Metformin Use and Mortality in Ambulatory Patients With Diabetes and Heart Failure

David Aguilar, MD; Wenyaw Chan, PhD; Biykem Bozkurt, MD; Kumudha Ramasubbu, MD; Anita Deswal, MD, MPH

Background—Despite the common coexistence of diabetes and heart failure (HF), the optimal medical treatment of diabetes in HF patients has not been well studied. We sought to compare the association between metformin use and clinical outcomes in a cohort of ambulatory patients with diabetes and established HF.

Methods and Results—Using propensity score–matched samples, we examined the association between metformin use and the risk of death or risk of hospitalization in a national cohort of 6185 patients with HF and diabetes treated in ambulatory clinics at Veteran Affairs medical centers. In this cohort, 1561 (25.2%) patients were treated with metformin. At 2 years of follow-up, death occurred in 246 (15.8%) patients receiving metformin and in 1177 (25.5%) patients not receiving metformin (P<0.001). In the propensity score–matched analysis (n=2874), death occurred in 232 (16.1%) patients receiving metformin compared with 285 (19.8%) patients not receiving metformin (hazard ratio, 0.76; 95% confidence interval, 0.63 to 0.92; P<0.01). In propensity score–matched analyses, HF hospitalization or total hospitalization rates were not significantly different between individuals treated with metformin compared with those not treated with metformin (hazard ratio, 0.93; 95% confidence interval, 0.74 to 1.18; and hazard ratio, 0.94; 95% confidence interval, 0.83 to 1.07, respectively).

Conclusions—Metformin therapy was associated with lower rates of mortality in ambulatory patients with diabetes and HF. Future prospective studies are necessary to define the optimal therapy for diabetic patients with HF. (Circ Heart Fail. 2011;4:53-58.)

Key Words: diabetes ■ heart failure ■ metformin ■ survival ■ prognosis

Diabetes mellitus and heart failure (HF) commonly coexist in the same patient. In a recent community-based survey in Olmstead County, investigators determined that 20% of individuals presenting with a first episode of HF had a prior diagnosis of diabetes. In addition, the investigators demonstrated that prevalence of diabetes in patients with HF had increased markedly over a 20-year period (3.8% per year) without signs of abatement. In hospitalized patients with decompensated HF, the prevalence of diabetes appears even greater than community-based surveys and may extend to 44%. Importantly, both community-based studies and clinical trials have demonstrated that the presence of diabetes in patients with HF is associated with increased risk of death compared with HF patients without diabetes. Therefore, efforts to adequately treat these patients have become increasingly important.

Clinical Perspective on p 58

The optimal diabetic treatment strategy in patients with diabetes and HF has not been well defined, and some studies have suggested potential harm associated with several antidiabetic medications. Metformin is a biguanide that decreases hepatic glucose production, improves glucose uptake and utilization, and improves insulin sensitivity. Until recently, metformin has been contraindicated in patients with HF because of concerns regarding risk of lactic acidosis. Subsequent retrospective, nonrandomized studies have demonstrated that metformin appears safe and may be associated with lower morbidity and mortality rates in diabetic patients with established HF when compared with other diabetic therapy. These nonrandomized studies are subject to inherent limitations of potential selection bias associated with metformin use. For example, it is possible that providers did not prescribe metformin in elderly patients with more advanced disease or renal insufficiency due to safety concerns. Although randomized controlled clinical trials are ideal to reduce potential selection bias, an initial attempt to perform a randomized controlled study of metformin use in diabetic patients with HF was terminated because of feasibility con-
cerns. Propensity score methods are statistical techniques developed to balance covariates in 2 groups in observational studies and therefore to reduce potential bias. Therefore, we sought to evaluate the relationship between metformin and mortality in a cohort of patients with diabetes and established HF using propensity score–matched analyses.

Methods

Study Design and Sample

We performed an observational study of a national cohort of veterans with HF treated in ambulatory clinics at Veteran Affairs (VA) medical centers using the VA External Peer Review Program (EPRP) data between October 2000 and September 30, 2002. The VA EPRP was created to assess and improve the quality of care for VA patients and has been described previously. The sampling pool of outpatients for EPRP included ambulatory patients with common chronic diseases such as HF, diabetes, ischemic heart disease (prior myocardial infarction), and chronic obstructive pulmonary disease identified by specific ICD-9 codes. Experienced data abstractors then reviewed electronic medical records for validation of sample selection criteria, including a documentation of a diagnosis of HF in the outpatient charts for the EPRP HF cohort. For further validation, 70 patients in EPRP cohort from the Houston VA were reviewed; documentation of a diagnosis of HF by a clinician in the electronic medical records was confirmed in 96% of cases. Patient-level data from the EPRP HF cohort were linked with 5 existing national VA databases to obtain further demographic, laboratory, pharmacy, and outcome data.

Individuals from the EPRP HF cohort who had diabetes as identified in the EPRP data (n=8842) and who were prescribed hypoglycemic medications in the pharmacy database (n=7147) were included in this study. Diabetic therapy was ascertained using pharmacy data and was based on prescriptions filled 90 days before the index outpatient visit or 30 days after the index outpatient visit. In addition to diabetic status and therapy, baseline demographics and concomitant cardiac medications were assessed at the index visit. The most recent laboratory data within 1 year before the index visit and up to 2 weeks after the index visit were used. Because of the important potential for confounding between metformin use and renal dysfunction, patients with missing creatinine values were excluded from these analyses (n=962), leaving a total of 6185 patients in the total cohort. Other missing laboratory values were imputed using the median value of the study cohort for that parameter and a dummy variable was used to indicate replacement of missing data. Glomerular filtration rate (GFR) was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation. Covariates that reflected diabetes severity included hemoglobin A1C and a variable that documented the presence of a diabetic complication including neuropathy, nephropathy, retinopathy, or peripheral vascular disease.

Primary and Secondary Outcomes

The primary outcome was time to death over 2 years of complete follow-up after the index visit. Secondary outcomes included time to hospitalization for HF (based on diagnosis-related group) and time to any hospitalization.

Statistical Analysis

Continuous variables are presented as means with standard deviations and categorical variables are presented with percentages. Differences in baseline demographics between groups were ascertained using $\chi^2$ tests for categorical variables and $t$ tests for continuous variables. Two-sided probability values <0.05 were considered significant.

Propensity scores, defined as the conditional probability of being treated given the covariates, were used to adjust for possible bias due to nonrandom assignments of patients to different treatments. A propensity score was created for each individual using logistic regression, in which the outcome variable was metformin use. This propensity model consists of 29 baseline variables: age; sex; race; body mass index; systolic and diastolic blood pressures; left ventricular ejection fraction; history of hypertension, peripheral vascular disease, cerebrovascular disease, atrial fibrillation, myocardial infarction, cancer, chronic obstructive pulmonary disease, and diabetic complications; HF hospitalization within the last 2 years; hemoglobin; glycylsosylated hemoglobin (hemoglobin A1C); sodium; blood urea nitrogen; GFR; total cholesterol; triglycerides; treatment with β-blockers, sulfonylurea, thiazolidinedione, insulin, statins, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.

We then performed a 1-to-1 matched analysis without replacement on the basis of the estimated propensity score of each patient. The nearest available Mahalanobis metric matching method was used to

| Table 1. Patient Characteristics of the Study Cohort (Before Propensity Match) |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Metformin (n=1561) | No Metformin (n=4624) | P Value |
| Age, y                         | 67.3±9.3         | 70.0±9.3         | <0.001      |
| Male, %                        | 92.2             | 93.9             | 0.02        |
| Race, %                        |                  |                  | <0.001      |
| White                           | 76.8             | 74.8             |            |
| Black                           | 8.3              | 12.8             |            |
| Other/unknown                   | 14.9             | 12.5             |            |
| BMI, kg/m²                      | 32.6±7.0         | 31.3±6.6         | <0.001      |
| SBP, mm Hg                      | 133±21           | 131±22           | 0.001       |
| LVEF, %                         |                  |                  | <0.001      |
| Normal or mildly reduced (LVEF ≥40%) | 46.6             | 44.3             |            |
| Moderate or severely reduced (LVEF <40%) | 33.2             | 39.4             |            |
| Unknown                         | 20.2             | 16.3             |            |
| Diabetes with complications, %  | 52.3             | 59.3             | <0.001      |
| Peripheral vascular disease, %  | 20.1             | 24.8             | <0.001      |
| Hypertension, %                 | 77.0             | 75.0             | 0.11        |
| Atrial fibrillation, %          | 25.7             | 30.0             | 0.001       |
| Past myocardial infarction, %   | 32.9             | 36.0             | 0.03        |
| Prior HF hospitalization within 2 y, % | 11.0             | 21.0             | 0.001       |
| COPD, %                        | 25.6             | 27.6             | 0.11        |
| Cancer, %                      | 13.6             | 17.8             | <0.001      |
| HbA1C, %                       | 7.8±1.6          | 7.6±1.6          | <0.001      |
| GFR, mL/min/1.73 m²            | 67.1±20.6        | 52.0±22.5        | <0.001      |
| BUN, mg/dL                     | 22.0±9.9         | 30.3±16.5        | <0.001      |
| Hemoglobin, mg/dL              | 13.6±1.6         | 13.2±1.8         | <0.001      |
| Cholesterol, mg/dL             | 175±41           | 171±42           | <0.01       |
| Medications                     |                  |                  |            |
| Insulin, %                     | 33.5             | 53.1             | <0.001      |
| Sulfonylurea, %                | 59.1             | 58.8             | 0.82        |
| TZD, %                         | 11.6             | 11.8             | 0.84        |
| ACE/ARB, %                     | 86.5             | 82.2             | <0.001      |
| Spironolactone                 | 24.2             | 26.1             | 0.11        |
| β-blocker, %                   | 59.5             | 61.4             | 0.18        |
| Statin, %                      | 59.7             | 55.5             | <0.01       |

Data expressed as mean±SD or percentage.

BMI indicates body mass index; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; HbA1C, hemoglobin A1C; BUN, blood urea nitrogen; TZD, thiazolidinedione; and ACE/ARB, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.
perform the matching and to select the final data set for analysis. It
has been shown that this method is better than other propensity
matching methods in balancing the covariates between 2 treatment
groups. After propensity score matching, baseline characteristics
were compared with \( t \) tests for categorical variables and
\( \chi^2 \) tests for continuous variables. In addition, we assessed the success of pro-
pensity score matching to balance covariates in the 2 groups using
standardized differences. Standardized differences of less than 10%
support the assumption of balance between the 2 groups.

Cox proportional hazards models stratified on matched pairs were
used to assess the relationship between metformin use and the
outcome of interest, which included time to death, time to heart
failure hospitalization, and time to any hospitalization. The propor-
tional hazards assumption was met using Schoenfield residuals.

Exploratory tests for potential interaction between metformin use
and outcomes in certain subgroups (obese patients, renal insuffi-
ciency, and previous myocardial infarction) were performed by
adding a cross-product term of these variables in the Cox model.

### Results

#### Baseline Characteristics

Of the 6185 patients in this cohort, 1561 (25.2\%) patients
were receiving metformin therapy. Baseline characteristics
for the entire cohort and for the propensity score–matched
cohort are demonstrated in Table 1 and Table 2, respectively.

Before matching, patients receiving metformin were more
likely to be younger and have a higher body mass index,
systolic blood pressure, glycosylated hemoglobin, cholesterol,
and GFR than patients not receiving metformin. Patients
receiving metformin were also less likely to have peripheral
vascular disease, prior myocardial infarction, hospitalization
for HF within the previous 2 years, diabetic complications,
and cancer. Patients receiving metformin were less likely to
receive insulin therapy but were more likely to have received
Unadjusted Clinical Outcomes
At 2 years of follow-up, 246 (15.8%) of patients receiving metformin and 1177 (25.5%) of patients not receiving metformin had died (unadjusted hazard ratio [HR], 0.58; 95% confidence interval [CI], 0.57 to 0.67; \( P<0.001 \)). Similarly, the proportions of patients hospitalized with HF (11.5% versus 16.4%, \( P<0.001 \)) and hospitalized for any cause (40.9% versus 47.9%, \( P<0.001 \)) were lower in patients receiving metformin compared with those not receiving metformin over the 2 years of follow-up.

Propensity Score–Matched Models
After propensity score matching, patient characteristics were similar in patients receiving metformin versus those not receiving metformin. In the propensity score–matched cohort (n=2874), death occurred in 232 (16.1%) patients receiving metformin compared with 285 (19.8%) patients not receiving metformin (Figure 1 and Table 3). Using Cox proportional hazard models, metformin therapy was associated with a reduced mortality in the subgroups of obese patients (body mass index \( >30 \) kg/m\(^2\)), renal insufficiency (GFR \( <60 \) mL/min/1.73 m\(^2\)), and those with a previous myocardial infarction (Figure 2). Additional exploratory subgroup analyses did not demonstrate a statistical interaction between metformin use and mortality in the subgroups of obese patients (body mass index \( >30 \) kg/m\(^2\)), renal insufficiency (GFR \( <60 \) mL/min/1.73 m\(^2\)), and those with a previous myocardial infarction (Figure 2).

Hospitalization events for the propensity score–matched cohort are shown in Table 3. In propensity score–matched analyses, there was no statistically significant difference in time to HF hospitalization or time to all-cause hospitalization between individuals treated with metformin compared with those not treated with metformin (HR, 0.93; 95% CI, 0.74 to 1.18; \( P=0.56 \); and HR, 0.94; 95% CI, 0.83 to 1.07; \( P=0.35 \), respectively).

Discussion
In a national cohort of ambulatory patients with diabetes and HF, metformin was prescribed for diabetic treatment in approximately 25% of patients. Using propensity score–matched analyses, we demonstrate that metformin therapy was associated with a survival benefit over 2 years of follow-up. This benefit was consistent across subgroups of diabetic patients with HF, including those patients with renal insufficiency, prior myocardial infarction, and obesity. In addition, there were no statistically significant differences in time to HF hospitalization or time to all-cause hospitalization over 2 years of follow-up between those patients receiving metformin compared with those not receiving metformin.

Until recently, the use of metformin has been contraindicated in patients with HF because of concerns regarding the potential risk of lactic acidosis.\(^7\) These concerns originally stemmed from reports of an association between phenformin, another biguanide, and several cases of lactic acidosis.\(^7\) In addition, in the first year of postmarketing surveillance after metformin was introduced in the United States, 47 patients treated with metformin were reported to have lactic acidosis (approximately 5 cases per 100,000 patients treated), 18 of whom had history of HF.\(^7\) Despite these initial reports, subsequent analyses revealed that the risk of lactic acidosis associated with metformin use was very low in patients with type 2 diabetes and may not be higher than diabetic patients not receiving metformin therapy.\(^7,18\)

Two previous retrospective cohort studies have demonstrated that metformin use appears safe and may be potentially beneficial in diabetic patients with established HF. In one of these studies, which included 16,417 Medicare beneficiaries with diabetes who were recently discharged from the hospital with a primary diagnosis of HF, metformin use was associated with a 13% lower risk of death and 8% lower risk of readmission for HF compared with diabetic patients not receiving insulin-sensitizing diabetic therapy at 1 year of follow-up.\(^16\) Furthermore, readmissions for metabolic acidosis were similar among patients not treated with an insulin sensitizer (2.6%) compared with those discharged with a prescription for metformin (2.3%, \( P=0.40 \)) in the Medicare population. Similarly, in a retrospective analysis of 1833 new users of oral diabetic therapy with HF, fewer deaths occurred in subjects receiving metformin monotherapy or combination therapy with metformin and sulfonylurea when compared with sulfonylurea therapy alone.\(^9\)

Despite the strengths of these previous retrospective cohort studies, several limitations exist. Multivariable modeling techniques were used in previous studies\(^9,10\) to control for potential confounding, but residual confounding may persist. Specifically, selection bias, in that physicians may prescribe metformin to patients with less severe disease, may contribute to the improved outcomes previously associated with metformin use. Propensity score methods are statistical techniques used to reduce the impact of treatment selection bias often seen in the estimation of treatment effects in nonran-
Our study extends the previous literature by using propensity score–matched analyses to examine the association between metformin use and outcomes in a national cohort of ambulatory patients with diabetes and HF. The sample size of the cohort and the large number of demographic and clinical variables available at baseline, including data on renal function, allow for propensity score matching on multiple variables and subsequent adequate balance of baseline characteristics between treated and untreated patients. The improved survival associated with metformin use persisted after propensity score–matched analyses and remained consistent with previously published estimates.9,10

There are several potential mechanisms beyond glycemic control through which metformin may improve outcomes in HF patients.6 Compared with several other diabetic treatment options, metformin is associated with a reduction in weight gain and improvements in measures of insulin resistance. In addition, metformin has been associated with improvements in endothelial function, lipoprotein metabolism, oxidative stress, and abnormalities of coagulation.6 These potential mechanisms may have contributed to the reduction in macrovascular events observed in a subset of overweight patients treated with metformin in the United Kingdom Prospective Diabetes Study (UKPDS) 3420 and in a recent study of patients with type 2 diabetes in which metformin was added to a background of insulin therapy.21

In addition to potential prevention of macrovascular events, metformin has been associated with improvements in cardiac function in both animal models of HF and models of diabetic cardiomyopathy. For example, metformin treatment is associated with improvements in measures of cardiac performance in streptozotocin-diabetic rats.22 More recently, metformin treatment led to improvements in survival and in left ventricular function in murine models of ischemia-induced HF.23 Similarly, metformin therapy prevented progression of HF in a canine model of pacing-induced HF.24 These beneficial cardiac effects appear to be mediated through activation of AMP-activated protein kinase and its downstream mediators, including endothelial nitric oxide.23,24

Despite the strength of this study, several limitations should be noted. Importantly, the incidence of lactic acidosis was not obtained. It is reassuring that total hospitalizations in the entire cohort and in the propensity score–matched sample were not increased in patients receiving metformin therapy, but, given the low reported incidence of potential lactic acidosis, our sample is not suitable to address the issue of safety. Nonetheless, our study, when combined with previously published studies in HF patients,10,11 adds to a growing body of literature that metformin use appears safe in diabetic patients with HF. Additionally, although propensity score–matched analyses were performed to minimize potential bias, residual bias and confounding may persist. For example, New York Heart Association classification was not available in this data set; we have attempted to address this limitation by using other important prognostic variables in a HF population, such as previous HF hospitalization and left ventricular ejection fraction. In addition, medication use was assessed only at baseline, and changes in medications over the time of follow-up are not available. Despite the total number of variables used to create the propensity score, the lack of these and other key variables may contribute to residual confounding.

In conclusion, in a cohort of patients with diabetes and established HF, prescription of metformin was associated with a survival benefit over 2 years of follow-up. Given the current burden and expected growth in the number of patients with diabetes and HF, it is critically important that future studies assess the optimal treatment strategy for glycemic control in this population. Addressing these issues will require carefully designed prospective observational studies to confirm safety and randomized controlled clinical trials to assess efficacy. Although these trials may be difficult to perform, they are required if we are to reduce the growing burden of diabetes and HF.

Acknowledgments
We thank the Office of Quality and Performance of the Veterans Health Administration for Providing External Peer Review Program data. The
views expressed in this article are those of the authors and do not necessarily represent those of the Department of Veteran Affairs.

Sources of Funding

This study was supported in part by VA Health Services Research and Development Service grant IIR 02-082-1 (to Dr Deswal). Dr Aguilar is a recipient of a NIH Mentored Career Development Award (SK01-HL092585-02).

Disclosures

None.

References


CLINICAL PERSPECTIVE

Diabetes mellitus and heart failure (HF) commonly coexist in the same patient, and, importantly, the presence of diabetes in HF patients is associated with increased morbidity and mortality. Therefore, efforts to adequately treat diabetes have become increasingly important. Historically, metformin has been contraindicated in HF patients because of concerns of lactic acidosis. Recent animal studies and retrospective studies of patients with diabetes and HF have suggested that metformin may in fact be beneficial. One important limitation of these previous human studies is the potential for selection bias, in that patients with more severe illness may be less likely to have been prescribed metformin. Propensity score methods are statistical techniques developed to balance covariates in 2 groups in observational studies and therefore reduce potential selection bias. In the present study of a national cohort of ambulatory patients with diabetes and established HF, we used propensity score–matched methods to assess the association between metformin and outcomes. Using these techniques, we demonstrate that metformin use was associated with lower rates of mortality at 2-year follow-up, without differences in HF hospitalizations or total hospitalizations between the 2 groups. Future prospective studies are needed to confirm the potential benefits and safety of metformin in diabetic patients with HF. Until these data are available, our study adds to a growing body of literature suggesting that metformin may be beneficial in this population.
Metformin Use and Mortality in Ambulatory Patients With Diabetes and Heart Failure
David Aguilar, Wenyaw Chan, Biykem Bozkurt, Kumudha Ramasubbu and Anita Deswal

Circ Heart Fail. 2011;4:53-58; originally published online October 15, 2010;
doi: 10.1161/CIRCHEARTFAILURE.110.952556
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/4/1/53

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/