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Clinical Outcomes With Metformin and Sulfonylurea Therapies Among Patients With Heart Failure and Diabetes

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ABSTRACT

OBJECTIVES The authors sought to characterize associations between initiation of metformin and sulfonylurea therapy and clinical outcomes among patients with comorbid heart failure (HF) and diabetes (overall and by ejection fraction [EF] phenotype).

BACKGROUND Metformin and sulfonylureas are frequently prescribed to patients with diabetes for glycemic control. The impact of these therapies on clinical outcomes among patients with comorbid HF and diabetes is unclear.

METHODS The authors evaluated Medicare beneficiaries hospitalized for HF in the Get With The Guidelines–Heart Failure Registry between 2006 and 2014 with diabetes and not prescribed metformin or sulfonylurea before admission. In parallel separate analyses for metformin and sulfonylurea, patients with newly prescribed therapy within 90 days of discharge were compared with patients not prescribed therapy. Multivariable models landmarked at 90 days evaluated associations between prescription of therapy, and mortality and hospitalization for HF (HHF) at 12 months. Negative control (falsification) endpoints included hospitalization for urinary tract infection, hospitalization for gastrointestinal bleed, and influenza vaccination. Prespecified subgroup analyses were stratified by EF ≤40% versus >40%.

RESULTS Of 5,852 patients, 454 (7.8%) were newly prescribed metformin and 504 (8.6%) were newly prescribed sulfonylurea. After adjustment, metformin prescription was independently associated with reduced risk of composite mortality/HHF (HR: 0.81; 95% CI: 0.67-0.98; $P = 0.03$), but individual components were not statistically significant. Findings among patients with EF >40% accounted for associations with mortality/HHF (HR: 0.68; 95% CI: 0.52-0.90) and HHF (HR: 0.58; 95% CI: 0.40-0.85) endpoints (all P for interaction ≤0.04). After adjustment, sulfonylurea initiation was associated with increased risk of mortality (HR: 1.24; 95% CI: 1.00-1.52; $P = 0.045$) and HHF (HR: 1.22; 95% CI: 1.00-1.48; $P = 0.050$) with nominal statistical significance. Associations between sulfonylurea initiation and endpoints were consistent regardless of EF (all P for interaction >0.11). Neither metformin initiation nor sulfonylurea initiation were associated with negative control endpoints.

CONCLUSIONS In this population of older U.S. adults hospitalized for HF with comorbid diabetes, metformin initiation was independently associated with substantial improvements in 12-month clinical outcomes, driven by findings among patients with EF >40%. By contrast, sulfonylurea initiation was associated with excess risk of death and HF hospitalization, regardless of EF. (J Am Coll Cardiol HF 2022;10:198–210) © 2022 by the American College of Cardiology Foundation.

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Several randomized clinical trials of antidiabetic therapies have shown varying effects on heart failure (HF) risk (1). For example, thiazolidinediones and the dipeptidyl peptidase-4 inhibitor saxagliptin have each been shown to increase risk for HF events (2-4). By contrast, sodium glucose cotransporter 2 (SGLT2) inhibitors are effective in preventing incident HF among patients with type 2 diabetes mellitus (DM), and in improving clinical outcomes among patients with established HF with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF) (5-7).

Despite mounting evidence supporting broad use of SGLT2 inhibitors, metformin and sulfonylureas continue to remain the most commonly used oral medications for DM, including among patients with comorbid HF (8). Likewise, although newer guidelines recognize the importance of SGLT2 inhibitor therapy for patients with type 2 DM (particularly in cases of comorbid HF or chronic kidney disease), they continue to endorse metformin as general first-line therapy because it is less costly, readily available, and widely used as baseline therapy in trials of other antidiabetic medications (9,10). Nonetheless, to date, the impact of both metformin and sulfonylurea therapies on cardiovascular and HF outcomes remains largely unknown. This uncertainty is particularly present for patients with established HF, a high-risk population for which safety with select oral antidiabetic therapies has historically proven a concern. Likewise, given differences in respective pathophysiology of HFrEF vs HFpEF, it is possible that differences in safety and cardiovascular risk reduction with metformin and sulfonylurea could vary by ejection fraction (EF).

With the increasing recognition SGLT2 inhibitors as an alternative oral medication proven to reduce cardiovascular risk, understanding the effects of metformin and sulfonylurea therapies on clinical outcomes among patients with HF and DM is increasingly relevant given their continued dominant use in routine practice. In this context, the GWTG-HF (Get With The Guidelines-Heart Failure) registry offers a novel opportunity to evaluate the comparative effectiveness of metformin and sulfonylurea therapies on clinical outcomes in a large nationally representative cohort of older U.S. adults hospitalized for HF with comorbid DM. In addition, the registry offers the ability to assess whether associations between use of each therapy and clinical outcomes differ among patients with reduced versus preserved EF.

ABBREVIATIONS AND ACRONYMS

CKD = chronic kidney disease

DM = diabetes mellitus

EF = ejection fraction

eGFR = estimated glomerular filtration rate

HF = heart failure

HHF = hospitalization for heart failure

HFrEF = heart failure with reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

SGLT2 = sodium glucose cotransporter 2

METHODS

DATA SOURCE. GWTG-HF is an ongoing, observational, hospital-based, quality improvement registry formed in 2005 by the American Heart Association. The registry includes patients hospitalized for HF, and those who develop symptoms attributable to HF during hospitalization such that HF was the primary diagnosis. IQVIA serves as the data collection and coordinating center for the American Heart Association's GWTG programs, and the Duke Clinical Research Institute serves as the data analytic center. As the primary purpose of the registry is for quality improvement, patient informed consent is waived under the Common Rule. The GWTG-HF protocol was approved by the institutional review boards at each participating center. For the current study, participants 65 years of age and older with fee-for-service Medicare coverage were linked to Medicare data using a validated technique (11).

STUDY POPULATION. We identified Medicare beneficiaries hospitalized for HF in the GWTG-HF registry between January 1, 2006, and December 31, 2014, who were discharged with a diagnosis or history of DM. To further confirm history of DM, a medication fill for any antidiabetic medication from January 1, 2006, to December 31, 2015, was additionally required for study inclusion. If multiple HF hospitalizations existed for a patient, the first hospitalization was considered the index hospitalization, and other hospitalizations were excluded.

Key reasons for patient exclusion from this study were: 1) left against medical advice, transferred to an acute care facility, or discharged to hospice care; 2) significant kidney disease, defined as chronic or in-hospital dialysis therapy, estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 at hospital discharge, or history of chronic kidney disease (CKD) with serum creatinine >2.0 mg/dL if eGFR data unavailable; and 3) died within 90 days of discharge

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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(Supplemental Figure 1). The rationale for the kidney function exclusion stemmed from contraindications and cautions against use of metformin (among patients with eGFR <30 mL/min/1.73 m^2 and 30 to 44 mL/min/1.73 m^2, respectively) and recognition that patients with CKD who are potentially less likely to receive metformin may confound associations between metformin and clinical outcomes. Identical kidney function selection criteria were prespecified for use in the sulfonylurea initiation analyses to mitigate potential differences in confounding driving differences between metformin and sulfonylurea results. We also excluded patients who had a medication fill for thiazolidinedione therapy within 90 days of discharge, given the established adverse effects of thiazolidinedione medications among HF patients. In addition, to capture patients newly initiating metformin or sulfonylurea therapy and likely naive to either medication, our primary analysis excluded patients with prescription fills for either therapy in the 12 months before index hospitalization.

EXPOSURE. The effectiveness of metformin and sulfonylurea therapies were separately evaluated in identical parallel analyses. For each therapy, exposure was defined as a medication fill for the respective medication within 90 days post-discharge. Patients with a medication fill were then compared with patients who did not have a medication fill for the respective therapy.

OUTCOMES. Prespecified clinical outcomes were all-cause mortality, hospitalization for HF, and the composite of all-cause mortality or HF hospitalization. Outcomes were assessed over a 12-month period, beginning at day 91 post-discharge (ie, landmark analysis with outcome assessment period beginning immediately after the 90-day exposure period detailed in the preceding text). Under the landmark analysis approach, hospitalizations that occurred within 90 days postdischarge were excluded from outcome analyses. Outcomes were identified using the Medicare Master Beneficiary Summary File and inpatient claims files (Supplemental Table 1).

STATISTICAL ANALYSES. In separate analyses for metformin and sulfonylurea, baseline patient characteristics were compared between patients initiated with the respective therapy versus those not initiated. Groups were compared using standardized mean differences, with a difference >10 indicating imbalance between groups.

To align with the early postdischarge period used to define exposure to metformin or sulfonylurea therapy, all outcome analyses were landmarked at 90 days postdischarge. Thus, the 12-month outcome assessment period extended from 3 months to 15 months following index hospital discharge. The unadjusted cumulative incidence of each outcome over 12-month follow-up was compared among patients initiating vs not initiating the respective therapy.

For metformin and sulfonylurea respectively, unadjusted and adjusted Cox proportional hazards models were used to derive HRs and assess associations between initiation of the therapy and 12-month clinical outcomes. All outcomes were assessed as time-to-first event. To help address potential selection bias or confounding, adjusted models included 29 prespecified covariates chosen by clinical judgment that spanned patient demographics, EF, vital signs, laboratories, medical history, HF medical and device therapies at time of discharge, and time from index hospitalization discharge to metformin/sulfonylurea medication fill (Supplemental Table 2). All models were weighted by the inverse probability of receiving metformin or sulfonylurea. If the propensity scores were extreme, overlap weighting was used. All models accounted for clustering of patients within hospitals by using a robust sandwich variance via the generalized estimating equation method. Cause-specific hazards were used to account for competing risk of mortality. The proportional hazards assumption was verified for each cause-specific model using plots of Schoenfeld residuals and the log-cumulative hazard. In addition, for all clinical endpoints, associations between initiation of each treatment and outcomes were assessed among subgroups of patients with EF ≤40% and EF >40%, and interaction testing was performed.

To assess risk of residual confounding, unadjusted and adjusted models were used to separately test associations between initiation of metformin or sulfonylurea and 3 falsification endpoints (ie, negative controls) chosen based on the lack of biologically plausible associations with either metformin or sulfonylurea (12). Falsification endpoints were hospitalization for urinary tract infection, hospitalization for gastrointestinal bleed, and vaccination for influenza.

As sensitivity analyses, the preceding analyses (with the exception of the subgroup analyses by EF group) for metformin and sulfonylurea were each repeated in the larger population of patients including those with use of the respective medication in the prior 12 months. Thus, populations examined in the parallel sensitivity analyses were a combination of new and prevalent users of each medication.

Missing patient-level covariates were imputed before entering models (Supplemental Table 3). Missing discharge values were imputed with

TABLE 1 Characteristics of Patients Initiated Versus Not Initiated on Metformin

	Metformin (n = 454)	No Metformin (n = 5,398)	Absolute Std. Diff, %
Age, y	74 (68-81)	76 (70-82)	17.10
Female	243 (53.5)	2,776 (51.4)	4.20
Race			12.48
White	320 (72.1)	3,846 (73.1)	
Black	61 (13.7)	860 (16.3)	
Other	63 (14.2)	554 (10.5)	
Median household income (indexed using CPI-U 2014 average), $	51,186 (44,489-59,313)	51,186 (45,220-60,288)	3.02
LVEF ≤40%[a]	193 (43.7)	2,197 (41.8)	3.80
Ejection fraction	45 (30-56)	45 (30-58)	4.35
Length of stay, days	4 (3-6)	4 (3-6)	2.80
Vital sign and laboratory data at discharge			
Heart rate, beats/min	78 (67-89)	74 (66-84)	22.17
Systolic blood pressure, mm Hg	124 (113-138)	126 (113-141)	2.99
Body mass index, kg/m^2	30.0 (26.4-36.3)	30.1 (26.0-35.7)	4.61
Potassium, mEq/L	4.0 (3.7-4.3)	4.0 (3.7-4.3)	0.95
BUN, mg/dL	22 (17-28)	22 (17-30)	3.12
Serum Cr, mg/dL	1.0 (0.8-1.1)	1.1 (0.9-1.3)	9.41
eGFR, MDRD formula	67 (55-81)	60 (51-72)	3.97
BNP, pg/mL	459 (194-813)	434 (199-861)	8.36
NT-BNP, pg/mL	4,160 (1,734-6,140)	2,775 (1,270-6,428)	9.84
Hemoglobin A_{1C}	7.1 (6.4-8.5)	7.1 (6.4-8.1)	9.53
Medical history			
Hypertension	380 (83.7)	4,484 (83.1)	1.66
Hyperlipidemia	79 (17.4)	777 (14.4)	3.44
Prior myocardial infarction	88 (19.4)	1,185 (22.0)	6.36
Prior cerebrovascular disease/TIA	66 (14.5)	997 (18.5)	10.62
Peripheral vascular disease	52 (11.5)	807 (15.0)	10.35
Smoker	68 (15.0)	519 (9.6)	16.37
Chronic obstructive pulmonary disease or asthma	149 (32.8)	1,763 (32.7)	0.33
Atrial fibrillation	138 (30.4)	1,850 (34.3)	8.31
Ischemic heart disease	249 (54.8)	3,471 (64.3)	19.38
ICD or CRT device	36 (7.9)	617 (11.4)	11.87
Heart failure medical therapy at discharge			
ACE inhibitor/ARB	355 (78.7)	3,806 (71.8)	16.82
Beta-blocker	368 (81.1)	4,413 (82.2)	3.92
MRA	83 (18.7)	972 (18.6)	8.99
Hydralazine nitrate	27 (6.1)	612 (11.9)	22.36
Loop diuretic	253 (95.5)	2,854 (95.5)	0.06
Background diabetes therapies			
Insulin	114 (25.1)	2,228 (41.3)	34.84
DPP-4 inhibitor	45 (9.9)	248 (4.6)	20.61
Sulfonylurea	133 (29.3)	271 (6.9)	60.90
Hospital characteristics			
Region			19.75
Northeast	138 (30.4)	1,805 (33.4)	
Midwest	96 (21.1)	1,351 (25.0)	
South	155 (34.1)	1,779 (33.0)	
West	65 (14.3)	463 (8.6)	
Academic/teaching hospital	323 (73.4)	3,859 (74.1)	1.53
No. of beds	348 (226-483)	375 (243-556)	8.19
Rural location	20 (4.8)	261 (5.2)	1.94

Values are median (interquartile range) or n (%). Std. diff is the standardized mean differences as represented by differences in means or proportions divided by the SE and multiplied by 10. Standardized mean differences >10 indicate imbalance between groups. [a]Among 5,433 patients with ejection fraction (EF) data, ejection fraction was measured during the index hospitalization in 3,091 (56.7%) patients, within the past year in 1,024 patients (18.9%), and more than 1 year ago in 146 patients (2.7%). Data on timing of ejection fraction were missing for 1,172 patients (21.6%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibition; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CPI-U = consumer price index for all urban customers; Cr = creatinine; CRT = cardiac resynchronization therapy; DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; MDRD = Modification of Diet in Renal Disease; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TIA = transient ischemic attack.

admission values when available, otherwise multiple imputation methods were used with 10 data sets. Hospital characteristics were not imputed. Rates of missing data for most variables were <8% with few exceptions (eGFR 31.1%, heart rate 20.5%, systolic blood pressure 19.2%). All statistical tests were 2-sided, with $P < 0.05$ considered statistically significant. All analyses were performed using SAS software version 9.4 (SAS Institute).

RESULTS

BASELINE CHARACTERISTICS. After all exclusions, 5,852 patients deemed naive to metformin and sulfonylurea therapy across 367 U.S. hospitals were included in the primary analysis (Supplemental Figure 1). Of 5,852 patients, 454 patients (7.8%) were newly prescribed metformin and 504 (8.6%) were newly prescribed sulfonylurea within 90 days of hospital discharge. Overall, 133 patients (2.3%) were newly initiated on both therapies. The median (interquartile range) age was 75 (69 to 82) years, 51.6% were women, 73.0% were White. Median ejection fraction was 45%, with 41.9% of patients having an EF ≤40%. Median eGFR at time of hospital discharge was 60 mL/min/1.73 m^2.

Metformin initiation. Compared with patients not treated with metformin, patients initiated on metformin therapy tended to be younger, more likely to be treated with an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and less likely to have ischemic heart disease and an implantable cardioverter-defibrillator or cardiac resynchronization therapy device (Table 1). Metformin initiators were also more likely to have received care at a hospital in the Western United States, and less likely to be treated with insulin. Otherwise, patients initiating and not initiating metformin were generally similar with respect to sex, household income, education level, EF, blood pressure, eGFR, natriuretic peptide level, hemoglobin A_{1c}, and index hospital characteristics.

Sulfonylurea initiation. Compared with patients not treated with sulfonylurea, patients initiated on therapy tended to have modestly longer index hospital lengths of stay, lower body mass index, higher level of N-terminal pro-B-type natriuretic peptide, and lower rates of comorbid atrial fibrillation (Table 2). Sulfonylurea initiators were also more likely to have received care at a hospital in the Western United States, and less likely to be treated with insulin. Patients initiating and not initiating sulfonylurea were generally similar with respect to age, sex, household income, education level, EF, vital signs, renal function, and HF medications.

OUTCOMES WITH METFORMIN INITIATION. Unadjusted rates of HF hospitalization (19.5 vs 25.8; $P = 0.005$) and composite of all-cause mortality or HF hospitalization (30.7 vs 39.7; $P = 0.004$) at 12 months were significantly lower among patients who were prescribed metformin compared with those who were not (Table 3, Figure 1). There was no significant difference in the unadjusted risk of all-cause mortality between groups (18.5 vs 20.5; $P = 0.24$).

In adjusted analysis, metformin initiation remained significantly associated with lower risk of composite all-cause mortality or HF hospitalization at 12 months (HR: 0.81 [95% CI: 0.67-0.98]; $P = 0.032$). After adjustment, associations between metformin initiation and all-cause mortality (HR: 1.06 [95% CI: 0.85-1.33]; $P = 0.59$) and HF hospitalization (HR: 0.80 [95% CI: 0.63-1.02]; $P = 0.072$) were not statistically significant. Metformin initiation was not significantly associated with any falsification endpoint in unadjusted or adjusted analyses.

In subgroup analysis stratified by EF ≤40% vs >40%, the association between metformin initiation and risk of HF hospitalization (P for interaction = 0.007) and composite all-cause mortality or HF hospitalization (P for interaction = 0.040) was significantly different between EF groups. For both endpoints, associations with substantially reduced risk were confined to patients with EF >40% (HF hospitalization HR: 0.58 [95% CI: 0.40-0.85]; composite endpoint HR: 0.68 [95% CI: 0.52-0.90]), with no suggestion of reduced risk among patients with EF ≤40% (Central Illustration). There was no evidence for significant subgroup interaction (P for interaction = 0.28) for all-cause mortality.

OUTCOMES WITH SULFONYLUREA INITIATION. The unadjusted rates of HF hospitalization (27.1 vs 25.1; $P = 0.35$) and composite of all-cause mortality or hospitalization for HF (42.1 vs 38.7; $P = 0.12$) were not significantly different among patients who were initiated on sulfonylurea therapy compared with those who were not (Table 4, Figure 2). The unadjusted risk of all-cause mortality was significantly higher among patients who were initiated on sulfonylurea therapy (23.8 vs 20.1; $P = 0.04$).

After adjustment, sulfonylurea initiation remained associated with a statistically significant excess risk of all-cause mortality (Table 4). (HR: 1.24 [95% CI: 1.00-1.52]; $P = 0.045$). In adjusted analyses, initiation of sulfonylurea therapy was also associated with higher risk of composite all-cause mortality or HF

TABLE 2 Characteristics of Patients Initiated Versus Not Initiated on Sulfonylurea

	Sulfonylurea (n = 504)	No Sulfonylurea (n = 5,348)	Absolute Std. Diff, %
Age, y	76 (70-83)	75 (69-82)	8.97
Sex, female	244 (48.4)	2,775 (51.9)	6.96
Race			11.87
White	351 (71.3)	3,815 (73.2)	
Black	71 (14.4)	850 (16.3)	
Other	70 (14.2)	547 (10.5)	
Median household income (indexed using CPI-U 2014 average), $	51,268 (44,024-61,120)	51,186 (45,220-60,225)	1.90
LVEF ≤40%	218 (44.5)	2,172 (41.7)	5.66
Ejection fraction[a]	45 (30-58)	47 (30-58)	8.61
Length of stay, days	5 (3-7)	4 (3-6)	13.36
Vital sign and laboratory data at discharge			
Heart rate, beats/min	74 (66-84)	74 (66-84)	4.20
Systolic blood pressure, mm Hg	126 (111-142)	126 (113-141)	0.71
Body mass index, kg/m^2	29.2 (25.4-34.0)	30.2 (26.1-36.0)	22.67
Potassium, mEq/L	4.0 (3.7-4.3)	4.0 (3.7-4.3)	1.28
BUN, mg/dL	23 (17-30)	22 (17-29)	2.53
Serum Cr, mg/dL	1.0 (0.8-1.2)	1.1 (0.9-1.2)	7.54
eGFR, MDRD formula	60 (52-73)	60 (52-72)	2.17
BNP, pg/mL	541 (229-947)	428 (197-843)	3.98
NT-BNP, pg/mL	3,706 (1,534-7,000)	2,781 (1,262-6,237)	14.54
Hemoglobin A_{1C}	7.3 (6.4-8.5)	7.1 (6.4-8.1)	7.15
Medical history			
Hypertension	423 (83.9)	4,441 (83.1)	2.35
Hyperlipidemia	74 (14.7)	782 (14.6)	11.58
Prior myocardial infarction	96 (19.0)	1,177 (22.0)	7.35
Prior cerebrovascular accident/TIA	83 (16.5)	980 (18.3)	4.91
Peripheral vascular disease	68 (13.5)	791 (14.8)	3.74
Smoker	59 (11.7)	528 (9.9)	5.95
Chronic obstructive pulmonary disease or asthma	168 (33.3)	1,744 (32.6)	1.53
Atrial fibrillation	148 (29.4)	1,840 (34.4)	10.85
Ischemic heart disease	302 (59.9)	3,418 (63.9)	8.25
ICD or CRT device	48 (9.5)	605 (11.3)	5.87
Heart failure medical therapy at discharge			
ACE inhibitor/ARB	375 (75.5)	3,786 (72.1)	7.74
Beta-blocker	400 (79.5)	4,381 (82.3)	7.48
MRA	104 (21.3)	951 (18.4)	8.20
Hydralazine nitrate	52 (10.9)	587 (11.5)	3.75
Loop diuretic	275 (95.5)	2,832 (95.5)	0.02
Background diabetes therapies			
Insulin	121 (24.0)	2,221 (41.5)	38.00
DPP-4 inhibitor	42 (8.3)	251 (4.7)	14.79
Metformin	133 (26.4)	321 (6.0)	57.59
Hospital characteristics			
Region			15.77
Northeast	163 (32.3)	1,780 (33.3)	
Midwest	116 (23.0)	1,331 (24.9)	
South	157 (31.2)	1,777 (33.2)	
West	68 (13.5)	460 (8.6)	
Academic/teaching hospital	356 (73.9)	3,826 (74.0)	0.43
No. of beds	367 (238-537)	375 (243-539)	2.35
Rural location	20 (4.4)	261 (5.3)	4.36

Values are median (interquartile range) or n (%). Std. diff is the standardized mean differences as represented by differences in means or proportions divided by the SE and multiplied by 10. Standardized mean differences >10 indicate imbalance between groups. [a]Among 5,433 patients with ejection fraction data, ejection fraction was measured during the index hospitalization in 3,091 (56.7%) patients, within the past year in 1,024 patients (18.9%), and more than 1 year ago in 146 patients (2.7%). Data on timing of ejection fraction were missing for 1,172 patients (21.6%).

Abbreviations as in Table 1.

TABLE 3 Association Between Metformin Initiation and Study Endpoints at 12 Months

Study Endpoint	Cumulative Incidence, %		HR (95% CI); *P* Value	
	Metformin (n = 454)	No Metformin (n = 5,398)	Unadjusted	Adjusted[a]
Effectiveness endpoints				
All-cause mortality	18.5	20.5	0.88 (0.70-1.10); 0.25	1.06 (0.85-1.33); 0.59
HF hospitalization	19.5	25.8	0.72 (0.58-0.89); 0.002	0.80 (0.63-1.02); 0.072
All-cause mortality/HF hospitalization	30.7	39.7	0.73 (0.61-0.87); 0.001	0.81 (0.67-0.98); 0.032
Falsification (negative control) endpoints				
Urinary tract infection	1.4	2.8	0.48 (0.22-1.06); 0.068	0.67 (0.31-1.48); 0.33
Gastrointestinal bleed	1.2	2.4	0.46 (0.16-1.33); 0.15	0.69 (0.24-2.03); 0.50
Vaccination for influenza	9.5	10.7	0.87 (0.63-1.20); 0.39	0.90 (0.61-1.32); 0.59

Values are %, unless otherwise indicated. [a]Adjusted for 29 pre-specified covariates including demographics (age, sex, race), EF, vital signs and laboratories (discharge values for systolic blood pressure, heart rate, and eGFR), medical history (anemia, atrial fibrillation/flutter, ischemic HF etiology, stroke/transient ischemic attack, hypertension, hyperlipidemia, chronic obstructive pulmonary disease/asthma, peripheral vascular disease, chronic kidney disease, active smoking), HF therapies at time of discharge (ACE inhibitor/ARB, beta-blocker, mineralocorticoid receptor antagonist, implantable cardioverter-defibrillator, cardiac resynchronization therapy), socioeconomics (county-level education level, median county-level income), index hospital characteristics (U.S. geographic region, teaching/non-teaching hospital status, number of hospital beds, urban/rural location), and time from index hospitalization discharge to metformin/sulfonylurea medication fill.

HF = heart failure; other abbreviations as in Table 1.

hospitalization (HR: 1.17 [95% CI: 1.00-1.37]; $P = 0.047$) and HF hospitalization (HR: 1.22 [95% CI: 1.00-1.48]; $P = 0.050$), both with marginal statistical significance. Sulfonylurea initiation was not significantly associated with any falsification endpoint in unadjusted or adjusted analyses.

In subgroup analysis stratified by EF, associations between sulfonylurea initiation and all clinical endpoints were consistent among patients with EF ≤40% and >40%, with no statistical evidence of heterogeneity (all *P* for interaction ≥0.11) (**Central Illustration**).

OUTCOMES WITH METFORMIN AND SULFONYLUREA AMONG COMBINED PREVALENT AND NEW USERS (SENSITIVITY ANALYSES). After including patients who had a medication fill for metformin or sulfonylurea in the 12 months before index hospitalization, the size of the analytic cohort increased to 11,570 patients. Of these patients, within 90 days of discharge, 2,888 (25.0%) were newly treated or continued treatment with metformin, and 3,114 (26.9%) were newly treated or continued treatment with sulfonylurea. Overall, 1,073 patients (9.3%) were treated with both therapies within 90 days of discharge.

The unadjusted cumulative incidence of all 12-month clinical outcomes was lower among patients treated with metformin than those who were not (all-cause mortality 17.8 vs 22.9; $P < 0.001$; HF hospitalization 23.0 vs 25.9; $P = 0.001$; all-cause mortality or HF hospitalization 34.6 vs 41.4; $P < 0.001$) (Supplemental Table 4, Supplemental Figure 2). The unadjusted cumulative incidence of hospitalization for urinary tract infection was also significantly less (2.0 vs 2.7; $P = 0.033$). After adjustment, treatment with metformin was independently associated with reduced risk of all-cause mortality (HR: 0.88 [95% CI: 0.79-0.97]; $P = 0.013$) and all-cause mortality or HF hospitalization (HR: 0.89 [95% CI: 0.82-0.97]; $P = 0.007$), but not HF hospitalization (HR: 0.94 [95% CI: 0.85-1.04]; $P = 0.25$). There were no significant associations between metformin treatment and falsification endpoints.

The unadjusted cumulative incidence of HF hospitalization was higher among patients treated with sulfonylurea therapy than those who were not (26.5 vs 24.6; $P = 0.039$), whereas rates of all-cause mortality (22.1 vs 21.5; $P = 0.49$) and composite all-cause mortality or HF hospitalization (40.5 vs 39.4; $P = 0.30$) were similar (Supplemental Table 5, Supplemental Figure 3). After adjustment for clinical factors, sulfonylurea treatment was associated with higher risk of HF hospitalization (HR: 1.13 [1.03-1.23]; $P = 0.012$), whereas there were no statistically significant associations with other effectiveness endpoints or falsification endpoints.

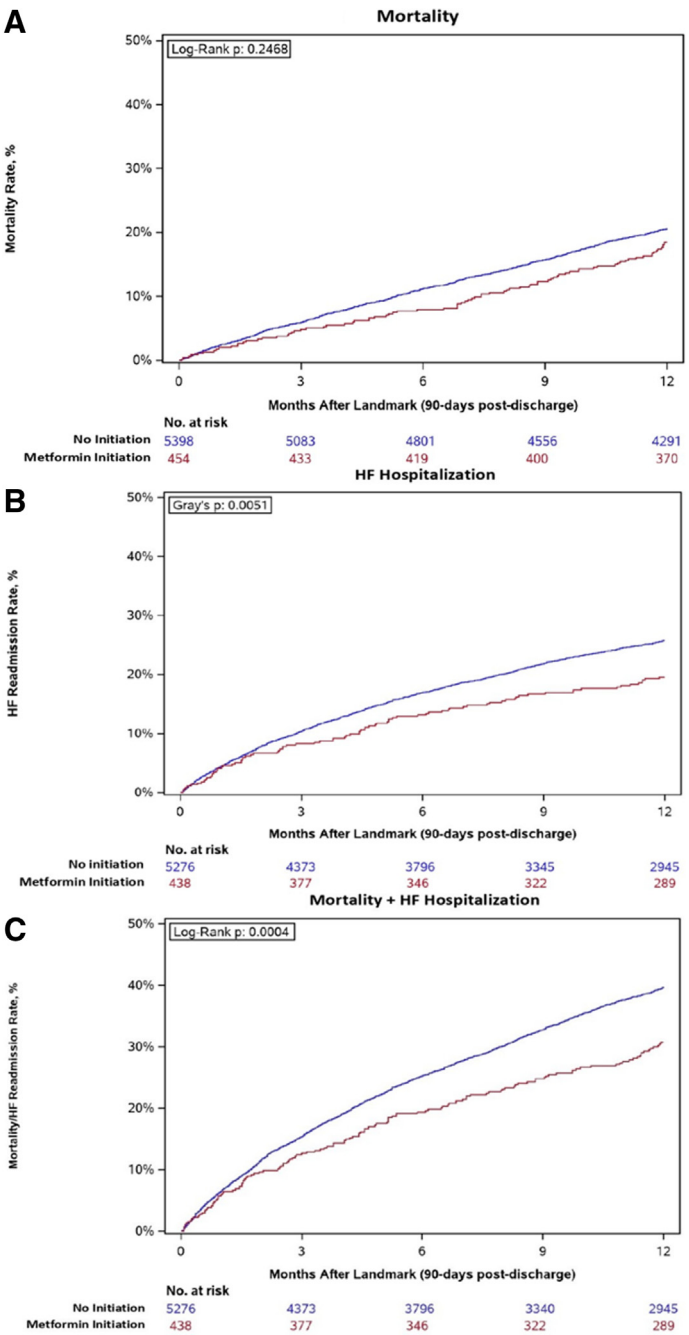
DISCUSSION

In this large cohort of older patients hospitalized for HF with comorbid DM, after adjustment for several domains of potential confounders, metformin initiation was independently associated with a lower risk of composite mortality and HF hospitalization. This association was exclusively driven by risk reduction among patients with EF >40%. By contrast, after adjustment, there was no signal of potential benefit or harm towards mortality or HF hospitalization with metformin initiation in HFrEF. Second, sulfonylurea initiation was independently associated with increased risk of mortality and HF hospitalization outcomes. These associations with excess clinical events were consistent among patients with EF ≤40% and >40%.

To our knowledge, we present the most comprehensive comparative effectiveness analysis of metformin and sulfonylurea therapy among patients with HF and DM in U.S. clinical practice. In this regard, several strengths and novel features warrant mention. First, as compared with other clinical practice analyses limited to use of diagnoses codes alone, this analysis used patient-level clinical data (eg, vital signs, laboratories) from the GWTG-HF registry. Access to these patient-level data facilitates more accurate selection of patients eligible for treatment (eg, eGFR criteria), more comprehensive risk adjustment, and improved generalizability of findings through more detailed description of patient profile. Importantly, patient-level data included precise recording of EF (as compared with reliance on diagnoses codes for systolic or diastolic HF) and allowed for subgroup analyses defined by the clinically relevant EF cut-point of 40%. Second, although GWTG-HF involves voluntary hospital participation, prior studies have supported its national representativeness (13). Likewise, by virtue of its primary purpose for quality improvement, the registry does not require patient informed consent, thus circumventing this form of selection bias and supporting the registry's representation of routine clinical practice. Third, recognizing that observational studies are potentially subject to bias despite sophisticated statistical adjustment, this analysis included 3 falsification endpoints, none of which were significantly associated with metformin or sulfonylurea therapy. Fourth, this analysis assessed associated outcomes among new users of therapy, an approach that may strengthen causal inference by obviating potential prevalent user bias. Nonetheless, to augment statistical power, this incident user approach was coupled with sensitivity analyses among the larger cohort of patients who were either continuing or initiating therapy. Results of both approaches were overall concordant, suggesting reduced clinical risk with metformin and excess clinical risk with sulfonylurea, and thus further supporting the robustness of the present findings.

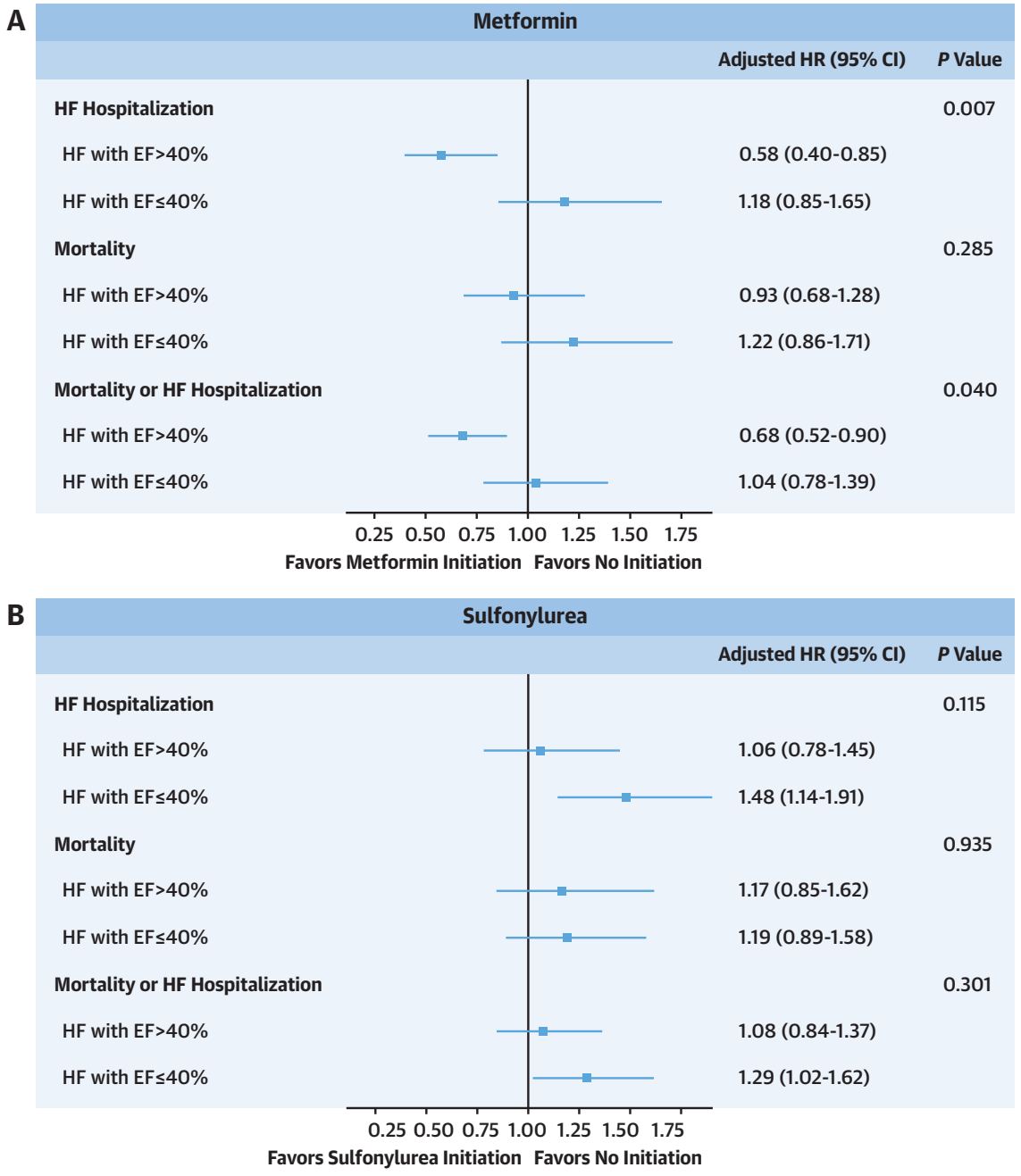
A post hoc analysis of the multinational SAVOR-TIMI 53 (Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications-Thrombolysis in Myocardial Infarction 53) trial of patients with type 2 DM found metformin to be independently associated with lower all-cause mortality, but noted this association only among patients without prior HF (14). Moreover, EF data were not available in that analysis, and thus the distribution of HFrEF versus HFpEF in the study population and associations with metformin within each EF phenotype could not be characterized (14). In this context, the current study among a large U.S. cohort with established HF offers new perspective, with metformin associated with meaningful

FIGURE 1 Cumulative Incidence of Mortality and Hospitalization Among Patients Initiated Versus Not Initiated on Metformin



Shown are Kaplan-Meier incidence curves of 12-month clinical outcomes. HF = heart failure.

CENTRAL ILLUSTRATION **Clinical Outcomes With Initiation of Metformin or Sulfonylurea Among Patients With Diabetes Mellitus and Heart Failure With Reduced Versus Preserved Ejection Fraction**



Khan, M.S. et al. J Am Coll Cardiol HF. 2022;10(3):198-210.

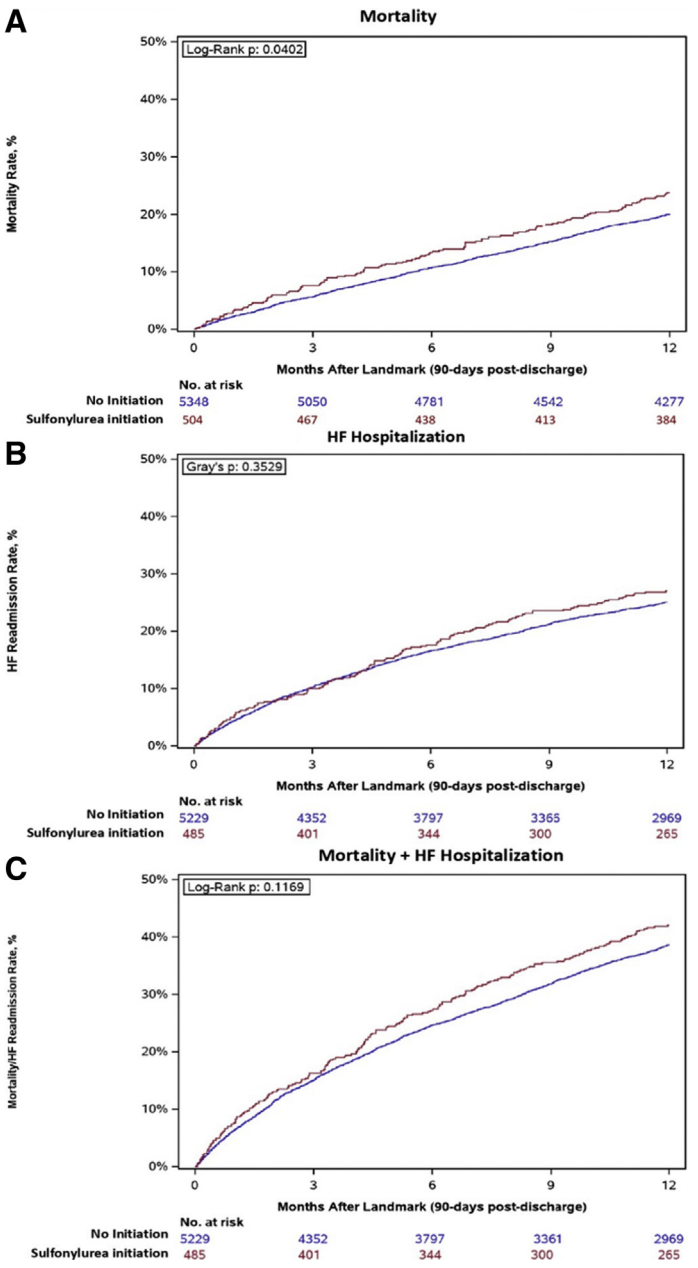
HRs and 95% CIs reflect risk of 12-month mortality and hospitalization for heart failure (HHF) endpoints with metformin **(A)** and sulfonylurea **(B)** initiation, stratified by EF ≤40% and EF >40%. EF = ejection fraction; HF = heart failure.

improvements in clinical outcomes. Likewise, the varying relationship between metformin initiation and clinical outcomes by EF phenotype warrants further consideration. Notably, these findings differ from an older study of patients with HF and DM receiving care from 1998 to 2001 where metformin was independently associated with reduced mortality and HF hospitalization, irrespective of EF (15). Yet, this same analysis also found thiazolidinediones associated with reduced mortality and did not include falsification endpoints, raising suspicion for residual confounding. More recently, an observational study by Richardson et al (16) from the Veterans Health Administration among patients with type 2 DM and CKD found metformin initiation associated with lower risk of HF hospitalization, compared with sulfonylurea, driven by findings among patients with HFrEF. However, given 88% of patients in the study by Richardson et al (16) did not have HF at baseline, those findings are most relevant to the primary prevention of HF, as compared with treatment of patients with DM and established HF in the current study. Specifically, the present analysis supports the need for future randomized clinical trials testing the effects of metformin therapy among patients with HFpEF and DM.

Understanding effectiveness of metformin in HFrEF has become increasingly important in the context of SGLT2 inhibitors becoming standard of care therapy for HFrEF (irrespective of type 2 DM status). At the same time, current American Diabetes Association guidelines still recommend metformin as the first-line pharmacological treatment for patients with type 2 DM, unless contraindicated or not tolerated (9). In a population most closely resembling the current study, the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) trial showed significant reductions in cardiovascular death and HF hospitalization with in-hospital or early postdischarge initiation of the dual SGLT1/SGLT2 inhibitor sotagliflozin among patients hospitalized for HF with type 2 DM, among which 48% were not receiving background metformin therapy (17). Thus, with data from SOLOIST-WHF and other outcome trials proving substantial clinical benefits with SGLT2 inhibitors, the lack of beneficial association with metformin among patients with HFrEF in the current study adds further support for prioritizing SGLT2 inhibitors before metformin as first-line therapy for type 2 DM in the setting of HFrEF.

Our findings regarding the higher risk of adverse outcomes associated with sulfonylurea prescription is consistent with other reports among patients with type 2 DM who were initiated on sulfonylureas who had higher risk of cardiovascular death and HF compared with similar patients who were initiated on metformin (18,19). The current data extend these findings to a high-risk older population of HF with reduced and preserved EF. These results are

FIGURE 2 Cumulative Incidence of Mortality and Hospitalization Among Patients Initiated Versus Not Initiated on Sulfonylurea



Shown are Kaplan-Meier incidence curves of 12-month clinical outcomes. HF = heart failure.

TABLE 4 Association Between Sulfonylurea Initiation and Study Endpoints at 12 Months

Study Endpoint	Cumulative Incidence, %		HR (95% CI); *P* Value	
	Sulfonylurea (n = 504)	No Sulfonylurea (n = 5,348)	Unadjusted	Adjusted[a]
Effectiveness endpoints				
All-cause mortality	23.8	20.1	1.22 (1.00-1.48); 0.045	1.24 (1.00-1.52); 0.045
HF hospitalization	27.1	25.1	1.11 (0.92-1.34); 0.27	1.22 (1.00-1.48); 0.050
All-cause mortality/HF hospitalization	42.1	38.7	1.12 (0.97-1.30); 0.12	1.17 (1.00-1.37); 0.047
Falsification (negative control) endpoints				
Urinary tract infection	2.1	2.8	0.78 (0.41-1.48); 0.45	0.96 (0.50-1.84); 0.89
Gastrointestinal bleed	3.0	2.3	1.34 (0.77-2.34); 0.31	1.29 (0.68-2.44); 0.44
Vaccination for influenza	11.0	10.6	1.07 (0.82-1.39); 0.64	1.19 (0.88-1.60); 0.25

Values are %, unless otherwise indicated. [a]Adjusted for 29 pre-specified covariates including demographics (age, sex, race), EF, vital signs and laboratories (discharge values for systolic blood pressure, heart rate, and eGFR), medical history (anemia, atrial fibrillation/flutter, ischemic HF etiology, stroke/transient ischemic attack, hypertension, hyperlipidemia, chronic obstructive pulmonary disease/asthma, peripheral vascular disease, chronic kidney disease, active smoking), HF therapies at time of discharge (ACE inhibitor/ARB, beta-blocker, mineralocorticoid receptor antagonist, implantable cardioverter-defibrillator, cardiac resynchronization therapy), socioeconomics (county-level education level, median county-level income), index hospital characteristics (US geographic region, teaching/non-teaching hospital status, number of hospital beds, urban/rural location), and time from index hospitalization discharge to metformin/sulfonylurea medication fill.

Abbreviations as in Tables 1 and 3.

especially relevant in the context of clinicians often choosing sulfonylureas as the initial choice of drug for patients with DM due to the lack of gastrointestinal side effects, ease of titration, low cost, and physician comfort level (8). In the setting of multiple antidiabetic therapies proven to have favorable (eg, SGLT2 inhibitors) or neutral effects on cardiovascular outcomes in both HF and type 2 DM populations, the suggestion of harm with sulfonylurea in the current study supports prioritizing use of alternative antidiabetic medications in patients with HF, if at all possible.

STUDY LIMITATIONS. Despite rigorous statistical adjustment with prespecified covariates, this observational study cannot definitively prove cause-effect relationships and residual and/or unmeasured confounding may remain. Second, this study was not structured to assess postdischarge adherence or persistence of metformin or sulfonylurea therapy, or the role of these factors in clinical outcomes. Thus, it is unclear whether patients initially filling prescriptions for metformin or sulfonylurea continued to have high exposure to the medication during follow-up. However, although adherence and persistence of therapy or the relative degree of downstream crossover between study groups are unknown, defining study group by initial exposure is most consistent with the "intention to treat" principle used in randomized clinical trials, where adherence to therapy is not considered in determination of efficacy. Although some degree of suboptimal persistence is likely for metformin, sulfonylurea, and other medications in clinical practice, the current study estimates the benefits/harms associated with metformin and sulfonylurea under the conditions of routine clinical practice. Third, although prior data suggest that patients with HF and mildly reduced EF 41% to 49% vs EF ≥50% may respond differently to medical therapies, sample size limitations prevented dedicated analysis of these separate EF subgroups in the current study. Fourth, covariate data were not entirely complete, and imputation was used, although rates of missing data were generally low. Fifth, this analysis excluded patients with severe CKD, and thus outcomes with metformin and sulfonylureas in such patients were not addressed. Lastly, this analysis was limited to Medicare beneficiaries age 65 years or older, and the degree to which these results generalize to younger patients with HF and DM is uncertain.

CONCLUSIONS

In this US cohort of older patients hospitalized for HF with DM, initiation of metformin therapy was associated with decreased 12-month mortality and HF hospitalization, driven by substantial associated benefits among patients with EF >40%. By contrast, sulfonylurea prescription was associated with excess risk of mortality and HF hospitalization regardless of EF. These findings support the potential use of metformin among patients with HFpEF and DM, and the need for confirmatory randomized clinical trials. In addition, in the context of multiple alternative antidiabetic medications being available with favorable or neutral effects on cardiovascular outcomes, these findings suggest that sulfonylureas may best be avoided among patients with HF and DM.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: These observational clinical practice data suggest that metformin therapy is a safe and potentially effective therapy for patients with adequate kidney function who have HF and DM, particularly among patients with EF >40%. By contrast, sulfonylurea therapy was associated with significant harm, irrespective of EF. In the context of multiple alternative antidiabetic therapies with favorable or neutral effects on cardiovascular outcomes, these data suggest that sulfonylurea therapy may best be avoided among patients with comorbid HF and DM.

TRANSLATIONAL OUTLOOK: These data support the need for confirmatory randomized clinical outcome trials to definitively assess the efficacy and safety of metformin as a therapy for patients with HFpEF and DM. With regard to sulfonylureas, given the frequent use of this therapy in clinical practice and the associated harms identified in the current study, future quality improvement initiatives may target deprescribing this therapy among patients with HF and DM, and replacement with an evidence-based therapy such as an SGLT2 inhibitor.

REFERENCES

1. Greene SJ, Vaduganathan M, Khan MS, et al. Prevalent and incident heart failure in cardiovascular outcome trials of patients with type 2 diabetes. *J Am Coll Cardiol*. 2018;71:1379–1390.

2. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366:1279–1289.

3. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet*. 2009;373:2125–2135.

4. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317–1326.

5. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.

6. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424.

7. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385(16):1451–1461. https://doi.org/10.1056/NEJMoa2107038

8. Vaduganathan M, Fonarow GC, Greene SJ, et al. Contemporary treatment patterns and clinical outcomes of comorbid diabetes mellitus and HFrEF: the CHAMP-HF registry. *J Am Coll Cardiol HF*. 2020;8:469–480.

9. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2021. *Diabetes Care*. 2021;44(suppl 1):S111-S124. https://doi.org/10.2337/dc21-S009

10. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41:255–323.

11. Hammill BG, Hernandez AF, Peterson ED, Fonarow GC, Schulman KA, Curtis LH. Linking inpatient clinical registry data to Medicare claims data using indirect identifiers. *Am Heart J*. 2009;157:995–1000.

12. Arnold BF, Ercumen A. Negative control outcomes: a tool to detect bias in randomized trials. *JAMA*. 2016;316:2597–2598.

13. Curtis LH, Greiner MA, Hammill BG, et al. Representativeness of a national heart failure quality-of-care registry: comparison of OPTIMIZE-HF and non-OPTIMIZE-HF Medicare patients. *Circ Cardiovasc Qual Outcomes*. 2009;2:377–384.

14. Bergmark BA, Bhatt DL, McGuire DK, et al. Metformin use and clinical outcomes among patients with diabetes mellitus with or without heart failure or kidney dysfunction: observations from the SAVOR-TIMI 53 trial. *Circulation*. 2019;140:1004–1014.

15. Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation*. 2005;111:583-590.

16. Richardson TL Jr, Hackstadt AJ, Hung AM, et al. Hospitalization for heart failure among patients with diabetes mellitus and reduced kidney function treated with metformin versus sulfonylureas: a retrospective cohort study. *J Am Heart Assoc*. 2021;10(8):e019211. https://doi.org/10.1161/JAHA.120.019211

17. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384:117-128.

18. Roumie CL, Min JY, D'Agostino McGowan L, et al. Comparative safety of sulfonylurea and metformin monotherapy on the risk of heart failure: a cohort study. *J Am Heart Assoc*. 2017;6(4):e005379. https://doi.org/10.1161/JAHA.116.005379

19. O'Brien MJ, Karam SL, Wallia A, et al. Association of second-line antidiabetic medications with cardiovascular events among insured adults with type 2 diabetes. *JAMA Netw Open*. 2018;1:e186125-e186125.

KEY WORDS diabetes, ejection fraction, heart failure, metformin, sulfonylurea

APPENDIX For supplemental figures and tables, please see the online version of this paper.