CLINICAL INVESTIGATIONS

Management of newly treated diabetes in Medicare beneficiaries with and without heart failure

Lauren B. Cooper^{1,2} | Xiaojuan Mi³ | Robert J. Mentz^{2,3} | Jennifer B. Green^{2,3} | Kevin J. Anstrom^{3,4} | Adrian F. Hernandez^{2,3} | Lesley H. Curtis^{2,3}

¹Inova Heart and Vascular Institute, Falls Church, Virginia

²Department of Medicine, Duke University School of Medicine, Durham, North Carolina

³Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina

⁴Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina

Corresponding Author: Lauren B. Cooper, MD, MHS, Inova Heart & Vascular Institute, 3300 Gallows Road, Falls Church, VA 22042 (lauren.cooper@inova.org).

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Background: Several diabetes mellitus (DM) therapies are associated with worse heart failure (HF) outcomes, yet limited data exist characterizing routine DM management based on HF status.

Hypothesis: DM medications prescribed for patients with HF will differ in meaningful ways from patients without HF, and co-morbidities will impact the choice of medications prescribed.

Methods: Using Medicare fee-for-service claims data, we identified patients with newly treated DM between 2008 and 2011 and used multivariable logistic regression to assess associations between baseline HF status and DM medication use. We used the cumulative incidence function to describe outcomes at 1 year by HF status and DM medication use.

Results: Of 35 603 patients with newly treated DM, 8965 (25.2%) had HF at baseline. Patients with HF had greater comorbidity, including renal dysfunction. After adjustment for baseline covariates, patients with HF had higher odds of initiation on insulin monotherapy (odds ratio: 1.72, 95% confidence interval: 1.59-1.87, $P < 0.001$) and lower odds of initiation on metformin (odds ratio: 0.66, 95% confidence interval: 0.62-0.71, $P < 0.001$) compared with patients without HF. Cumulative incidence of 1-year mortality was higher among patients with HF than among those without (22.4% vs 6.4%) and highest among those prescribed insulin.

Conclusions: Patients with HF were more likely to be initiated on insulin monotherapy than were patients without HF, who were more likely to be initiated on metformin. Studies of comparative effectiveness and safety are needed for DM treatment options in patients with comorbid HF.

KEYWORDS

Heart failure/cardiac transplantation/cardiomyopathy/myocarditis

1 | INTRODUCTION

The American Diabetes Association (ADA) recommends a stepped pharmacological treatment approach for the management of type 2 diabetes mellitus (T2DM), starting with metformin; then adding 1 additional agent—a sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, sodium-glucose transporter 2 (SGLT2) inhibitor, or insulin as needed to achieve glucose targets; then adding a third agent or more complex regimens if needed.¹ However, given known side effects and contraindications to different classes of medications, treatment strategies are routinely chosen and adjusted based on comorbid conditions. Specifically, for patients with heart failure (HF), thiazolidinediones are largely contraindicated and metformin should

be avoided in those with severe HF or significant renal dysfunction.²⁻⁴ Despite these guidelines, it is unknown how diabetes mellitus (DM) is routinely managed in the HF population and whether management or outcomes differ from patients without HF. Therefore, we used Medicare claims data to describe the treatments and explore outcomes of patients with newly treated DM based on HF status.

2 | METHODS

2.1 | Data sources

We used Medicare claims data for a nationally representative 5% sample of fee-for-service Medicare beneficiaries from January 1, 2007, through December 31, 2012. The data included inpatient

files for institutional claims associated with hospitalizations, outpatient files for institutional claims not associated with hospitalizations, and carrier files for noninstitutional claims.^{5,6} Medicare Part D files included information on prescription medications. Denominator files included demographic characteristics, information about Medicare eligibility and enrollment, and mortality.

2.2 | Study population

We identified Medicare fee-for-service beneficiaries who were age ≥ 65 years who had a diagnosis of T2DM as defined by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes 250.x0 or 250.x2 and who filled prescriptions for DM medications between January 1, 2008, and December 31, 2011. The index date was defined as the date of the first prescription claim for a DM medication. To establish the presence of comorbid conditions and prior medication use, we required patients to have ≥ 1 year of continuous enrollment in fee-for-service Medicare and Medicare Part D before the index date. To ensure that patients were newly treated, we required that patients had no DM medication claims in the year before the index date.

2.3 | Medications

DM medications of interest were identified in the Medicare Part D files by a search for generic drug names for the following classes of medications: insulin, biguanides (eg, metformin), sulfonylureas (eg, glipizide, glyburide, gliclazide, glimepiride), thiazolidinediones (eg, rosiglitazone, pioglitazone), DPP-4 inhibitors (eg, sitagliptin, saxagliptin, linagliptin, alogliptin), and GLP-1 antagonists (eg, exenatide, liraglutide, albiglutide, taspoglutide). We excluded SGLT2 inhibitors from the analysis due to the limited use of these drugs during the period of interest. If multiple medications were initiated, each medication was counted individually; and for combination medications, each component was counted separately. Insulin was counted in 2 ways, as insulin monotherapy or insulin in combination with another therapy.

2.4 | Outcomes

The outcomes of interest were mortality, all-cause hospitalization, and HF hospitalization at 1 year after initiation of treatment for DM. We determined all-cause mortality based on death dates in Medicare denominator files, all-cause hospitalization based on the earliest admission date from subsequent inpatient claims, and HF hospitalization based on claims with a primary diagnosis of HF. We calculated time to admission as days from the index date to the subsequent admission date. We excluded hospitalizations for rehabilitation.

2.5 | Covariates

We obtained data on demographic characteristics, including age, sex, and race, from the Medicare summary files, and data on comorbid conditions from claims in the year before the index date. We identified HF hospitalizations from inpatient claims with a primary

diagnosis of HF. We grouped chronic kidney disease (CKD) as none, stage 1 to 4, and stage 5 or end-stage renal disease. To identify other comorbid conditions, including the prevalence of HF, we used the definitions provided by Birman-Deych et al⁷ and Quan et al,⁸ which are based on ICD-9-CM diagnosis codes in any position on inpatient, outpatient, or carrier claims. We included both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). To identify prior medication use—including statins, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), β -blockers, mineralocorticoid receptor antagonists (MRAs), and loop diuretics—we searched for the generic names of these medications on Medicare Part D claims for the 6 months before the index date.

2.6 | Statistical analysis

We summarized baseline characteristics and prior medications prescribed for the study population by prevalence of HF, using frequencies with percentages for categorical variables and medians with interquartile ranges for continuous variables. We tested for differences between groups using χ^2 tests for categorical variables and Kruskal-Wallis tests for continuous variables.

We used multivariable logistic regression analysis to assess associations between baseline characteristics and each DM medication initiation among newly treated patients with DM, and among newly treated patients with DM and CKD. We used a 2-tailed α of 0.05 to establish statistical significance and report 95% confidence intervals (CIs).

We describe observed outcomes by groups based on medication use. Due to small numbers, we excluded GLP-1 inhibitors in the outcomes analyses. For mortality, we calculated cumulative incidence based on Kaplan-Meier estimates and evaluated differences between groups using log-rank tests. For all hospitalization outcomes and incident HF, we calculated incidence based on estimates from the cumulative incidence function, which accounts for the competing risk of mortality, and evaluated differences between medication groups using Gray tests.

We used SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) for all analyses. The institutional review board of the Duke University Health System approved the study.

3 | RESULTS

Of 35 603 Medicare beneficiaries with newly treated T2DM, 8965 (25.2%) had HF. In the overall population, 37.9% were men, 79.4% were white, and the median age was 73 years (Table 1). The group of patients with HF was older, with a median age of 78 years. The HF group had greater comorbidity, especially with respect to atrial fibrillation, ischemic heart disease, and CKD. Among patients with HF, 12.4% had been hospitalized in the previous 6 months.

Compared with patients without HF, patients with HF were more frequently initiated on insulin monotherapy (31.7% vs 10.6%) and less frequently initiated on metformin (37.4% vs 66.4%; Table 2). Despite

TABLE 1 Baseline characteristics of patients with newly treated T2DM by prevalence of HF

Characteristic	No HF, n = 26 638	HF, n = 8965	P Value
Median age, y	73.0 (69.0–80.0)	78.0 (72.0–85.0)	<0.001
Age group, y			<0.001
66–69	7505 (28.2)	1408 (15.7)	
70–74	7170 (26.9)	1712 (19.1)	
75–79	5271 (19.8)	1798 (20.1)	
≥80	6692 (25.1)	4047 (45.1)	
Male sex	10 077 (37.8)	3399 (37.9)	0.89
Race			<0.001
Black	2636 (9.9)	1124 (12.5)	
White	21 151 (79.4)	7130 (79.5)	
Other/unknown	2851 (10.7)	711 (7.9)	
Comorbid conditions			
AF	2595 (9.7)	3775 (42.1)	<0.001
COPD	6491 (24.4)	5132 (57.2)	<0.001
Hyperlipidemia	20 420 (76.7)	6562 (73.2)	<0.001
HTN	23 035 (86.5)	8528 (95.1)	<0.001
Ischemic heart disease	7828 (29.4)	6183 (69.0)	<0.001
OSA	1404 (5.3)	1003 (11.2)	<0.001
PVD	5189 (19.5)	3851 (43.0)	<0.001
Renal function			<0.001
No CKD	24 736 (92.9)	6626 (73.9)	
Stages 1–4	1482 (5.6)	1665 (18.6)	
Stage 5 or ESRD	420 (1.6)	674 (7.5)	
Stroke/TIA	3421 (12.8)	2689 (30.0)	<0.001
HF hospitalizations in the past year			<0.001
0	26 638 (100)	7855 (87.6)	
1	0	866 (9.7)	
2	0	168 (1.9)	
≥3	0	76 (0.8)	
Medications 6 months before the index date			
ACEI/ARB	14 348 (53.9)	5138 (57.3)	<0.001
β-Blocker	10 477 (39.3)	5593 (62.4)	<0.001
Loop diuretic	3386 (12.7)	5253 (58.6)	<0.001
MRA	458 (1.7)	875 (9.8)	<0.001
Statin	14 120 (53.0)	4721 (52.7)	0.57

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HF, heart failure; HTN, hypertension; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; OSA, obstructive sleep apnea; PVD, peripheral vascular disease; T2DM, type 2 diabetes mellitus; TIA, transient ischemic attack.

Data are presented as n (%) or median (IQR).

contraindications, 3.7% of HF patients were prescribed a thiazolidinedione.

Patients age ≥70 years had higher odds of being initiated on a sulfonylurea or DPP-4 inhibitor and lower odds of being initiated on metformin compared with patients age <70 years (Table 3). Compared with white patients, black patients had higher odds of being initiated on insulin monotherapy or combination therapy and lower odds of being initiated on metformin. The odds of insulin monotherapy initiation were higher for patients with cardiovascular comorbidities such as atrial fibrillation, ischemic heart disease, peripheral vascular disease, and cerebrovascular disease. Compared with patients without HF, patients with HF had higher odds of being initiated on insulin

monotherapy (odds ratio [OR]: 1.72, 95% CI: 1.59–1.87) and lower odds of being initiated on metformin (OR: 0.66, 95% CI: 0.62–0.71). In addition to lower odds of metformin initiation (OR: 0.75, 95% CI: 0.63–0.90), patients with a prior HF hospitalization also had lower odds of being initiated on a DPP-4 inhibitor (OR: 0.69, 95% CI: 0.48–0.99), compared with patients without prior HF hospitalizations.

Patients with renal insufficiency had higher odds of being on insulin monotherapy, sulfonylureas, thiazolidinediones, or DPP-4 inhibitors and lower odds of being on metformin compared with patients without CKD. In the subgroup analysis of patients with CKD, the odds of being initiated on insulin monotherapy were 51% higher for patients with concomitant HF compared with patients without HF

TABLE 2 Medications prescribed at baseline among patients with newly treated T2DM by HF status

Medication	No HF, n = 26 638	HF, n = 8965	P Value
Insulin	2824 (10.6)	2846 (31.7)	<0.001
Insulin plus other	290 (1.1)	169 (1.9)	<0.001
Metformin	17 700 (66.4)	3356 (37.4)	<0.001
Sulfonylureas ¹	5704 (21.4)	2496 (27.8)	<0.001
Thiazolidinediones ²	1350 (5.1)	331 (3.7)	<0.001
DPP-4 inhibitors ³	1005 (3.8)	431 (4.8)	<0.001
GLP-1 inhibitors ⁴	48 (0.2)	15 (0.2)	0.80

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HF, heart failure; T2DM, type 2 diabetes mellitus.

Data are presented as n (%).

¹ Sulfonylureas include glipizide, glyburide, gliclazide, and glimepiride.

² Thiazolidinediones include rosiglitazone and pioglitazone.

³ DPP-4 inhibitors include sitagliptin, saxagliptin, linagliptin, and alogliptin.

⁴ GLP-1 inhibitors include exenatide, liraglutide, albiglutide, taspoglutide, and lixisenatide.

(OR: 1.51, 95% CI: 1.29-1.78; see Supporting Information, Table 1, in the online version of this article).

Over 1 year of follow-up, compared with the non-HF group, the HF group had a higher cumulative incidence of mortality (22.4% vs 6.4%; $P < 0.001$), all-cause hospitalization (51.3% vs 24.4%; $P < 0.001$), and HF hospitalization (8.5% vs 0.9%; $P < 0.001$). Notably, in the group of patients without baseline HF, almost 1% of patients were hospitalized for HF at 1 year.

For patients with a history of HF, those prescribed insulin had a higher cumulative incidence of death and all-cause hospitalization compared with those prescribed a sulfonylurea, thiazolidinedione, DPP-4 inhibitor, or metformin (Figure 1). Those prescribed metformin had the lowest cumulative incidence of mortality, HF hospitalization, and all-cause hospitalization at 1 year. For patients without a history of HF, those prescribed insulin had the highest cumulative incidence of HF during the year following initiation of DM medications, whereas those prescribed thiazolidinediones or metformin had the lowest cumulative incidence (Figure 2).

TABLE 3 Associations between selected baseline characteristics and medication initiation among patients with newly treated T2DM (N = 35 603)

Characteristic	Insulin		Insulin Combination		Metformin	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
HF	1.72 (1.59-1.87)	<0.001	1.20 (0.93-1.54)	0.16	0.66 (0.62-0.71)	<0.001
HF hospitalizations						
0	1.00 [Ref]		1.00 [Ref]		1.00 [Ref]	
1	1.06 (0.90-1.25)	0.47	0.70 (0.40-1.23)	0.22	0.75 (0.63-0.90)	<0.001
2	1.01 (0.72-1.42)	0.96	0.24 (0.03-1.73)	0.16	0.79 (0.53-1.18)	0.25
≥3	1.01 (0.62-1.65)	0.98	1.07 (0.26-4.49)	0.92	0.53 (0.26-1.06)	0.07
Comorbid conditions						
CKD						
None	1.00 [Ref]		1.00 [Ref]		1.00 [Ref]	
Stages 1-4	2.02 (1.84-2.21)	<0.001	1.24 (0.92-1.66)	0.15	0.32 (0.29-0.35)	<0.001
Stage 5 or ESRD	4.42 (3.84-5.09)	<0.001	1.20 (0.77-1.88)	0.42	0.11 (0.09-0.14)	<0.001
HTN	1.08 (0.97-1.22)	0.17	0.83 (0.61-1.13)	0.24	0.87 (0.80-0.94)	<0.001
Hyperlipidemia	0.49 (0.46-0.53)	<0.001	0.62 (0.50-0.77)	<0.001	1.40 (1.32-1.48)	<0.001
AF	1.24 (1.15-1.35)	<0.001	1.18 (0.92-1.50)	0.19	0.85 (0.79-0.90)	<0.001
COPD	1.52 (1.42-1.63)	<0.001	1.24 (1.01-1.52)	0.04	0.82 (0.78-0.86)	<0.001
OSA	0.85 (0.75-0.96)	0.01	0.96 (0.66-1.38)	0.81	1.28 (1.16-1.41)	<0.001
Ischemic heart disease	1.36 (1.26-1.46)	<0.001	1.16 (0.93-1.44)	0.20	0.78 (0.74-0.83)	<0.001
PVD	1.62 (1.51-1.74)	<0.001	0.99 (0.80-1.23)	0.96	0.79 (0.74-0.83)	<0.001
Stroke/TIA	2.45 (2.28-2.63)	<0.001	1.87 (1.50-2.32)	<0.001	0.62 (0.58-0.66)	<0.001
Age group, y						
66-69	1.00 [Ref]		1.00 [Ref]		1.00 [Ref]	
70-74	0.93 (0.84-1.03)	0.17	0.80 (0.61-1.04)	0.10	0.87 (0.81-0.93)	<0.001
75-79	0.99 (0.90-1.10)	0.91	0.72 (0.54-0.96)	0.03	0.69 (0.64-0.74)	<0.001
≥80	1.41 (1.28-1.54)	<0.001	0.81 (0.63-1.05)	0.12	0.41 (0.39-0.44)	<0.001
Male sex	0.99 (0.92-1.06)	0.69	1.01 (0.83-1.23)	0.90	0.92 (0.88-0.97)	0.001
Race						
Black	2.10 (1.91-2.29)	<0.001	1.82 (1.41-2.33)	<0.001	0.65 (0.60-0.70)	<0.001
White	1.00 [Ref]		1.00 [Ref]		1.00 [Ref]	
Other	1.09 (0.97-1.21)	0.14	1.50 (1.12-2.01)	0.01	0.95 (0.88-1.03)	0.22
Medications						
ACEI/ARB	0.74 (0.69-0.79)	<0.001	1.12 (0.92-1.37)	0.24	1.22 (1.17-1.29)	<0.001

TABLE 3 Continued

Characteristic	Insulin		Insulin Combination		Metformin	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
β-Blocker	0.83 (0.77-0.89)	<0.001	0.80 (0.65-0.98)	0.03	1.10 (1.04-1.15)	<0.001
MRA	0.87 (0.75-1.01)	0.06	1.19 (0.78-1.82)	0.41	0.97 (0.85-1.10)	0.61
Loop diuretic	1.25 (1.15-1.35)	<0.001	1.28 (1.02-1.62)	0.03	0.74 (0.69-0.78)	<0.001
Statin	0.77 (0.72-0.83)	<0.001	0.97 (0.79-1.20)	0.80	1.32 (1.26-1.39)	<0.001

Characteristic	Sulfonylurea		Thiazolidinedione		DPP-4	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
HF	1.05 (0.98-1.13)	0.16	0.86 (0.74-1.01)	0.06	1.04 (0.89-1.20)	0.64
HF hospitalizations						
0	1.00 [Ref]		1.00 [Ref]		1.00 [Ref]	
1	1.14 (0.98-1.33)	0.09	0.69 (0.44-1.07)	0.10	0.69 (0.48-0.99)	0.04
2	1.13 (0.81-1.58)	0.46	0.30 (0.07-1.21)	0.09	0.51 (0.22-1.17)	0.11
≥3	1.52 (0.95-2.43)	0.08	0.68 (0.17-2.82)	0.60	0.72 (0.26-1.99)	0.52
Comorbid conditions						
CKD						
None	1.00 [Ref]		1.00 [Ref]		1.00 [Ref]	
Stages 1–4	1.50 (1.38-1.63)	<0.001	1.27 (1.07-1.52)	0.01	1.61 (1.37-1.90)	<0.001
Stage 5 or ESRD	1.24 (1.07-1.42)	0.003	1.36 (1.03-1.80)	0.03	1.35 (1.02-1.79)	0.03
HTN	0.99 (0.91-1.08)	0.88	0.93 (0.79-1.10)	0.40	0.98 (0.80-1.19)	0.82
Hyperlipidemia	0.90 (0.84-0.96)	<0.001	1.37 (1.20-1.56)	<0.001	1.53 (1.32-1.78)	<0.001
AF	0.99 (0.92-1.06)	0.82	0.83 (0.71-0.97)	0.02	1.22 (1.06-1.41)	0.01
COPD	0.96 (0.91-1.02)	0.15	1.00 (0.90-1.13)	0.94	1.01 (0.90-1.14)	0.82
OSA	0.84 (0.75-0.93)	<0.001	0.88 (0.71-1.10)	0.27	1.22 (1.00-1.49)	0.05
Ischemic heart disease	1.07 (1.01-1.14)	0.02	1.05 (0.93-1.18)	0.41	1.12 (0.99-1.27)	0.08
PVD	0.85 (0.80-0.90)	<0.001	1.08 (0.95-1.21)	0.25	1.22 (1.08-1.38)	<0.001
Stroke/TIA	0.88 (0.82-0.95)	<0.001	0.94 (0.82-1.09)	0.42	0.96 (0.84-1.11)	0.62
Age group, y						
66–69	1.00 [Ref]		1.00 [Ref]		1.00 [Ref]	
70–74	1.16 (1.08-1.25)	<0.001	0.89 (0.78-1.03)	0.11	1.09 (0.93-1.28)	0.31
75–79	1.40 (1.30-1.52)	<0.001	1.03 (0.89-1.19)	0.72	1.26 (1.07-1.48)	0.01
≥80	1.81 (1.68-1.95)	<0.001	1.07 (0.93-1.23)	0.36	1.35 (1.15-1.58)	<0.001
Male sex	1.23 (1.17-1.30)	<0.001	1.10 (0.99-1.22)	0.07	0.95 (0.85-1.06)	0.36
Race						
Black	1.13 (1.04-1.23)	0.004	1.01 (0.85-1.20)	0.89	0.90 (0.75-1.09)	0.27
White	1.00 [Ref]		1.00 [Ref]		1.00 [Ref]	
Other	1.06 (0.98-1.16)	0.16	1.79 (1.56-2.05)	<0.001	1.46 (1.24-1.71)	<0.001
Medications						
ACEI/ARB	0.97 (0.92-1.03)	0.32	1.11 (1.00-1.23)	0.05	1.12 (1.00-1.25)	0.05
β-Blocker	1.03 (0.97-1.08)	0.35	0.79 (0.71-0.88)	<0.001	1.04 (0.93-1.17)	0.49
MRA	1.19 (1.05-1.35)	0.01	1.04 (0.77-1.40)	0.79	1.21 (0.93-1.56)	0.16
Loop diuretic	1.33 (1.24-1.42)	<0.001	0.81 (0.70-0.94)	0.01	0.88 (0.76-1.01)	0.07
Statin	0.86 (0.82-0.91)	<0.001	0.78 (0.71-0.87)	<0.001	1.00 (0.89-1.12)	0.99

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4; ESRD, end-stage renal disease; HF, heart failure; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; OSA, obstructive sleep apnea; PVD, peripheral vascular disease; Ref, reference; T2DM, type 2 diabetes mellitus; TIA, transient ischemic attack.

4 | DISCUSSION

In this study, we found that newly treated DM is managed differently for patients with and without concomitant HF. A majority of patients without HF were initiated on metformin, consistent with guideline

recommendations.¹ However, patients with HF had significantly lower rates of metformin initiation, though the guidelines state that metformin may be used in patients with stable HF and normal renal function. The group of patients with HF had higher rates of initiation of therapy with insulin monotherapy, a sulfonylurea, or a DPP-4

FIGURE 1 Cumulative incidence of (A) mortality, (B) all-cause hospitalization, and (C) HF hospitalization among patients with a history of HF ($n = 8965$; $P < 0.001$). Abbreviations: DPP-4, dipeptidyl peptidase-4; HF, heart failure.

inhibitor. Patients with other cardiovascular comorbid conditions and renal insufficiency were also more likely to be initiated on insulin monotherapy compared with patients without these conditions. Given concerns about adverse events and contraindications to metformin and thiazolidinediones in some patients with HF, it is not

FIGURE 2 Cumulative incidence of HF among patients without a history of HF ($n = 26\,638$; $P < 0.001$). Abbreviations: DPP-4, dipeptidyl peptidase-4; HF, heart failure.

surprising that alternative agents are used more frequently as the initial DM medication for patients with HF compared with patients without HF.

Practice patterns of DM medication use in HF patients have shifted over time, likely due to data supporting the safety and efficacy of metformin in patients with stable HF, and risk of HF and edema with thiazolidinediones.^{9–14} Black-box warnings for these drugs have been modified accordingly. The original black-box warning for metformin stated it was absolutely contraindicated in HF patients due to the risk of lactic acidosis, but it has since been modified such that now the warning is only for patients with acute or unstable HF or with additional comorbid conditions, including CKD.¹⁵ Although HF was not a known side effect of thiazolidinediones when they were first approved, a black-box warning has since been added indicating that they are contraindicated in patients with symptomatic or New York Heart Association class III or IV HF.^{16,17}

Previous studies compared DM medication use in patients with and without HF. In a study of Medicare beneficiaries from 2000 to 2001, only 11.2% of patients received metformin at the time of discharge from a HF hospitalization, whereas 16.1% of patients received a thiazolidinedione.¹⁸ In our contemporary study of patients with newly treated DM, patients with chronic HF had higher rates of metformin use and lower rates of thiazolidinedione use compared with prior studies.

Our findings are consistent with current recommendations, as patients with a prior HF hospitalization—suggesting more severe or unstable symptoms—had lower odds of being initiated on metformin. Furthermore, among patients with renal insufficiency, those with HF were less likely to be initiated on metformin compared with those without HF. Thus, it appears that providers are following guidelines with respect to the use of antihyperglycemic agents in patients with severe HF and HF with concomitant renal insufficiency. Patients with a prior HF hospitalization and those with CKD and HF were also less likely to be initiated on a DPP-4 inhibitor. This finding may reflect avoidance of relatively new drugs for unstable or complex patients, due to less familiarity with the newer agents.

Our study showed a higher incidence of mortality, all-cause hospitalization, and HF hospitalization in patients with HF compared with patients without HF. For patients without a history of HF, the cumulative incidence of HF hospitalization was 0.9% at 1 year, consistent with previous reports.¹⁹

For patients with a history of HF, those initiated on insulin had a higher incidence of both mortality and all-cause hospitalizations, compared with those initiated on metformin, sulfonylureas, thiazolidinediones, or DPP-4 inhibitors. Specifically, those initiated on metformin had the lowest incidence of 1-year mortality and all-cause hospitalization. This finding may suggest that patients with significant comorbid conditions, more severe DM, or other high-risk characteristics were more likely to be initiated on insulin rather than other medications. However, metformin therapy has been associated with lower mortality and fewer hospitalizations in HF patients with both new-onset and established DM.^{14,20–22}

For patients with prior HF, the incidence of HF hospitalization was lowest in the metformin group and highest in the sulfonylurea group. This finding may reflect that patients with more severe HF have fewer DM medication options, and thus the sickest patients may have been on a sulfonylurea as compared with other medications.

In the first year after starting treatment for DM, some patients without a history of HF developed HF. Previous research has reported the incidence of HF in a Medicare population as 12.6 per 100 person-years.²³ We found that patients treated with insulin had the highest incidence of incident HF, and those on metformin had the lowest incidence.

4.1 | Study limitations

Our study has limitations. The population was limited to Medicare fee-for-service beneficiaries, and the results may not be generalizable to other populations. Furthermore, 2012 is the most recent year for which Medicare claims data were available, so our data may not represent current patterns of medication use. In addition, there are several limitations inherent in the use of Medicare claims data. Because we did not have measurements of ejection fraction or functional data, we were unable to ascertain the type or severity of HF. We used the number of prior HF hospitalizations as a marker of disease severity. Similarly, we did not have glycated hemoglobin values and thus were unable to examine medication use by degree of glycemic control. The lack of detailed clinical information in claims-only data prevented the use of propensity methodology for comparison groups. Because we used prescription claims, we were only able to tell if a medication was filled and were unable to tell if the medication was taken as prescribed. In addition, we were unable to capture whether a medication was prescribed but never filled, though previous studies found an 85% to 89% prescription fill rate for newly treated DM.^{24,25}

5 | CONCLUSION

Certain antidiabetic medications are contraindicated or should be used with caution in HF patients due to increased risk of adverse

effects. In this retrospective study, newly treated DM was treated differently in patients with HF compared with patients without HF; however, some patients were initiated on contraindicated medications. Patients with HF who were initiated on metformin had a lower incidence of morbidity and mortality than patients initiated on other antidiabetic medications.

The results of this study should prompt further study in this area. Certainly, when more contemporary data are available, descriptions of the changes in practice patterns with novel DM medications in patients with HF would be valuable. Furthermore, given the wide variation in DM medication use among patients with HF, studies of comparative effectiveness and safety are urgently needed.

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Conflicts of interest

Dr. Mentz has received research support from Amgen, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Novartis, Otsuka, and ResMed; honoraria from HeartWare, Janssen, Luitpold Pharmaceuticals, Novartis, ResMed, and Thoratec; and has served on an advisory board for Luitpold Pharmaceuticals. Dr. Green has received research support from AstraZeneca, GlaxoSmithKline, Janssen, and Merck, and has served as a consultant to Boehringer Ingelheim and Merck. Dr. Anstrom has received research support from Bayer and Merck. Dr. Hernandez has received research support from the American Heart Association, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Merck, and Portola; and has served as a consultant or scientific advisor to Amgen, AstraZeneca, Bayer, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, MyoKardia, Novartis, Ortho McNeil-Janssen, Pfizer, Pluristem, and Sensible. Dr. Curtis has received research support from Gilead, GlaxoSmithKline, and Novartis; and has served on an advisory board for Amgen.

REFERENCES

- Standards of medical care in diabetes—2015: summary of revisions. *Diabetes Care*. 2015;38(suppl):S4.
- Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14–S80.
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140–149.
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [published correction appears in *Diabetes Care*. 2012;36:490]. *Diabetes Care*. 2012;35:1364–1379.
- Eapen ZJ, Hammill BG, Setoguchi S, et al. Who enrolls in the Medicare Part D prescription drug benefit program? Medication use among patients with heart failure. *J Am Heart Assoc*. 2013;2:e000242.

6. Piccini JP, Mi X, DeWald TA, et al. Pharmacotherapy in Medicare beneficiaries with atrial fibrillation. *Heart Rhythm*. 2012;9:1403–1408.
7. Birman-Deych E, Waterman AD, Yan Y, et al. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. *Med Care*. 2005;43:480–485.
8. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43:1130–1139.
9. Masoudi FA, Inzucchi SE, Wang Y, et al. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation*. 2005;111:583–590.
10. Dargie HJ, Hildebrandt PR, Riegger GA, et al. A randomized, placebo-controlled trial assessing the effects of rosiglitazone on echocardiographic function and cardiac status in type 2 diabetic patients with New York Heart Association functional class I or II heart failure. *J Am Coll Cardiol*. 2007;49:1696–1704.
11. Delea TE, Edelsberg JS, Hagiwara M, et al. Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. *Diabetes Care*. 2003;26:2983–2989.
12. Singh S, Loke YK, Furberg CD. Thiazolidinediones and heart failure: a teleo-analysis. *Diabetes Care*. 2007;30:2148–2153.
13. Home PD, Pocock SJ, Beck-Nielsen H, et al; RECORD Study Team. 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.
14. Eurich DT, Weir DL, Majumdar SR, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34 000 patients. *Circ Heart Fail*. 2013;6:395–402.
15. Glucophage [package insert]. Princeton, NJ: Bristol-Myers Squibb Company, 2015. http://packageinserts.bms.com/pi/pi_glucophage_xr.pdf. Accessed August 18, 2016.
16. Avandia [package insert]. Research Triangle Park, NC: GlaxoSmithKline, 2014. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Avandia/pdf/AVANDIA-PI-MG.PDF. Accessed August 18, 2016.
17. Actos [package insert]. Deerfield, IL: Takeda Pharmaceutical America, Inc., 2011. <http://general.takedapharm.com/content/file.aspx?filetypecode=actospi&cacheRandomizer=dcd4900e-c015-4c18-867b-d3a0080be477>. Accessed August 18, 2016.
18. Masoudi FA, Wang Y, Inzucchi SE, et al. Metformin and thiazolidinedione use in Medicare patients with heart failure. *JAMA*. 2003;290:81–85.
19. Vaur L, Gueret P, Lievre M, et al; DIABHYCAR Study Group. Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the DIABHYCAR (type 2 Diabetes, Hypertension, Cardiovascular Events and Ramipril) study [published correction appears in *Diabetes Care*. 2003;26:2489]. *Diabetes Care*. 2003;26:855–860.
20. Romero SP, Andrey JL, Garcia-Egido A, et al. Metformin therapy and prognosis of patients with heart failure and new-onset diabetes mellitus: a propensity-matched study in the community. *Int J Cardiol*. 2013;166:404–412.
21. Aguilar D, Chan W, Bozkurt B, et al. Metformin use and mortality in ambulatory patients with diabetes and heart failure. *Circ Heart Fail*. 2011;4:53–58.
22. Eurich DT, Majumdar SR, McAlister FA, et al. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. *Diabetes Care*. 2005;28:2345–2351.
23. Bertoni AG, Hundley WG, Massing MW, et al. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care*. 2004;27:699–703.
24. Center for Drug Evaluation and Research, US Food and Drug Administration. *Guidance for Industry: Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. Silver Spring, MD: US Department of Health and Human Services; December 2008.
25. McMurray JJ, Gerstein HC, Holman RR, et al. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. *Lancet Diabetes Endocrinol*. 2014;2:843–851.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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