians treating heart failure in patients with type 2 diabetes find their options limited, since metformin is considered "absolutely" contraindicated in such patients and thiazolidinediones are "relatively" contraindicated (6). Thus, only sulfonylureas, acarbose, and insulin therapy remain as options; however, acarbose is associated with high rates of intolerance (6), and insulin is associated with much reluctance on the part of patients and providers. Moreover, insulin therapy has also been associated with an increased risk of heart failure (7,8). It is not surprising, therefore, that 10% of Medicare patients with heart failure and diabetes use metformin (9), a practice repeatedly deemed "inappropriate" (9–11). Is the use of metformin in diabetic patients with heart failure truly inappropriate? Metformin improves glycemic control and other cardiovascular risk factors (such as lipids) (12–14), and in obese diabetic subjects, metformin reduces mortality (15). In a large population-based observational study, we also demonstrated that use of metformin was associated with reduced risk for all-cause and cardiovascular-related mortality compared with sulfonylurea monotherapy (16). Perhaps metformin is beneficial in patients with heart failure.

Although the contraindication to metformin arose over concerns about the *potential* for lactic acidosis and its relation to phenformin (another biguanide that was removed from the market after 306 cases of lactic acidosis were reported in the 1970s), there is a paucity of evidence that actually links metformin with lactic acidosis (17,18). Indeed, the near-absence of any cases of lactic acidosis in large observational studies and the fact that metformin levels do not correlate with lactate levels in individuals who do develop lactic acidosis supports the viewpoint that metformin may be "an innocent bystander" in sick patients rather than a causal agent (19,20). As noted by Misbin (17), "the increased risk of lactic acidosis (attributable to metformin) is either zero or so close to zero that it cannot be factored into ordinary clinical decision making." By corollary, 2 decades ago, β-blockers were considered contraindicated in heart failure, and commonly accepted "quality indicators" for the use of β-blockers explicitly stated that people with left ventricular dysfunction or heart failure were "ineligible" for receipt of β-blockers (21). Numerous trials have since refuted these concerns and established β-blockers as cornerstones in the treatment of heart failure.

Like β-blockers, it could be that "in-

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Abbreviations: CDS, chronic disease score.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying editorial, p. 2585.

appropriate" use of metformin in heart failure may actually be associated with improved outcomes relative to other antidiabetic therapies. Masoudi et al. (22) recently described a large-scale observational study suggesting metformin therapy was associated with reduced risk for all-cause mortality at 1 year in a hospitalized elderly Medicare population with heart failure and type 2 diabetes. Because all subjects were recently hospitalized with heart failure and were older than 65 years of age, it is uncertain if these benefits can be expected in a much broader lower-risk population of patients with heart failure and type 2 diabetes. Furthermore, given the short duration of follow-up (i.e., 1 year), it is unclear if these benefits might persist. We designed this study to examine outcomes, both short and long term, in a broad unselected population-based cohort of patients with heart failure and type 2 diabetes who were treated with metformin or other oral antidiabetic medications.

RESEARCH DESIGN AND METHODS

— We analyzed data from the computerized databases of Saskatchewan Health. These databases have been described in detail elsewhere (16,23–25). Briefly, Saskatchewan Health is a provincial government department providing universal health coverage for ~1 million people in Saskatchewan, Canada. Databases include the demographic and vital statistics, outpatient prescription drugs, hospital claims, and outpatient physician services. These databases have been used in numerous epidemiological studies evaluating safety of drug therapies and are considered to be both high quality and comprehensive (16,23–25).

First, we identified 12,272 new users of oral antidiabetic agents based on prescription claims between 1 January 1991 and 31 December 1996 who were aged ≥30 years and who had health coverage and were eligible for drug benefits at least 1 year before the index prescription (16,23). Federal employees (e.g., Royal Canadian Mounted Police) and inmates of federal penitentiaries, constituting ~1% of the population, are not captured in these databases. In addition, registered Indians do not receive drug benefits from the province. Therefore, ~9% of the population is not included in this analysis (16,23).

Then we identified those subjects with a record of a hospital stay or physician service for heart failure, based on *International Classification of Diseases, Ninth Revision,* code 428, between 1 December 1991 and 31 December 1999 (26,27). The index date for the diagnosis of heart failure was defined as the date of the first hospital or physician record. Individuals with prevalent heart failure (i.e., those with a hospital record for heart failure in the 3 years before starting oral antidiabetic agent) and/or those subjects who ever had prescription claims for insulin therapy were excluded. We then categorized new users of oral antidiabetic agents with incident heart failure into three mutually exclusive groups according to oral antidiabetic prescription claims throughout the follow-up period (i.e., 1 January 1991 to 31 December 1999): sulfonylurea monotherapy, metformin monotherapy, or combination therapy. Combination therapy was defined as any use of metformin and sulfonylurea therapy throughout the follow-up period. All subjects were prospectively followed until death, termination of Saskatchewan Health coverage, or 31 December 1999, providing a maximum follow-up of 9 years.

Our primary outcome was all-cause mortality, both at 1 year (i.e., short term) and by the end of the follow-up period (i.e., long term). Secondary outcomes were all-cause hospitalizations at 1 year and at the end of the follow-up period. We also evaluated the effects of antidiabetic therapy on a composite outcome commonly used in heart failure trials, namely all-cause hospitalization or all-cause mortality (3).

Analysis

Using Cox proportional hazards regression models, unadjusted and adjusted hazard ratios (HRs) and 95% CIs were calculated to assess the relationship between antidiabetic drug use and outcomes. The sulfonylurea monotherapy cohort served as the reference group for all estimates. Potential confounding variables included in all multivariate models were age, sex, a modified chronic disease score (CDS) (16,23), therapies known to affect heart failure outcomes (i.e., ACE inhibitors, angiotensin II blockers, β-blockers, antiplatelet agents, nitrates, lipid-lowering therapies, antiarrhythmic agents, and spironolactone), and total physician visits before heart failure diagnosis. The CDS provides an indication of burden of concurrent comorbidities by identifying specific drug therapies during the follow-up period (28–30). The CDS is well validated, and higher scores are associated with increased mortality, hospitalization rates, and health resource utilization (28–30) and it has been shown to be comparable to other comorbidity indexes (31).

To adjust for potential selection bias, we also calculated a "propensity score" using standard methods and included this as a covariate in all multivariate models (32). The inclusion of the propensity score in the analysis made no significant difference in the HR point estimates obtained (i.e., <1% change in point estimates) or the width of confidence intervals. Because our basic findings were unchanged, we present models without propensity scores. All analyses were conducted using SPSS version 12.

RESULTS

— Of the 12,272 new users of oral antidiabetic agents during the years of our study, 2,793 (23%) had a hospital or physician record for heart failure. Excluding the 625 cases of prevalent heart failure and the 335 subjects who were ever treated with insulin, we identified 1,833 eligible subjects with incident heart failure who were treated with oral antidiabetic agents. Of this cohort, 773 (42%) were treated with sulfonylureas alone, 208 (11%) were treated with metformin alone, and 852 (47%) received both a sulfonylurea and metformin. The mean age of our cohort was 72 ± 10.7 (SD) years, 57% were male, and mean follow-up was 2.5 ± 2.0 years after the diagnosis of heart failure. The sulfonylurea group was slightly older, had fewer comorbidities, and had fewer prescription claims for heart failure–related medications compared with either the metformin monotherapy or combination groups (Table 1).

All-cause mortality at 1 year

At 1 year, compared with the 200 deaths in the sulfonylurea monotherapy group (26%), there were 29 deaths (14%, unadjusted HR 0.52, 95% CI 0.35–0.76) in the metformin monotherapy group and 97 deaths (11%, 0.41, 0.32–0.52) in the metformin-sulfonylurea combination therapy group. After controlling for age, sex, CDS, drug therapies known to affect heart failure outcomes, and total physician visits before heart failure diagnosis, we found that metformin alone (adjusted HR 0.66, 95% CI 0.44–0.97) or in combination with other agents (0.54, 0.42–0.70) was associated with reduced 1-year all-cause mortality compared with sulfo-

Table 1—*Study cohort characteristics*

	Sulfonylurea monotherapy	Metformin monotherapy	Combination therapy	*P**
n	773	208	852	—
Age (years)	74.8 ± 10.1	72.5 ± 10.6	70.0 ± 10.9	<0.001
Sex (M)	451 (58)	123 (59)	472 (55)	0.40
Duration of follow-up after diagnosis of heart failure (years)	2.3 ± 2.0	2.3 ± 1.8	2.8 ± 2.0	<0.001
CDS	10.7 ± 3.7	11.6 ± 3.6	11.7 ± 3.7	<0.001
Median	10.0	11.0	11.0	
Total physician visits†	41.6 ± 44.5	48.0 ± 40.0	52.3 ± 48.3	<0.001
Myocardial infarction	72 (9)	20 (10)	91 (11)	0.645
Ischemic heart disease	152 (16)	32 (15)	130 (15)	0.874
Cerebrovascular disease	88 (11)	19 (9)	84 (10)	0.490
Other diseases of arteries, arterioles, and capillaries	27 (4)	6 (3)	29 (3)	0.91
Medications‡				
Thiazide diuretics	214 (28)	59 (11)	263 (31)	0.36
Loop diuretics	595 (77)	157 (76)	691 (81)	0.061
ACE inhibitors	476 (62)	148 (71)	644 (76)	<0.001
Angiotensin II blockers	38 (5)	17 (8)	75 (9)	0.008
Antiplatelet therapy	300 (39)	92 (44)	359 (42)	0.24
Antiarrhythmic agent	369 (48)	109 (52)	423 (50)	0.45
β-Blockers	251 (33)	90 (43)	369 (43)	<0.001
Spironolactone	113 (15)	29 (14)	114 (13)	0.77
Lipid therapy	123 (16)	49 (24)	225 (26)	<0.001
Nitroglycerin	357 (46)	106 (51)	447 (53)	0.04

Data are *n*, *n* (%), or means ± SD. *Omnibus *P* values from χ^2 test or ANOVA. †Total physician visits before heart failure diagnosis. ‡Categories not mutually exclusive.

nylurea monotherapy in patients with incident heart failure (Table 2).

All-cause mortality: longer term

At the end of follow-up (mean 2.5 years, median 2.1 years), compared with the 404 deaths in the sulfonylurea monotherapy group (52%), there were 69 deaths (33%, unadjusted HR 0.63, 95% CI 0.49–0.82) in the metformin monotherapy group and 263 deaths (31%, 0.50, 0.43–0.58) in the metformin-sulfonylurea combination therapy group (Fig. 1). In multivariate regression analyses, we found that metformin alone (adjusted HR 0.70, 95% CI 0.54–0.91) or in combination with other agents (0.61, 0.52–0.72) was associated with reduced all-cause mortality compared with sulfonylurea monotherapy (Table 2; Figs. 1 and 2).

Although they are not an end point of the study, we also evaluated cause-specific deaths. The numbers of cardiovascular-related deaths were 224 (55.4%) in the sulfonylurea monotherapy group, 36 (52.2%, adjusted HR 0.63, 95% CI 0.45–0.90) for metformin monotherapy, and 145 (55.1%, 0.58, 0.47–0.72) in the combination therapy group. There was no significant difference with respect to diabetes-related deaths between the cohorts: 40 (9.9%) for sulfonylurea monotherapy, 3 (4.3%, 0.48, 0.15–1.58) for metformin monotherapy, and 28 (10.6%, 0.95, 0.58–1.58) for combination therapy. Of the diabetes-related deaths, six deaths were attributed to hypoglycemia (two in the sulfonylurea monotherapy group, none for metformin monotherapy, and four for combination therapy; $P > 0.05$).

All-cause hospitalizations

At 1 year, compared with the 406 hospitalizations in the sulfonylurea monotherapy group (53%), there were 102 hospitalizations (49%) in the metformin monotherapy group and 435 hospitalizations (51%) in the metformin-sulfonylurea combination therapy group. At the end of follow-up, there were 538 hospitalizations in the sulfonylurea monotherapy group (70%) compared with 143 hospitalizations (69%) in the metformin monotherapy group and 632 hospitalizations (74%) in the metformin-sulfonylurea combination therapy group. Multivariable anal-

Table 2—*Adjusted HRs (95% CI) from multivariate Cox proportional hazards models*

	All-cause mortality		All-cause hospitalization		Combined end point	
	1 year	Study end	1 year	Study end	1 year	Study end
Sulfonylurea monotherapy*	1.0	1.0	1.0	1.0	1.0	1.0
Metformin monotherapy	0.66 (0.44–0.97)	0.70 (0.54–0.91)	0.84 (0.67–1.04)	0.87 (0.73–1.05)	0.79 (0.65–0.98)	0.83 (0.70–0.99)
Combination therapy	0.54 (0.42–0.70)	0.61 (0.52–0.72)	0.92 (0.80–1.06)	0.93 (0.83–1.05)	0.86 (0.75–0.98)	0.86 (0.77–0.96)

*Sulfonylurea monotherapy cohort is the reference group.

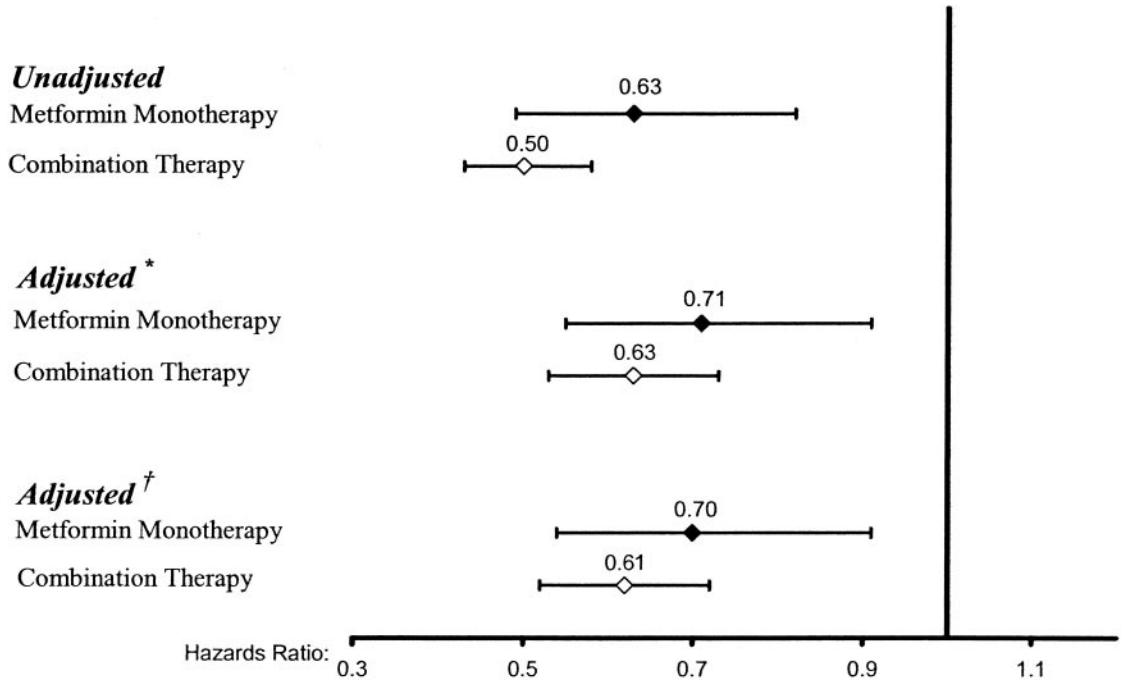

Figure 1—*All-cause mortality at study end according to oral antidiabetic exposure. Sulfonylurea monotherapy cohort is the reference group. *Adjusted for age, sex, chronic disease score, and drug therapies. †Adjusted for age, sex, chronic disease score, drug therapies, and total physician visits.*

yses demonstrated no significant association between use of various oral antidiabetic agents and hospitalizations (Table 2).

Composite outcome (all-cause hospitalization or all-cause mortality)

At 1 year, composite events occurred in 480 patients in the sulfonylurea monotherapy group (63%), with 115 events (55%, unadjusted HR 0.80, 95% CI 0.65–0.98) in the metformin monotherapy group and 480 (56%, 0.82, 0.72–0.93) in the metformin-sulfonylurea combination therapy group. At the end of follow-up, there were 658 deaths and/or hospitalizations in the sulfonylurea monotherapy group (85%) compared with 160 (77%, 0.84, 0.71–1.00) in the metformin monotherapy group and 681 (80%, 0.83, 0.75–0.93) in the metformin-sulfonylurea combination therapy group. After adjusting for the same covariates as in our other analyses, we found that metformin alone (adjusted HR 0.79, 95% CI 0.65–0.98) or in combination with other agents (0.86, 0.75–0.98) was associated with reduced 1-year composite end points. At the end of the follow-up, adjusted HR (95% CI) for the composite end point was 0.83 (0.70–0.99) for metformin monotherapy and 0.86 (0.77–0.96) for combination therapy, compared with sulfonylurea monotherapy (Table 2).

CONCLUSIONS — In our population of newly treated diabetic patients over the age of 30 years, the prevalence of heart failure was 23%, which is almost identical to the 22% reported in a nationally representative sample of Medicare claims in the U.S. (26). We found that heart failure patients with type 2 diabetes who used metformin (either alone or in combination with a sulfonylurea) had lower all-cause mortality rates than sulfonylurea users, even after adjusting for multiple confounding variables. Importantly, we also found that metformin exposure was not associated with an increase in hospitalizations, supporting the premise that it appears to be safe in this vulnerable population. Moreover, there were no hospitalizations or deaths in any of the cohorts attributed to metabolic acidosis throughout the follow-up period.

Although an observational study such as ours cannot conclusively prove that an agent is efficacious, it can raise hypotheses that may or may not warrant a clinical trial. The first step in deciding whether an observational result mandates a clinical trial is to consider whether the finding is pathophysiologically sound. Is it plausible that metformin use in patients with diabetes and heart failure would reduce mortality? Metformin therapy has been shown to improve hyperinsulinemia in patients with type 2 diabetes (33). It is therefore conceivable that, through this action, metformin therapy may be associated with improved outcomes in patients with heart failure and type 2 diabetes (16). At the very least, our study suggests that metformin is not associated with an increased risk of adverse outcomes in heart failure patients when compared with sulfonylurea therapy (the most commonly prescribed oral antidiabetic agents, which increase endogenous insulin secretion and may be associated with adverse cardiovascular outcomes) (16,34,35).

The strengths of our study include the large unselected population-based sample of subjects with heart failure and type 2 diabetes, comprehensiveness and quality of the databases used, the relatively long duration of follow-up, and the ability to control for the effects of comorbidities and drug therapies known to affect outcomes in patients with heart failure. In addition, it has been suggested that observational studies, such as ours, are the preferred method for examining issues related to medication safety in the real world (36).

There are also several limitations that need to be considered. First, we did not have access to data on subjects' glycemic control. Several observational studies have indicated that tight glycemic control may be associated with a reduced risk of developing heart failure (37,38). Furthermore, tight glycemic control also im-

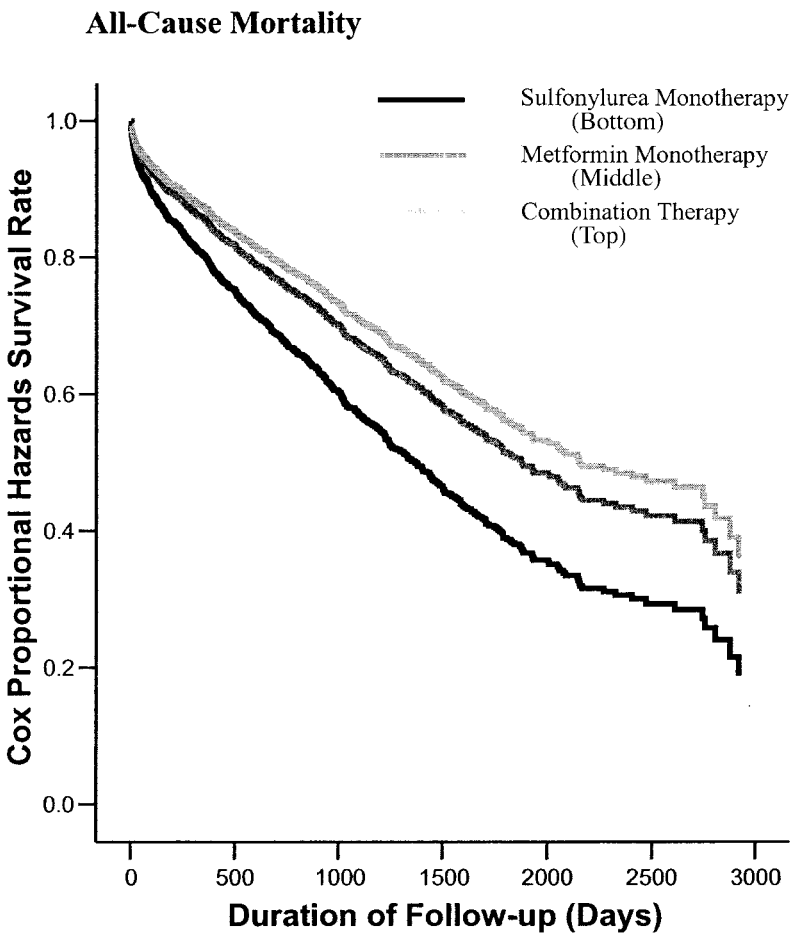

Figure 2—*Adjusted Kaplan-Meier survival curves at study end in patients with heart failure and type 2 diabetes, stratified by oral antidiabetic exposure.*

proves outcomes in patients with diabetes (4,5,15,38). Although metformin is equipotent to sulfonylurea therapy in controlling blood glucose levels (12), metformin therapy may have been used in subjects who were perceived to have "less severe" diabetes compared with subjects in the sulfonylurea monotherapy group. If this was the case, however, we would have expected to see higher mortality and hospitalization rates in the combination therapy group, since the use of combination therapy would suggest even higher glycemic levels or more severe diabetes (33). The significant reduction in morbidity and mortality observed in the combination therapy group compared with the sulfonylurea monotherapy implies that glycemic control is not the sole explanation for our findings.

Second, our results may be attributed to selection bias in that physicians may have withheld metformin in subjects perceived to be at an increased risk of adverse events or death. However, we did adjust for those factors shown to be prognostic in heart failure (age, sex, comorbidities, and proven efficacious medications such as ACE inhibitors, β-blockers, spironolactone, and antiplatelet agents), and we believe that by restricting our analysis to incident cases of heart failure, we minimized the possibility that there were important differences among patients. Moreover, metformin users had a higher number of comorbidities and would have been expected to have a greater, not lesser, risk of mortality. To address this issue further, we also conducted a propensity score analysis; this did not, however, alter the main effects or our study findings.

Third, we do not have any clinical or laboratory information on factors such as functional status, severity of heart failure, left ventricular function, or renal failure. The lack of renal function data is particularly important, since it is an independent predictor of poor outcomes in heart failure (2). Although it is possible that people in the metformin group had lower rates of renal failure and because at least 40% of all patients with symptomatic heart failure have reduced renal function (39), it is likely that a significant proportion of people in our study who were exposed to metformin would have had renal dysfunction.

Despite a lack of any high-quality evidence, metformin is currently considered contraindicated in patients with heart failure and type 2 diabetes. And yet, we found that vulnerable patients exposed to metformin had lower mortality, less morbidity, and fewer hospitalizations than patients exposed to the much more commonly prescribed sulfonylureas. Conventional wisdom and practice guidelines have created a practice environment where all of the patients in our study who were taking metformin would be considered to be victims of "inappropriate" or "unsafe" prescribing. Whether our findings are sufficiently robust to either liberalize the careful use of metformin in diabetic heart failure patients or simply engender sufficient equipoise to mandate a randomized trial is a question of clinical judgment. Although "patient safety" studies often seem to focus on finding and reducing the use of previously widely prescribed medications that are of unproven benefit or even harmful, our study should serve as a reminder that there is another side to the patient safety coin—some medications that are currently considered contraindicated may have been defined as such on the basis of little or no evidence beyond pathophysiological rationale. Since this rationale alone is considered insufficient evidence for efficacy, it should also be insufficient to declare harm. We believe that the onus in the patient safety literature should shift to acknowledge that both types of patient safety issues can lead to suboptimal prescribing practices.

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