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ORIGINAL RESEARCH

Hospitalization for Heart Failure Among Patients With Diabetes Mellitus and Reduced Kidney Function Treated With Metformin Versus Sulfonylureas: A Retrospective Cohort Study

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BACKGROUND: Metformin and sulfonylurea are commonly prescribed oral medications for type 2 diabetes mellitus. The association of metformin and sulfonylureas on heart failure outcomes in patients with reduced estimated glomerular filtration rate remains poorly understood.

METHODS AND RESULTS: This retrospective cohort combined data from National Veterans Health Administration, Medicare, Medicaid, and the National Death Index. New users of metformin or sulfonylurea who reached an estimated glomerular filtration rate of 60 mL/min per 1.73 m^2 or serum creatinine of 1.5 mg/dL and continued metformin or sulfonylurea were included. The primary outcome was hospitalization for heart failure. Echocardiogram reports were obtained to determine each patient's ejection fraction (EF) (reduced EF <40%; midrange EF 40%–49%; ≥50%). The primary analysis estimated the cause-specific hazard ratios for metformin versus sulfonylurea and estimated the cumulative incidence functions for heart failure hospitalization and competing events. The weighted cohort included 24 685 metformin users and 24 805 sulfonylurea users with reduced kidney function (median age 70 years, estimated glomerular filtration rate 55.8 mL/min per 1.73 m^2). The prevalence of underlying heart failure (12.1%) and cardiovascular disease (31.7%) was similar between groups. There were 16.9 (95% CI, 15.8–18.1) versus 20.7 (95% CI, 19.5–22.0) heart failure hospitalizations per 1000 person-years for metformin and sulfonylurea users, respectively, yielding a cause-specific hazard of 0.85 (95% CI, 0.78–0.93). Among heart failure hospitalizations, 44.5% did not have echocardiogram information available; 29.3% were categorized as reduced EF, 8.9% as midrange EF, and 17.2% as preserved EF. Heart failure hospitalization with reduced EF (hazard ratio, 0.79; 95% CI, 0.67–0.93) and unknown EF (hazard ratio, 0.84; 95% CI 0.74–96) were significantly lower in metformin versus sulfonylurea users.

CONCLUSIONS: Among patients with type 2 diabetes mellitus who developed worsening kidney function, persistent metformin compared with sulfonylurea use was associated with reduced heart failure hospitalization.

Key Words: chronic kidney disease ■ heart failure hospitalization ■ type 2 diabetes mellitus

More healthcare resources are spent on diabetes mellitus than any other medical condition in the United States.[1] In 2015, the Centers for Disease Control and Prevention noted that about 9.4% of the population, including >30 million Americans, were living with type 2 diabetes mellitus (T2D).[2,3] Patients with T2D often develop secondary complications, including impaired kidney function

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CLINICAL PERSPECTIVE

What Is New?

- Persistent use of metformin after kidney function decline is associated with reduced risk of heart failure hospitalizations compared with sulfonylurea drugs.
- The reduced risk of heart failure hospitalization was statistically significant in those hospitalized with reduced ejection fraction and unknown ejection fraction.

What Are the Clinical Implications?

- This study adds evidence to the growing body of literature demonstrating metformin's association with beneficial cardiovascular effects compared with sulfonylurea in patients with mild to moderate renal dysfunction.

Nonstandard Abbreviations and Acronyms

T2D	type 2 diabetes mellitus
VHA	Veterans Health Administration

and heart failure. Heart failure is the most common cause of hospitalization among veterans and patients with Medicare. Furthermore, a diagnosis of T2D is associated with a 33% increase in the odds of a hospitalization for heart failure.[4,5]

Among veterans, metformin and sulfonylureas remain the most commonly used oral medications for T2D, even as kidney function declines.[6] However, limited data about heart failure outcomes exist for these older medications, particularly among those patients with reduced kidney function. Metformin and sulfonylureas exert their glucose lowering effects via distinct mechanisms; metformin improves insulin sensitivity and is typically weight neutral, whereas the sulfonylurea class increases endogenous insulin secretion. Hyperinsulinemia exerts many end-organ and systemic effects, including weight gain and fluid retention. Physiologically, these changes in hemodynamics can lead to or worsen hypertensive heart disease, left ventricular hypertrophy, and subsequent remodeling, thus increasing the risk of decompensated heart failure.[7]

Before 2016, metformin was restricted for patients with serum creatinine levels ≥1.5 mg/dL in men and ≥1.4 mg/dL in women. In 2016, the Food and Drug Administration changed its guidance and now recommends that metformin can be used in patients with mild to moderate kidney disease, until a patient reaches an estimated glomerular filtration rate (eGFR) of 30 mL/min per 1.73 m^2.[8] Because of the recommendations to reduce the use of metformin for those with diabetes mellitus and reduced kidney function, there is limited understanding of the impact of metformin on heart failure outcomes among this high-risk group. Our aim was to test the hypothesis that among patients with T2D who developed reduced kidney function, the risk of heart failure hospitalizations would be lower among patients who persisted on metformin versus sulfonylureas.

METHODS

Statement of Research Reproducibility

The protocol, statistical code, and deidentified and anonymized data sets are available from Dr Roumie with a written request per the Transparency and Openness Promotion Guidelines.

Study Design and Data Sources

We assembled a retrospective cohort of Veterans Health Administration (VHA) patients.[6] Pharmacy data included medication dispensed, date filled, days supplied, and number of pills dispensed. Demographic, diagnostic, and procedure information identified inpatient and outpatient VHA encounters. We collected laboratory results and vital signs data from clinical sources. For Medicare or Medicaid enrollees, we obtained enrollment, claims files, and prescription (Medicare Part D) data.[9,10] Dates and cause of death were obtained from vital status and the National Death Index files.[11,12] The institutional review board of VHA Tennessee Valley Healthcare System approved this study with a waiver of consent.

Study Population

The population comprised veterans aged 18 years and older who were regular users of VHA care, defined as an encounter or prescription filled at least once every 365 days for 2 or more years before cohort entry. We identified patients with new-onset T2D by selecting those who were new users of metformin, glipizide, glyburide, or glimepiride. New users were patients who filled a first glucose-lowering prescription without any diabetic drug filled in the 180 days before that first fill. We followed these patients with diabetes mellitus longitudinally and selected patients who experienced a decline in kidney function. Patients were required to persist with their initial monotherapy with no medication gaps for >180 days or medication switching before reaching the kidney threshold to be eligible for cohort entry.

The index date and start of follow-up was the date of reaching a reduced kidney function threshold, defined as either an eGFR of <60 mL/min per 1.73 m^2 or serum

creatinine level of ≥1.5 mg/dL for men or ≥1.4 mg/dL for women (Figure S1). The index date and cohort entry were restricted to the period between January 1, 2002 and December 30, 2015 to allow sufficient collection of baseline data and to allow follow-up through December 31, 2016. We excluded patients who added or switched glucose-lowering medications at or before the kidney threshold or had a single episode of dialysis, organ transplantation, or enrollment in hospice care at or within the 2 years before reaching the reduced kidney function threshold.

Exposure

The study exposures were persistent use of metformin or a sulfonylurea (glyburide, glipizide, and glimepiride) after reaching the reduced kidney threshold. Follow-up began on the date the kidney threshold (eGFR <60 mL/min per 1.73 m^2 or serum creatinine level 1.4/1.5 mg/dL) was fulfilled and continued through an outcome (heart failure hospitalization), a competing risk (drug nonpersistence or death), or a censoring event (loss to follow-up or end of the study). Competing risks were defined as informative events that may have been influenced by the study medications. Nonpersistence was defined as 90 days without an antidiabetic drug or the addition of or switch to a different glucose-lowering drug.[13] Censoring events were defined as noninformative events not likely to be influenced by study medications; loss to follow-up was defined as the 181st day of no VHA contact (inpatient, outpatient, or pharmacy use), or study end (December 31, 2016).

Outcomes

The primary outcome was hospitalization with a primary discharge diagnosis of heart failure, cardiomyopathy, or hypertensive heart disease with heart failure. Events were defined by primary discharge diagnosis codes of the *International Classification of Diseases, Ninth or Tenth Revision* (*ICD-9*; *ICD-10*) before or after 2015.[14] *ICD-9 , Clinical Modification* codes included the following: 425.X, 428.X, 404.01, 404.03, 404.11, 404.13, 398.91, 402.01, 402.11, 402.91, 404.91, and 404.93. *ICD-10* codes included: I50.2*, I50.3*, I50.9, I42.9, I13.0, I13.2, I09.81, and I11.0. A heart failure hospitalization could also be captured if there was a diagnosis-related group code for heart failure (diagnosis-related group code 127 before fiscal year 2008 and 291–293 after fiscal year 2008).[15,16] The outcome date was the admission day.

To further understand the type of heart failure that was associated with the hospitalization, we used the Natural Language Processing echocardiogram algorithm developed and reported previously by Patterson et al.[17] Only echocardiogram reports conducted within the VHA were available to determine heart failure type on the basis of ejection fraction (EF) (reduced <40%, midrange 40%–49%, and preserved ≥50%). The echocardiogram used for heart failure classification was the study obtained closest to the day of admission and up to 7 days after admission. If no echocardiogram was obtained during that heart failure hospitalization, we evaluated echocardiograms for each patient up to 1 year before that admission and used the one closest to the date of admission. If no echocardiogram was available, including any obtained for a hospitalization outside of the VHA and within the Medicare claims files, then heart failure hospitalization type was considered unknown.

Covariates

Study covariates were included as the closest measured to the date of cohort entry and up to 720 days before the reduced kidney function threshold. Covariates included age, sex, race, fiscal year, number of months from initial antidiabetic medication to reaching the reduced kidney function threshold (diabetes mellitus duration), and Veterans Integrated Service Network of care. Each Veterans Integrated Service Network of care is a geographic designation for the VHA and allowed a more granular estimation of geographic variation of diabetes mellitus care. Physiologic variables were also collected for up to 720 days before the kidney threshold and defined as the most recent measure before kidney threshold. Physiologic variables included body mass index (calculated as weight in kilograms divided by height in meters squared), blood pressure, glycated hemoglobin, low-density lipoprotein, hemoglobin, proteinuria, and creatinine values (both historical and the creatinine at cohort entry).

Creatinine was used to calculate eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation.[18,19] Healthcare utilization (hospitalization, nursing home use, number of outpatient visits or medications, and Medicare or Medicaid insurance use) was measured in the year before the reduced kidney function threshold. We collected data on smoking and comorbidities as defined in Table S1. Selected medications filled within 180 days before the reduced kidney function threshold were also covariates. Because race is associated with heart failure outcomes, we collected patient self-reported categorical race from VHA data and supplemented those data with patients with Medicare self-reported categorical race data to minimize missing values.[20]

Statistical Analysis

The primary analysis accounted for 2 competing risks, medication nonpersistence and all-cause

death, and compared the cause-specific hazard of heart failure hospitalizations between metformin versus sulfonylurea users (referent) using a propensity score–weighted model. The propensity score modeled the probability of metformin or sulfonylurea at the time of the reduced kidney function threshold and included covariates, Veterans Integrated Service Network, and an indicator of missing covariates. Missing covariates were handled with multiple imputations using 20 iterations of chained imputations adjusted for canonical variates.[21] We used matching weights derived from the propensity score to balance both exposure groups on observed covariates (detailed methods in Table S2, Figures S2 and S3).[22–24] Standardized mean differences were calculated as the difference between groups in number of standard deviations, because this is the preferred measure of covariate balance when dealing with large sample sizes.[25] Smaller standardized mean difference values indicate less difference between groups, with 0 indicating perfect balance in mean or proportion.

Cox proportional hazards models estimated the cause-specific hazard ratios (HRs) for metformin versus sulfonylurea (referent) in the weighted cohort while adjusting for the aforementioned covariates. Separate analyses were conducted for each type of heart failure hospitalization (reduced, midrange, preserved, or unknown EF). For each type of heart failure, all of the other types of heart failure were combined and called "other heart failure hospitalization," and considered a competing risk. For the cause-specific hazard model of heart failure hospitalization, the concordance averaged 0.88 across the multiple imputed data sets indicating good predictive ability. The Akaike information criterion (AIC) for the unadjusted cause-specific hazard model for heart failure hospitalization was 59 664.79, and the average AIC for the adjusted model was 54 352.34.

Statistical significance for the 2-sided *P* value was set at 0.05. Fulfillment of the proportional hazards assumptions was verified through examination of Schoenfeld residuals over time.[26] Cumulative incidence plots for the weighted cohort were generated using the Aalen-Johansen estimator.[27] When estimating potentially causal associations, it is preferable to report the cause-specific HRs with competing risks treated as censored outcomes.[28] However, this approach will yield biased estimates of cumulative incidence. Thus, the Aalen-Johansen estimator is used. The outcome, heart failure hospitalization, and the competing risks of nonpersistence and death were treated as terminal states.

Sensitivity and Subgroup Analysis

A planned sensitivity analysis excluded patients who were enrolled in Medicare Advantage during the baseline period and censored patients' follow-up upon enrollment in Medicare Advantage programs. In this sensitivity analysis, Medicare Advantage (Part C) individuals were excluded because their claims tended to be missing or incomplete during the time frame of the study.[29] We also conducted subgroup analyses and tested for effect modification by stratifying by the following covariates: age (≥65, <65 years), race (Black and non-Black), history of cardiovascular disease (yes, no) and history of heart failure (yes, no). Analyses were conducted using R.[30]

RESULTS

Study Cohort and Patient Characteristics

The study identified 67 762 new metformin users and 28 979 new sulfonylurea users who persisted on treatment, reached the reduced kidney function threshold, and satisfied cohort entry criteria (Figure 1). This cohort of persistent new users represented 55.3% of 174 882 new users of metformin or sulfonylurea who remained persistent on medication and reached the reduced kidney function threshold. We excluded 59 464 whose regimens changed before or on the day that the kidney threshold was reached. There were 12 505 who met the kidney threshold outside the prespecified study time frame, 5647 who had no supply of metformin or sulfonylurea in the 90 days before reaching the kidney threshold, and those with hospice care (n=219), organ transplant (n=206), data error (n=75), or dialysis use in the past 2 years (n=25). After propensity score calculation and weighting, the cohort included 24 685 metformin and 24 804 sulfonylurea users (54% glipizide, 45% glyburide, and 1% glimepiride).

The unweighted full cohort of patients were 96.5% men and 82.8% White. Metformin and sulfonylurea users had similar baseline characteristics. However, metformin users were younger than sulfonylurea users (median age 67 years versus 71 years, respectively). After weighting, patient characteristics were similar between metformin and sulfonylurea including age 70 years (interquartile range [IQR], 63–78) versus 70 years (IQR, 63–78), glycated hemoglobin 6.5% (IQR, 6.1–7.1) versus 6.6% (IQR, 6.1–7.2), and eGFR 55.8 (IQR, 51.6–58.2) versus 55.8 (IQR, 51.6–58.2), respectively, at the time of reduced kidney function threshold. The historical eGFR before cohort entry was also reduced (69.6 mL/min [IQR, 64.6–77.0]), and the difference between these 2 eGFRs was 14.6 mL/min (IQR, 9.6–23.5) for metformin and 14.6 mL/min (IQR, 9.6–23.2) for sulfonylurea. The median time between these 2 eGFR measures was 4.6 months (IQR, 2.4–7.0) for metformin users and 5.0 months (IQR, 2.6–7.5) for sulfonylurea users.

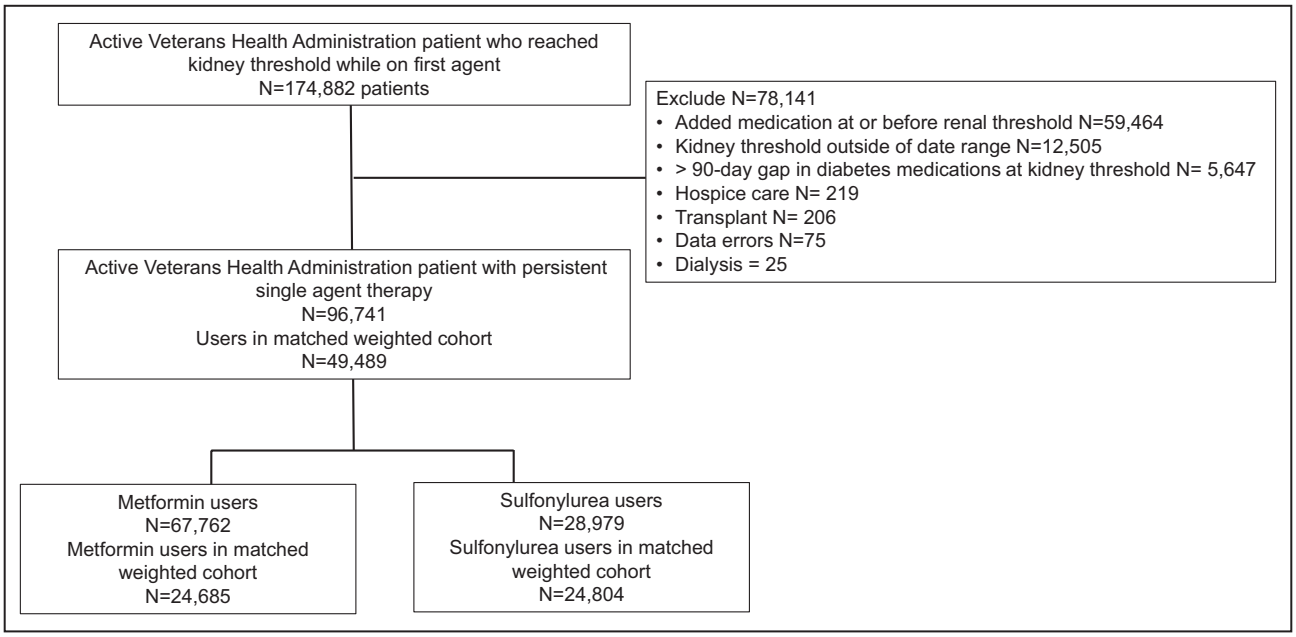

Figure 1. Flow of eligible patients in the Veterans Health Administration diabetes mellitus kidney disease cohort.
Weighted number uses matching weights derived from the propensity score to balance both exposure groups on observed covariates.

The prevalence of underlying congestive heart failure and cardiovascular disease was balanced between metformin and sulfonylurea users (heart failure 12.1% versus 12.1%, CVD 31.6% versus 31.7%, respectively) (Table 1). The median observed follow-up in the weighted cohort was 1.03 years (IQR, 0.35–2.58) for patients taking metformin and 1.17 years (IQR, 0.46–2.66) for sulfonylurea.

Primary Outcome: Hospitalization for Heart Failure

After propensity score weighting, there were 775 heart failure hospitalization events among metformin patients with reduced kidney function, and 992 events among patients taking sulfonylurea; this yielded 16.9 (95% CI, 15.8–18.1) versus 20.7 (95% CI, 19.5–22.0) events per 1000 person-years of use, respectively. After covariate adjustment, the cause-specific HR for heart failure hospitalizations was 0.85 (95% CI, 0.78–0.93) among metformin compared with sulfonylurea users (Table 2). The Aalen-Johansen plot demonstrates the cumulative probability of heart failure hospitalizations over a 5-year period (Figure 2 and Figure S4). Cumulative probability of a heart failure hospitalization between metformin and sulfonylurea was 1.6% versus 2.0% at 1 year and 3.0% versus 3.8% at 5 years. These estimates accounted for the competing risks of nonpersistence (82.8% metformin versus 80.8% sulfonylurea) and noncardiovascular death (3.1% versus 4.2%). Among nonpersistent metformin users, 58.4% stopped the drug, and 41.6% added another drug (7.3% added insulin, 82.9% added sulfonylurea, 6.6% added an alternative agent, and 3.3% added more than one medication). Among nonpersistent sulfonylurea users, 60.2% stopped the drug, and 39.8% added another drug (15.8% added insulin, 69% added metformin, 10.7% added an alternative agent, and 4.5% added more than one medication).

Heart Failure Hospitalization Type

Of the 775 metformin and 992 sulfonylurea users hospitalized for heart failure, 44% (340 out of 775) versus 45% (447 out of 992) did not have an echocardiogram, 28% (214 out of 775) versus 31% (303 out of 992) had reduced EF, 9% (73 out of 775) versus 9% (85 out of 992) had midrange EF, and 19% (148 out of 775) versus 16% (157 out of 992) had preserved EF respectively. Results were consistent in all types of heart failure hospitalizations and statistically significant for heart failure with reduced EF, with a cause-specific HR of 0.79 (95% CI, 0.68–0.93), and in those with unknown EF, with a cause-specific HR of 0.84 (95% CI, 0.74–0.96) (Table 2 and Figure 3).

Sensitivity and Subgroup Analysis

Sensitivity analysis, which excluded patients with Medicare Advantage, were consistent with the results of the main findings (Table 2). Results were also consistent in all subgroups, although in small subgroups some confidence intervals crossed 1 (Figure 4 and Table S3).

DISCUSSION

Among patients with T2D who developed worsening kidney function, persistent metformin use was

Table 1. Patient Characteristics at Cohort Entry of Reduced Kidney Function

	Full Unweighted Cohort		Weighted Cohort		
	Metformin	Sulfonylurea	Metformin	Sulfonylurea	
	N=67 762	N=28 979	N=24 685	N=24 804	SMD*
Age, y†	67 [62–74]	71 [63–79]	70 [62–77]	70 [62–77]	<0.001
Men, n (%)	64 933 (95.8)	28 462 (98.2)	24 195 (98.0)	24 312 (98.0)	<0.001
Race, n (%)					0.001
Other§	1473 (2.2)	528 (1.8)	457 (1.9)	463 (1.9)	
Black	9884 (14.6)	4925 (17.0)	4036 (16.4)	4048 (16.3)	
White	56 405 (83.2)	23 526 (81.2)	20 191 (81.8)	20 293 (81.8)	
Medication start to kidney threshold, mo†	16.2 [6.5–35.1]	13.6 [5.9–29.0]	14.0 [5.8–30.2]	14.0 [6.0–30.3]	0.01
Years of cohort entry, n (%)					0.03
2002–2003	3167 (4.7)	4904 (16.9)	2925 (11.8)	2919 (11.8)	
2004–2005	5786 (8.6)	5737 (19.8)	4481 (18.2)	4443 (17.9)	
2006–2007	9075 (13.4)	6101 (21.0)	5208 (21.1)	5439 (21.9)	
2008–2009	9952 (14.7)	4051 (14.0)	3875 (15.7)	3894 (15.7)	
2010–2011	12 237 (18.0)	3341 (11.6)	3366 (13.6)	5049 (13.3)	
2012–2013	12 854 (19.0)	2619 (9.0)	2652 (10.8)	2600 (10.4)	
2014–2015	14 691 (21.6)	2226 (7.7)	2178 (8.8)	2222 (9.0)	
Clinical variables					
Body mass index, kg/m^2†	31.1 [27.7–35.2]	30.1 [26.9–34.1]	30.4 [27.1–34.4]	30.3 [27.1–34.3]	0.004
Missing BMI measure, n (%)	11 519 (17.0)	5733 (19.8)	4610 (18.7)	4635 (18.7)	<0.001
Systolic blood pressure, mm Hg†	129 [118–140]	131 [120–143]	131 [119–142]	131 [119–142]	0.003
Diastolic blood pressure, mm Hg†	73 [65–80]	71 [64–80]	72 [64–80]	72 [64–80]	<0.001
Laboratory variables					
HbA1c, %†	6.5 [6.1–7.0]	6.6 [6.1–7.3]	6.5 [6.1–7.1]	6.6 [6.1–7.2]	0.006
Missing HbA1c, n (%)	2768 (4.1)	1138 (3.9)	1010 (4.1)	995 (4.0)	0.004
Hemoglobin, g/dL†	14.0 [12.9–15.0]	14.1 [13.0–15.2]	14.1 [13.0–15.1]	14.1 [13.0–15.2]	0.003
Missing hemoglobin, n (%)	3630 (5.4)	1712 (5.9)	1513 (6.1)	1508 (6.1)	0.002
Estimated glomerular filtration rate at cohort entry†	55.9 [51.7–58.2]	55.8 [51.5–58.2]	55.8 [51.6–58.2]	55.8 [51.6–58.2]	0.002
Estimated glomerular filtration rate before cohort entry†	70.5 [65.1–78.6]	69.2 [64.5–76.5]	69.6 [64.7–77.0]	69.6 [64.7–77.0]	<0.001
Serum creatinine, mg/dL†	1.33 [1.24–1.43]	1.33 [1.24–1.43]	1.33 [1.24–1.43]	1.33 [1.24–1.43]	0.002
Low-density lipoprotein, mg/dL†	85 [67–106]	89 [72–111]	88 [70–110]	88 [71–110]	0.001
Missing low-density lipoprotein, n (%)	1323 (2.0)	1139 (3.9)	797 (3.2)	798 (3.2)	<0.001
Urine protein on urinalysis, n (%)					0.002
Negative	32 970 (48.7)	13 517 (46.6)	11 651 (47.2)	11 706 (47.2)	
Trace or 1+	10 072 (14.9)	4185 (14.4)	3574 (14.5)	3606 (14.5)	
2+	2187 (3.2)	983 (3.4)	803 (3.3)	808 (3.3)	
3+/4+/trace to 4+	632 (0.9)	483 (1.7)	347 (1.4)	348 (1.4)	
Missing urine protein measure, n (%)	21 901 (32.3)	9811 (33.9)	8309 (33.7)	8335 (33.6)	
MACR stage, n (%)					0.003
A1, <30 mg/g normal to mild increase albuminuria	29 664 (43.8)	10 626 (36.7)	9472 (38.4)	9532 (38.4)	
A2, 30–300 mg/g moderate increase albuminuria	7400 (10.9)	3076 (10.6)	2675 (10.8)	2676 (10.8)	
A3 and positive, >300 mg/g severely increased albuminuria	1815 (2.7)	931 (3.2)	769 (3.1)	763 (3.1)	
Missing MACR measure	28 883 (42.6)	14 346 (49.5)	11 768 (47.7)	11 833 (47.7)	
Baseline comorbidities, n (%)‡					
Malignancy	7199 (10.6)	3514 (12.1)	2891 (11.7)	2907 (11.7)	<0.001

(*Continued*)

Table 1. Continued

	Full Unweighted Cohort		Weighted Cohort		
	Metformin	Sulfonylurea	Metformin	Sulfonylurea	
	N=67 762	N=28 979	N=24 685	N=24 804	SMD*
Liver disease	1131 (1.7)	820 (2.8)	596 (2.4)	593 (2.4)	0.002
HIV	235 (0.3)	118 (0.4)	95 (0.4)	97 (0.4)	0.001
Congestive heart failure	5527 (8.2)	4218 (14.6)	2988 (12.1)	3010 (12.1)	<0.001
Cardiovascular disease	17 701 (26.1)	9811 (33.9)	7798 (31.6)	7869 (31.7)	0.003
Stroke	1900 (2.8)	1031 (3.6)	833 (3.4)	830 (3.3)	0.002
Transient ischemic attack	710 (1.0)	410 (1.4)	321 (1.3)	331 (1.3)	0.003
Serious mental illness	16 591 (24.5)	5827 (20.1)	5048 (20.4)	5122 (20.6)	0.005
Smoking	8749 (12.9)	3552 (12.3)	3064 (12.4)	3086 (12.4)	<0.001
Chronic obstructive pulmonary disease	10 304 (15.2)	5266 (18.2)	4196 (17.0)	4234 (17.1)	0.002
History of respiratory failure	1967 (2.9)	963 (3.3)	791 (3.2)	791 (3.2)	<0.001
History of kidney disease	73 (0.1)	52 (0.2)	35 (0.1)	38 (0.2)	0.002
History of sepsis	961 (1.4)	511 (1.8)	397 (1.6)	403 (1.6)	0.001
History of pneumonia	2179 (3.2)	1426 (4.9)	1057 (4.3)	1074 (4.3)	0.002
Arrhythmias	9511 (14.0)	5469 (18.9)	4289 (17.4)	4320 (17.4)	0.001
Cardiac valve disease	1894 (2.8)	1196 (4.1)	898 (3.6)	907 (3.7)	0.001
Parkinson	496 (0.7)	311 (1.1)	228 (0.9)	231 (0.9)	<0.001
Urinary tract infection	2267 (3.3)	1375 (4.7)	1035 (4.2)	1046 (4.2)	0.001
Osteomyelitis	309 (0.5)	198 (0.7)	155 (0.6)	153 (0.6)	0.002
Osteoporosis	475 (0.7)	239 (0.8)	196 (0.8)	202 (0.8)	0.002
Falls	147 (0.2)	73 (0.3)	55 (0.2)	57 (0.2)	0.001
Fractures	1258 (1.9)	679 (2.3)	549 (2.2)	549 (2.2)	<0.001
Amputation	230 (0.3)	170 (0.6)	116 (0.5)	120 (0.5)	0.002
Retinopathy	508 (0.7)	399 (1.4)	290 (1.2)	291 (1.2)	<0.001
Use of medications, n (%)					
ACE inhibitors	43 233 (63.8)	18 811 (64.9)	15 968 (64.7)	16 091 (64.9)	0.004
Angiotensin receptor blockers	8697 (12.8)	3109 (10.7)	2816 (11.4)	2807 (11.3)	0.003
β-blockers	33 342 (49.2)	14 798 (51.1)	12 514 (50.7)	12 587 (50.7)	0.001
Calcium channel blockers	19 721 (29.1)	8667 (29.9)	7381 (29.9)	7415 (29.9)	<0.001
Thiazide/potassium-sparing diuretics	29 986 (44.3)	11 573 (39.9)	10 103 (40.9)	10 195 (41.1)	0.004
Loop diuretics	10 317 (15.2)	6621 (22.8)	4957 (20.1)	4983 (20.1)	<0.001
Other antihypertensives	18 461 (27.2)	7833 (27.0)	6719 (27.2)	6728 (27.1)	0.002
Lipid-lowering statins	49 915 (73.7)	18 671 (64.4)	16 548 (67.0)	16 698 (67.3)	0.006
Nonstatin lipid-lowering agents	13 167 (19.4)	4665 (16.1)	4246 (17.2)	4273 (17.2)	<0.001
Antiarrhythmic digoxin and inotropes	4395 (6.5)	3143 (10.8)	2260 (9.2)	2272 (9.2)	<0.001
Anticoagulants	6029 (8.9)	3099 (10.7)	2488 (10.1)	2496 (10.1)	<0.001
Nitrates	7812 (11.5)	4715 (16.3)	3628 (14.7)	3664 (14.8)	0.002
Aspirin	14 373 (21.2)	6543 (22.6)	5360 (21.7)	5408 (21.8)	0.002
Platelet inhibitors	6241 (9.2)	3100 (10.7)	2574 (10.4)	2593 (10.5)	<0.001
Antipsychotics	5415 (8.0)	1992 (6.9)	1740 (7.0)	1762 (7.1)	0.002
Oral glucocorticoids	5050 (7.5)	2139 (7.4)	1795 (7.3)	1813 (7.3)	0.001
Indicators of healthcare utilization					
Hospitalization within year (Veterans Health), n (%)	9077 (13.4)	4517 (15.6)	3576 (14.5)	3630 (14.6)	0.004
Hospitalizations within 30 d (Veterans Health), n (%)	2510 (3.7)	1197 (4.1)	942 (3.8)	961 (3.9)	0.003
Hospitalizations within y (Medicaid/Medicare), n (%)	5634 (8.3)	3597 (12.4)	2771 (11.2)	2788 (11.2)	<0.001
Hospitalizations within 30 d (Medicaid/Medicare), n (%)	987 (1.5)	581 (2.0)	439 (1.8)	452 (1.8)	0.003

(*Continued*)

Table 1. Continued

	Full Unweighted Cohort		Weighted Cohort		
	Metformin	Sulfonylurea	Metformin	Sulfonylurea	
	N=67 762	N=28 979	N=24 685	N=24 804	SMD*
Medicaid insurance use in past year, n (%)	663 (1.0)	435 (1.5)	323 (1.3)	331 (1.3)	0.002
Medicare insurance use in past year, n (%)	21 437 (31.6)	10 540 (36.4)	8810 (35.7)	8815 (35.5)	0.003
Nursing home encounters, n (%)	201 (0.3)	137 (0.5)	97 (0.4)	101 (0.4)	0.002
No. of medications†	7 [5–11]	7 [4–10]	7 [4–10]	7 [4–10]	0.003
Outpatient visits in past year†	6 [3–11]	6 [4–11]	6 [3–11]	6 [3–11]	0.002
Medicare Advantage use, n (%)	10 253 (15.1)	4339 (15.0)	3771 (15.3)	3785 (15.3)	<0.001

ACE indicates angiotensin-converting enzyme; HbA1c, glycated hemoglobin; MACR, microalbumin to creatinine ratio; and SMD, standardized mean difference.

*SMDs are the absolute difference in means or percent divided by an evenly weighted pooled standard deviation, or the difference between groups in number of standard deviations. In the weighted cohort, all standardized differences were not statistically significant (see Figure S3 for the plot of the SMDs of the prematched and matched cohort).

†Median [interquartile range].

‡Definitions of comorbidities can be found in Table S1.

§Other races include: Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander

associated with reduced heart failure hospitalization compared with sulfonylurea. We found that the risk difference between sulfonylurea and metformin was 0.8% (95% CI, 0.7–0.9) at 5 years. Our results were consistent when we evaluated the outcomes of heart failure hospitalizations with a reduced or unknown EF;

Table 2. Rates, Adjusted Hazard Ratios, and Confidence Intervals for HF Hospitalization and HF Type for Metformin Versus Sulfonylurea Users With Reduced Kidney Function

	Metformin	Sulfonylurea
No. at risk matched weighted	n=24 685	n=24 804
Primary outcome: HF hospitalization	775	992
Person-years	45 865	47 882
Unadjusted rate/1000 person-years (95% CI)	16.9 (15.7–18.1)	20.7 (19.5–22.0)
Adjusted HR (95% CI)*	0.85 (0.78–0.93)	Reference
HF hospitalization type: reduced ejection fraction	214	303
Unadjusted rate/1000 person-years (95% CI)	4.67 (4.1–5.3)	6.33 (5.7–7.1)
Adjusted HR (95% CI)†	0.79 (0.67–0.93)	Reference
HF hospitalization type: midrange ejection fraction	73	85
Unadjusted rate/1000 person-years (95% CI)	1.6 (1.3–2.0)	1.8 (1.4–2.2)
Adjusted HR (95% CI)†	0.94 (0.71–1.26)	Reference
HF hospitalization type: preserved ejection fraction	148	157
Unadjusted rate/1000 person-years (95% CI)	3.2 (2.7–3.8)	3.3 (2.8–3.8)
Adjusted HR (95% CI)†	0.97 (0.79–1.20)	Reference
HF hospitalization type: unknown ejection fraction	340	447
Unadjusted rate/1000 person-years (95% CI)	7.4 (6.7–8.2)	9.3 (8.5–10.2)
Adjusted HR (95% CI)†	0.84 (0.74–0.96)	Reference
Sensitivity analysis: exclude Medicare Advantage	N=20 914	N=21 019
HF hospitalization	676	862
Person-years	36 939	38 766
Unadjusted rate/1000 person-years (95% CI)	18.3 (17.0–19.7)	22.2 (20.8–23.8)
Adjusted HR (95% CI)*	0.85 (0.77–0.93)	Reference

HF indicates heart failure; and HR, hazard ratio.

*Primary analysis considers patients persistent on regimen until they do not have antidiabetic medications for 90 days. Model adjusted for full list of covariates: demographics, clinical information derived from the electronic health record, comorbidities, use of medications, and healthcare utilization. All continuous variables modeled as restricted cubic splines.

†Primary analysis considers patients persistent on regimen until they do not have antidiabetic medications for 90 days. Reduced model to allow for convergence. All covariates in above model except: Veterans Integrated Service Networks of care regrouped into regions (North, South, Midwest, West) and excluded HIV, history of kidney disease, osteomyelitis, osteoporosis, falls, sepsis, Parkinson, amputation, and retinopathy.

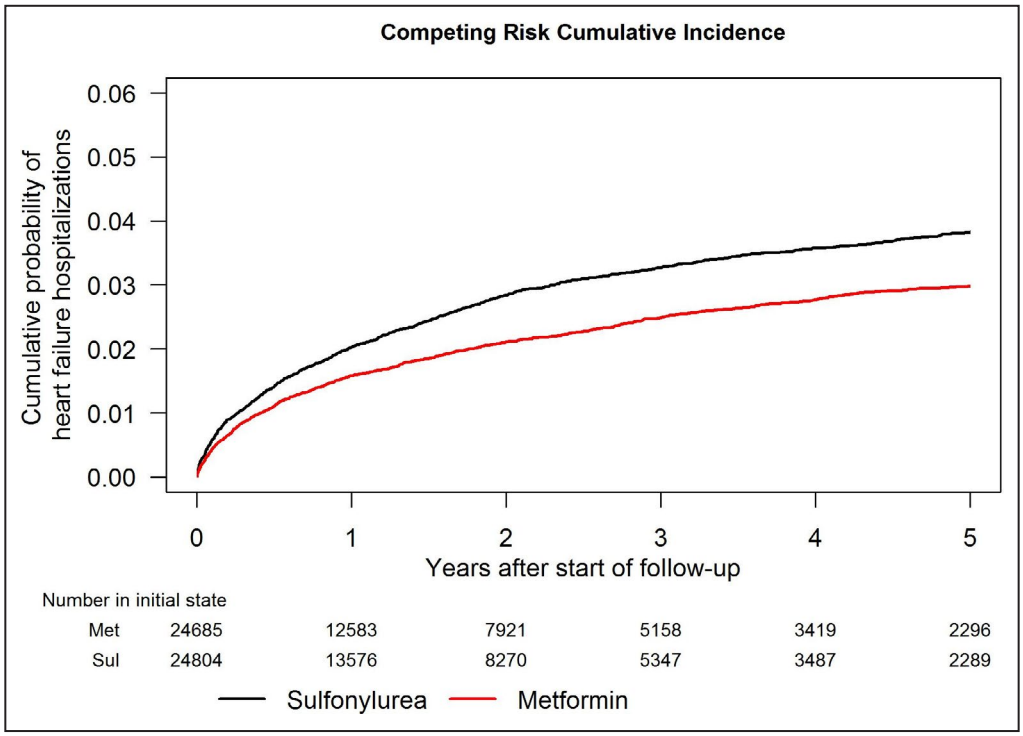

Figure 2. Aalen-Johansen cumulative incidence demonstrating heart failure event hospitalizations in weighted cohort.
Met indicates metformin; and Sul, sulfonylurea.

the number of events with both midrange and preserved EF heart failure hospitalizations was limited. Although there is consensus that metformin is a first-line diabetes mellitus treatment, metformin is often discontinued when kidney disease develops. The revised label for metformin use based on the Food and Drug Administration's 2016 safety advisory states that metformin can be safely used in patients with mild kidney function impairment (45–60 mL/min per 1.73 m^2) and in some patients with moderate kidney function impairment (eGFR, 30–45 mL/min per 1.73 m^2).[8] This study adds to the limited observational evidence for the beneficial association of metformin compared with sulfonylurea on heart failure outcomes among those who develop reduced kidney function.[6,31]

Our findings are consistent with the results of a study by Masoudi et al., which was restricted to patients with underlying heart failure and evaluated heart failure rehospitalizations among a cohort of 16 417 Medicare beneficiaries with diabetes mellitus.[32] In multivariable models, treatment with metformin was associated with significantly lower risks of heart failure readmission (HR, 0.92; 95% CI, 0.86–0.99) when compared with those who did not use an insulin-sensitizing agent (sulfonylurea or insulin). These results remained when confined to those with creatinine of >1.5 mg/dL (HR, 0.91; 95% CI, 0.84–0.99). Physiologically, these findings are thought to be related to the nonglycemic cardiac benefits of metformin on insulin sensitization, which include weight neutrality as well as modest improvement in lipoprotein and triglyceride levels.[33] Although the Masoudi et al. study evaluated the association of readmission stratified by EF at the index hospitalization, our study evaluated the association of metformin or sulfonylurea with the type of heart failure hospitalization. This study can potentially inform the association of metformin and sulfonylurea with the physiologic changes that may be associated with heart failure type in certain patient populations.

Although our study has strengths including its large sample size and day-by-day ascertainment of medication exposures to reduce misclassification and control for multiple covariates, there are limitations that should be noted. First, incident therapy persistence with either metformin or sulfonylureas at the kidney threshold was required and excluded many patients who discontinued, added, or switched to other medications at or before reaching the kidney threshold. By design, we also excluded those who began diabetes mellitus treatment after the onset of reduced kidney function. This study-specified criteria allow us to make inferences and interpret study results among a population of patients who continue to use medications after reaching the kidney threshold. Medication changes can occur for multiple reasons, including comorbid status, provider preference, or rate of

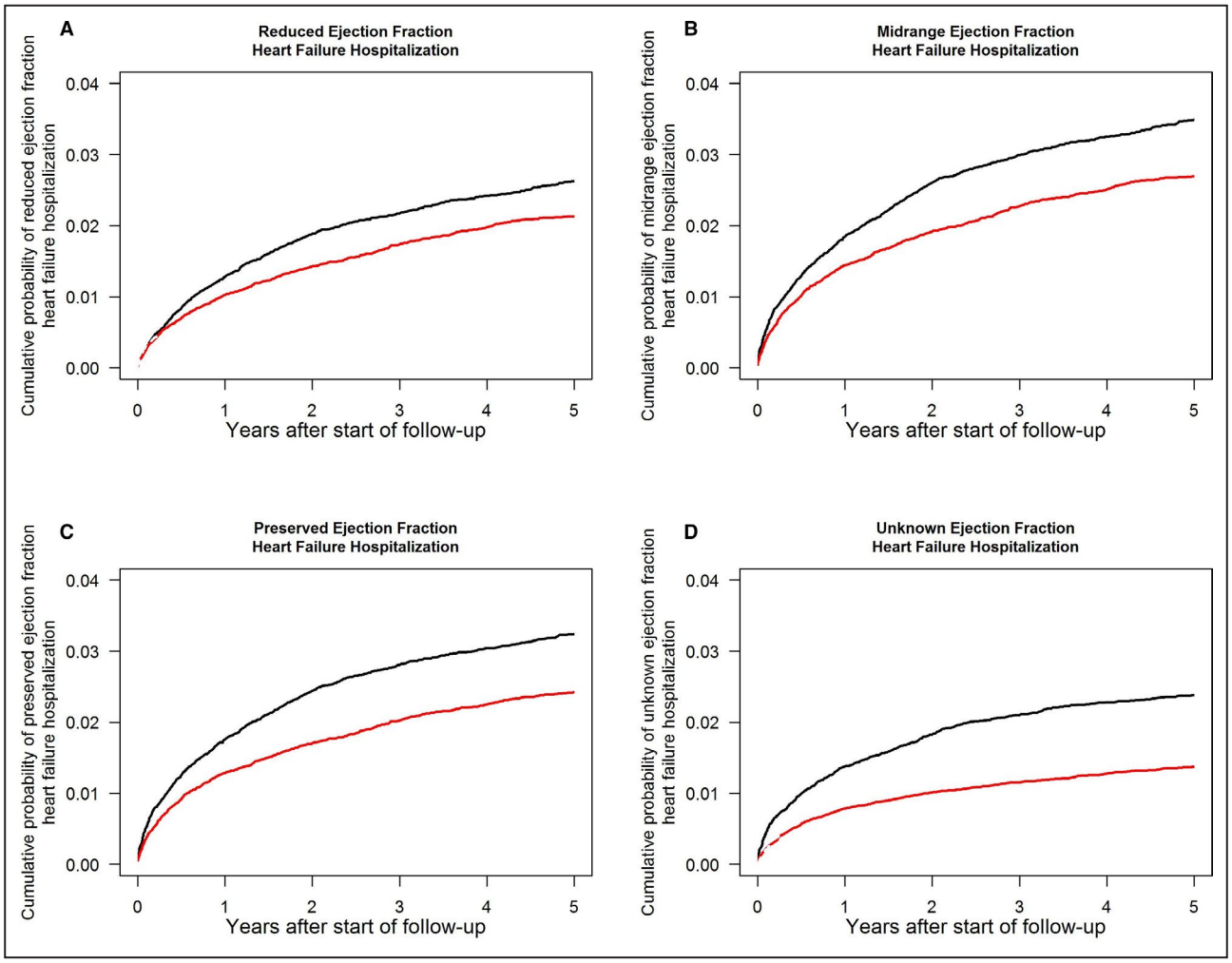

Figure 3. Aalen-Johansen cumulative incidence for the type of heart failure hospitalization.
A, Heart failure reduced ejection fraction. **B**, Heart failure midrange ejection fraction. **C**, Heart failure preserved ejection fraction. **D**, Heart failure unknown ejection fraction.

progression of kidney disease; therefore, these results should not necessarily be extrapolated to those who change or switch medications. Furthermore, newer agents such as DPP4, TZD, GLP1RA, and SGLT2s, although sometimes used as first-line treatments, were outside of the scope of the study question. Second, because many veterans were not receiving all their care at VHA facilities, some data from hospitalizations, including echocardiography data, were not available. The high percentage of patients without echocardiography data (≈45% of all heart failure hospitalizations) suggests that cardiac care was received outside the VA using their Medicare benefits. Because of the high proportion of missing echocardiography data, the results evaluating association with the heart failure type should be interpreted with caution. Third, cohort entry and the start of follow-up was either an elevated serum creatinine or reduced eGFR of <60 mL/min per 1.73 m^2. It is possible that for some patients this kidney threshold may represent an acute kidney injury event rather than progression to chronic kidney disease; however, the historical eGFR was also reduced, indicating deteriorating kidney function rather than solely an acute event. Fourth, despite use of multiple analytic techniques, including propensity score weighting and covariate adjustment, residual confounding may exist, and furthermore, we did not adjust for the multiple comparisons made in the study. Finally, the study population was mostly elderly White men, and may not represent the larger population of patients with diabetes mellitus and reduced kidney function. Results may not be generalizable to women or populations with lower representation in the VHA system.

In conclusion, this study found that among the population of patients with diabetes mellitus and reduced

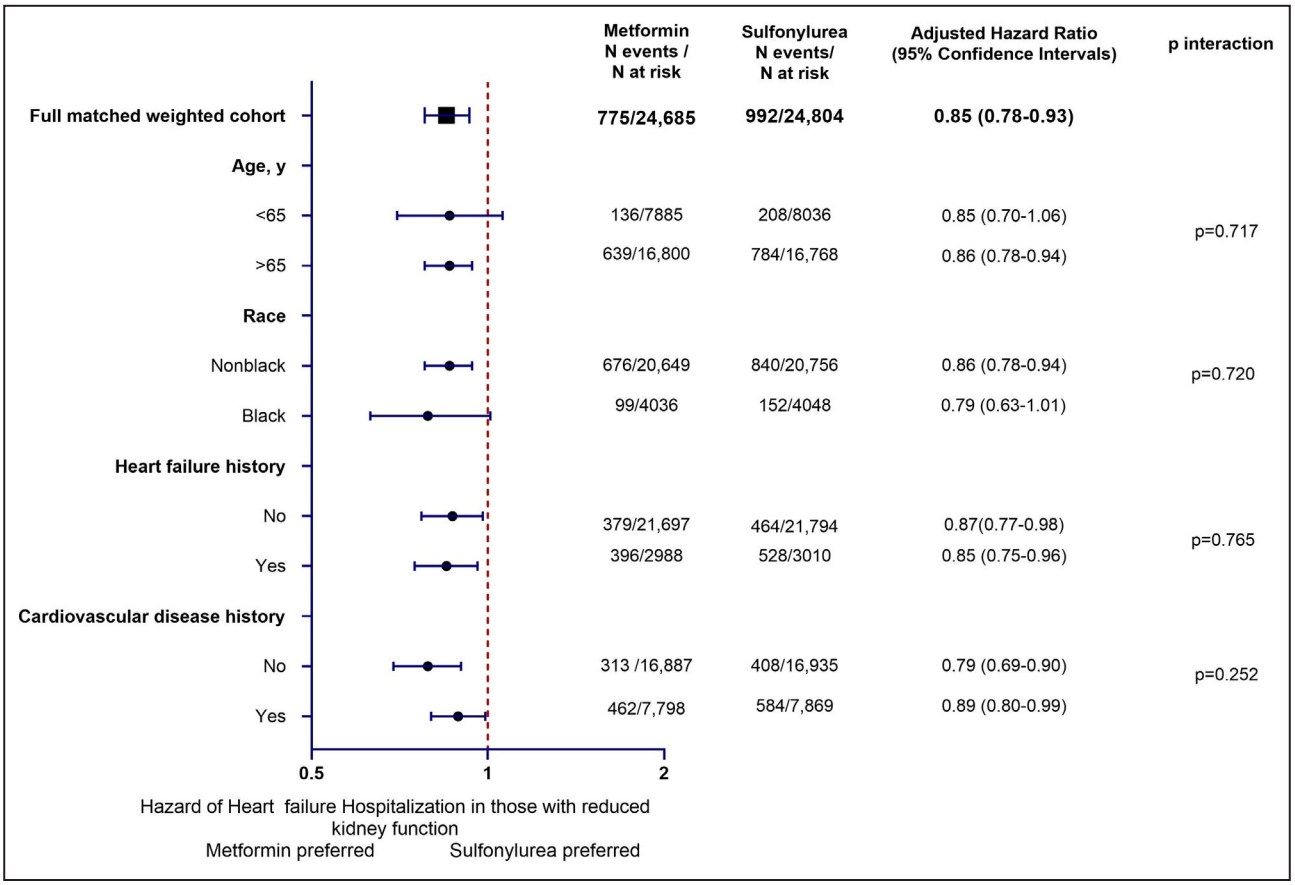

Figure 4. Forest plot demonstrating the adjusted hazard ratio of heart failure hospitalization among patients in different subgroups.

kidney function, persistent metformin use was associated with reduced heart failure hospitalization compared with sulfonylurea.

ARTICLE INFORMATION

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The protocol, statistical code, and deidentified and anonymized data set are available from Dr Roumie with a written request.

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Disclosures

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Supplementary Material

Tables S1–S3
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Definitions of comorbid conditions based on codes in 720 days before reaching kidney threshold; Definitions of medications used are restricted to prescription fill in the 180 days before reaching kidney threshold

Covariate Condition	Inclusive conditions	Definition†
Malignancy	Cancer excluding non melanoma skin cancer	ICD 9- CM diagnosis codes:140.X-208.X (exclude 173) ICD10 diagnosis codes: C00* - C96*; D37* -D48*
Liver failure	End stage liver disease	ICD 9- CM diagnosis codes: 570.X- 573.X ICD10 diagnosis codes: K72*; K70.*; K73.*; K74.*; K76.*
Respiratory Failure	Respiratory failure/ Pulmonary Embolism/Hypertension	ICD 9- CM diagnosis codes: 518.81, 518.83, 518.84, 799.1, 415.X, 416.X ICD10 diagnosis codes: J96.*; R092; I26.9*; I27.*
Congestive Heart Failure	CHF (excluding post procedure-CHF)	ICD 9- CM diagnosis codes: 428.X, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 ICD10 diagnosis codes: I11.0, I13.0, I13.2, I50.9, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43
Cardiovascular disease	1. MI	ICD 9- CM diagnosis codes: 410.X, 412.X, 429.7X ICD10 diagnosis codes: I21*
	2. Obstructive coronary disease	ICD 9- CM diagnosis codes: 411.X, 413.X, 414.X ICD10 diagnosis codes: I24.*; I25.*; I20.* ICD9-CM procedure codes: 36.01, 36.02, 36.03, 36.05, 36.09, 36.10-36.19 CPT procedure codes: 33533-36, 33510-23, 33530, 92980-82,92984, 92995-6, 92974
	3. Peripheral artery disease or revascularization	ICD 9- CM diagnosis codes: 440.2X, 442.2, 443.1, 443.9, 445.0X ICD10 diagnosis codes: I70.2*; I72.*; I77.*; I73.9; I75.* ICD9-CM procedure codes:38.08-09, 38.18, 38.38, 38.39, 38.48, 38.49, 38.88, 38.89, 39.25, 39.29, 39.5, 84.1X CPT procedure codes: 35226,35256, 35286, 35351, 35355, 35371, 35372, 35381, 35454, 35456, 35459, 35473, 35474, 35482, 35483, 35485, 35492, 35493, 35495, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35571, 35583, 35585, 35587, 35646, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 34800, 34802-5
	4. Carotid revascularization	ICD9-CM procedure codes: 38.12, 38.11, 00.61, 00.63, 39.28 CPT procedure codes: 35301, 0005T, 0006T, 0007T, 0075T, 0076T, 37215, 37216 ICD10 procedure code: 031H0AG, 031H0JG, 031H0KG, 031H0ZG, 031J09G, 031J0AG, 031J0JG, 031J0KG,031H09G, 031J0ZG, 037H34Z, 037H3DZ, 037H3ZZ, 037H44Z, 037H4DZ, 037H4ZZ, 037J3DZ, 037J3ZZ, 037J44Z, 037J4DZ, 037J4ZZ, 037K34Z, 037K3DZ, 037K3ZZ, 037K4DZ, 037K4ZZ, 037L34Z, 037L3DZ, 037L3ZZ, 037L44Z, 037L4DZ, 037L4ZZ, 037M34Z, 037M3DZ, 037M3ZZ, 037M44Z, 037M4DZ, 037M4ZZ, 037N34Z, 037N3DZ, 037N3ZZ, 037N44Z, 037N4DZ, 037N4ZZ, 037P34Z, 037P3DZ, 037P3ZZ, 037P44Z, 037P4DZ, 037P4ZZ, 037Q34Z, 037Q3DZ, 037Q3ZZ, 037Q44Z, 037Q4DZ, 037Q4ZZ, 03CH0ZZ, 03CH3ZZ, 03CH4ZZ, 03CJ0ZZ, 03CJ3ZZ, 03CJ4ZZ, 03CK0ZZ, 03CK3ZZ, 03CK4ZZ, 03CL0ZZ, 03CL3ZZ, 03CL4ZZ, 03CM0ZZ, 03CM3ZZ, 03CM4ZZ, 037J34Z, 03CN0ZZ, 03CN3ZZ, 03CN4ZZ, 03CP0ZZ, 03CP3ZZ, 037K44Z, 03CP4ZZ, 03CQ0ZZ, 03CQ3ZZ, 03CQ4ZZ HCPCS procedure code: S2211
TIA		ICD 9- CM diagnosis codes: 435.X ICD10 diagnosis codes: G45.0; G45.1;G45.8; G45.9; I67.848
Stroke		ICD 9- CM diagnosis codes: 430.X, 431.X. 434.X, 436.X

		ICD10 diagnosis codes: I67.89, I60.9, I61.9, I63.30, I63.40 , I63.50, I66.09, I66.19, I66.29, I66.9, I67.89
Serious Mental illness	1. Dementia	ICD 9- CM diagnosis codes: 290.X, 291.2, 292.82, 294.1X, 331.0-331.1X, 331.82 ICD 10 diagnosis codes: F03.9;F01.5*; F10.27; F19.97; F02.80; F02.81; G30.9; G31.* Medications: Donepezil, Rivastigmine, Galantamine, Tacrine, Memantine Bethanechol, Ambenonium, Atomoxetine, Ergoloid Mesylates, Dihydrogenated Ergot, Neostigmine, Physostigmine, Pyridostigmine, Riluzole, Hydergine
	2. Depression,	ICD 9- CM diagnosis codes: 311, 300.4, 296.2, 296.3, V79.0 ICD 10 diagnosis codes: F33.9, F34.1, F32.*
	3. Schizophrenia,	ICD 9- CM diagnosis codes: 295.X ICD 10 diagnosis codes: F20.*
	4. Bipolar disorder	ICD 9- CM diagnosis codes: 296.0, 296.4X, 296.5X, 296.6X, 296.7, 296.80, 296.89 ICD 10 diagnosis codes: F30.* F31.*
	5. Post traumatic stress disorder	ICD 9- CM diagnosis codes: 309.81 ICD 10 diagnosis codes: F43.10; F43.12
Cardiac valve disease		ICD 9- CM diagnosis codes: 394.X, 395.X, 396.X, 424.0, 424.1 ICD 10 diagnosis codes: I05.*; I06.*; I08.*; I34.*; I35.*;
Arrhythmia	Atrial fibrillation/flutter	ICD 9- CM diagnosis codes: 427.3X ICD 10 diagnosis codes: I48.91, I48.92
Smoking		ICD 9- CM diagnosis codes:305.1, V15.82, 989.84 ICD 10 diagnosis codes: F17.200, Z87.891, T65.211A, T65.212A, T65.213A, T65.214A, T65.221A, T65.222A, T65.223A, T65.224A, T65.292A, T65.293A, T65.294A Medications: Varenicline tartrate, Nicotine Replacement (gum, patch, lozenge)
COPD/ Asthma		ICD 9- CM diagnosis codes:491.X, 492.X, 493.X, 496.X, V17.5, V81.3 ICD 10 diagnosis codes: J41.0, J41.1, J44.9, J44.1, J44.0, J41.8, J42-J43.9, J45.20, J45.22, J45.21, J45.990,J45.991, J45.909, J45.998, J45.902, J45.901, Z13.83
HIV		ICD 9- CM diagnosis codes: 042, 079.53, 795.71, V08 ICD 10 diagnosis codes: B20.*; B97.35; Z21
Parkinson's Disease		ICD 9- CM diagnosis codes: 332 ICD 10 diagnosis codes: G20; G21.* Medications: Apokyn, Apomorphine, Carbidopa/levodopa, Entacapone, Pergolide, Pramipexole, Ropinirole, Rotigotine, Selegiline, Tolcapone, Zelapar, Azilect/Rasagiline, Emsam, Isocarboxazid, Phenelzine, Tranylcypromine, Biperiden/Akineton, Comtan/Entacapone, Safinamide, Trihexyphenidyl
Urinary Tract / Kidney Infection		ICD 9- CM diagnosis codes: 590.*, 599.0*, 595.0 ICD 10 diagnosis codes: N11.*; N39.* N30.*
Osteomyelitis		ICD 9- CM diagnosis codes: 730.* ICD 10 diagnosis codes: M86.1*; M86.2*; M86.6*; M86.9*; A02.24
Sepsis/Bacteremia		ICD 9- CM diagnosis codes: 995.91, 995.92, 038.*, 036.2, 790.7 ICD 10 diagnosis codes: A41.9; R65.20; A41.*; A39.4; R78.81
Pneumonia		ICD 9- CM diagnosis codes: 480.*-486.*, 487.0 ICD 10 diagnosis codes: J11.*; J12.*; J13.*; J14.*; J15.*; J16.*; J17.*; J18.*
Fractures (any)		ICD 9- CM diagnosis codes: 733.1*, 800.*-829.*, E887 ICD 10 diagnosis codes: M84.*; M80.*; S02; *; S12.*; S22.*; S32.*; S42.*; S52.*; S62.*; S72.*; S82.*; S92.*
Falls		ICD 9- CM diagnosis codes: E880.*, E881.*, E884.*, E885.9

Osteoporosis		ICD 10 diagnosis codes: Z98.8, W18.30XA,W18.49XA,W01.110A,W01.198A,W19.XXXA ICD 9- CM diagnosis codes: 733.0* ICD 10 diagnosis codes: M81.*
Retinopathy		ICD 9- CM diagnosis codes: 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 362.07 ICD 10 diagnosis codes: E08.311; E08.319; E08.3211; E08.3212; E08.3291; E08.3292; E08.3293; E08.3299; E08.3219; E08.3213; E08.3313; E08.3312; E08.3311; E08.3319; E08.3391; E08.3392; E08.3393; E08.3399; E08.3411; E08.3412; E08.3413; E08.3419; E08.3491; E08.3492; E08.3493; E08.3499; E08.3511; E08.3512; E08.3513; E08.3519; E08.3521; E08.3522; E08.3523; E08.3529; E08.3531; E08.3532; E08.3533; E08.3539; E08.3541; E08.3542; E08.3543; E08.3549; E08.3551; E08.3552; E08.3553; E08.3559; E08.3591; E08.3592; E08.3593; E08.3599; E11.311; E11.3491; E11.3492; E11.3493; E11.3499; E11.3591 ; E11.3592; E11.3593 ; E11.3599 ; E11.3591; E11.3592; E11.3593; E11.3599; E11.3291; E11.3292; E11.3293; E11.3299; E11.3391; E11.3392; E11.3393; E11.3399; E11.3491; E11.3492; E11.3493; E11.3499; E11.319
Amputations		ICD 9- CM diagnosis codes: V49.75; V49.76; V49.77 ICD 10 diagnosis codes: Z89.519; Z47.81; Z89.6*
Medications		
Antipsychotics	Atypical and typical antipsychotic medications	Lithium, Clozapine, Haloperidol, Loxapine, Lurasidone, Molindone, Olanzapine, Paliperidone, Quetiapine Fumerate; Risperidone, Aripiprazole, Asenapine, Ziprasidone, Chlorpromazine, Fluphenazine, Fluphenazine Deconate, Mesoridazine, Perphenazine, Thioridazine, Thiothixene; Trifluoperazine; Triflupromazine, Asenapine, Chlorprothixene, Iloperidone, Molindone, Promazine, Piperacetazine, Methotrimeprazine, Acetophenazine, Fazaclo/clozapine, Molindone
ACE Inhibitors alone/combination		Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril
ARBs alone/combination		Candesartan, Eprosartan, Irbesartan, Losartan, Azilsartan, Olmesartan, Telmisartan, Valsartan
Beta-blockers		Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carteolol, Carvedilol, Esmolol, Labetalol, Metoprolol Tartrate, Metoprolol Succinate, Propranolol, Penbutolol, Pindolol, Nadolol, Sotalol, Timolol, Nebivolol
Calcium Channel Blockers		Amlodipine, Isradipine; Felodipine, Nifedipine, Nifedipine ER, Nicardipine; Diltiazem, Verapamil, Nimodipine; Nisoldipine; Bepridil, Amlodipine/Atorvastatin, Clevidipine Butyrate; Mibefradil
Thiazide diuretics/ Potassium sparing diuretics		Chlorothiazide, Chlorthalidone, Hydrochlorothiazide, Methyclothiazide, Trichlormethiazide, Metolazone, Indapamide, Eplerenone; Amiloride, Spironolactone, Triamterene, Hydrochlorothiazide/Triamterene, Hydrochlorothiazide/Spironolactone, Bendroflumethiazide, Benzthiazide, Cyclothiazide, Hydroflumethiazide, Polythiazide, Quinethazone
Other Antihypertensives		Doxazosin, Prazosin, Terazosin, Clonidine, Guanabenz, Guanfacine, Hydralazine, Methyldopa, Metyrosine, Reserpine, Minoxidil, Alfuzosin, Silodosin, Alseroxylon, Cryptenamine, Deserpidine, Diazoxide, Guanethidine, Mecamylamine, Pargyline, Rescinnamine, Trimethaphan Camsylate

Anti-arrhythmics Digoxin and other inotropes	1. Digoxin	Digoxin, Digitalis
	2. Anti- Arrythmics	Adenosine, Amiodarone, Lidocaine, Flecainide, Ibutilide, , Procainamide, Propafenone, Ropafenone, Quinidine, Disopyramide, Verapamil, Dofetilide, Mexiletine, Moricizine, Tocainide
Anticoagulants and Platelet inhibitors, not aspirin	1. Anticoagulants	Warfarin, Argatroban, Bivalirudin, Dalteparin, Enoxaprin, Eptifibatide, Fondaparinux, Heparin, Lepirudin, Tirofiban, Tinzaparin, Reviparin, Nadroparin, Ardeparin, Certoparin, Dabigatran
	2. Platelet Inhibitors	Clopidogrel, Ticlopidine, Aspirin/Dipyridamole, Dipyridamole alone, Abciximab, Factor IX, Factor VIIa, Factor VIII, Prasugrel, Ticagrelor
Statins		Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin, Rosuvastatin, Cerivastatin Pitavastatin, Lovastatin ER, Ezetimibe/Simvastatin, Lovastatin/Niacin, Amlodipine/Atorvastatin
Non-Statin lipid lowering drugs		Cholestyramine, Colesevelam, Clofibrate, Colestipol, Niacin, Niacinamide, Fish Oil Concentrate, Omega 3 Fatty Acids, Gemfibrozil, Fenofibrate, Fenofibric Acid, Ezetimibe Omacor, Tricor/Fenofibrate, Ezetimibe/Simvastatin
Nitrates		Amyl Nitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Erythrityl Tetranitrate, Nitroglycerin (all forms--SA, Patch, SL, Ointment; Aerosol spray), Ranolazine
Aspirin		Aspirin, Aspirin/ Dipyridamole
Loop Diuretics		Furosemide, Ethacrynic acid, Bumetanide, Torsemide

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; COPD = chronic obstructive pulmonary disease; CPT = Current Procedural Terminology; ICD-9- CM = International Classification of Diseases, Ninth Revision; ICD 10= International Classification of Diseases, Tenth Revision; MI = myocardial infarction; TIA = transient ischemic attack.
If medications are combinations of 2 drug classes then a patient is recorded as using both medications.
† Each co-morbid condition was defined as present if there was 1 specified inpatient or 2 specified outpatient codes separated by 30 days, or 1 specified procedure code or prescription for a medication defining that comorbid condition before reaching the creatinine threshold. Medications were searched in the pharmacy data using both generic and trade names.

Table S2. Propensity Score and matching weights.

	Chi-Square	*d.f.*
Demographics		
Age	447.5060	2
Sex	79.9732	1
Race	234.0883	2
Months from hypoglycemic start until kidney threshold	36.4252	2
Contraindication date	6729.1397	2
VISN of Care	411.7694	20
Clinical and Laboratory Variables		
BMI	33.7798	2
Systolic Blood Pressure mm/Hg	109.1884	2
Diastolic Blood Pressure mm/Hg	61.4631	2
Hemoglobin	176.1627	2
GFR	11.4684	2
GFR Historical	141.9702	2
Creatinine	4.5171	2
LDL Cholesterol	37.4538	2
A1c	698.9345	2
Urine protein	41.1133	4
MACR	13.4003	3
Healthcare Utilization		
VA hospitalizations last year	4.3184	1
VA hospitalizations last 30 days	0.06193	1
Medicare/ Medicaid hospitalizations last year	0.1408	1
Medicare/ Medicaid hospitalizations last 30 days	0.2567	1
Medicaid use	2.9956	1
Medicare Use	2.4304	1
Nursing Home Use	4.1648	1
Number of Outpatient visits	2.7400	2
Number of Outpatient medications	2.6481	2
Medicare Advantage	0.1385	1
Comorbidities		
Malignancy	8.6775	1
Liver disease	180.7042	1
HIV	4.6900	1
CHF	127.2097	1
CVD	14.8503	1
Stroke	1.4069	1
TIA	0.1718	1
Serious Mental Illness	8.0234	1
Smoking	0.3326	1
Chronic Obstructive Pulmonary Disease	0.5558	1
Respiratory failure	0.8908	1
History of past Kidney disease	7.2260	1
Sepsis	3.2198	1
Pneumonia	8.8354	1

Arrhythmias	0.0048	1
Cardiac valve	0.0124	1
Parkinson	5.0405	1
Urinary Tract Infection	8.4827	1
Osteomyelitis	5.0060	1
Osteoporosis	0.0007	1
Falls	0.6413	1
Fractures	11.2282	1
Amputation	7.6748	1
Retinopathy	24.2671	1
Medications		
ACE	2.2147	1
ARB	5.9925	1
Beta Blocker	1.3101	1
Calcium Channel Blocker	0.2828	1
Thiazide diuretics	17.8336	1
Loop diuretics	116.6502	1
Other Antihypertensives	0.2216	1
Statins	251.3593	1
Non Statin lipid lowering medications	35.7974	1
Antiarrhythmics	11.8559	1
Anticoagulants	0.6175	1
Nitrates	22.4489	1
Aspirin	0.1187	1
Platelet Inhibitors Non aspirin	8.3869	1
Antipsychotics	2.7228	1
Oral Glucocorticoids	10.3705	1
Indicators of Missing Clinical Variables		
BMI Missing	12.8465	1
Blood Pressure Missing	0.2052	1
Hemoglobin Missing	26.9811	1
GFR Historical	33.6278	1
LDL Cholesterol Missing	1.2948	1
A1c Missing	48.2832	1

The cohort was composed of all eligible persons who reached the kidney threshold and were using metformin or sulfonylurea for diabetes treatment. The weighted cohort was formed using matching weights, derived using propensity scores. Treatment groups were balanced on baseline covariates by up or downweighting patients to more closely resemble each other. Table 1 in the paper lists baseline covariates included. For simplicity, Table 1 presents date of reaching kidney threshold by year, whereas the date of reaching kidney threshold and date of cohort entry is treated as a continuous covariate in the model. Missing covariate values were multiply imputed and indicators for each variable's missingness was included in the propensity score (PS) model to account for potential informative missingness. The propensity scores used to create the matching weights were obtained using the last imputed data set and a regression model whose coefficients are found by averaging the coefficient estimates of all the imputed data sets. The PS model is displayed below.
The weighted analysis balances the covariate distributions by assigning various weights to the patients in both exposure groups such that the weighted groups resemble each other group

(average treatment effect in evenly matchable units [ATM]). When comparing metformin and sulfonylurea users, both the metformin and sulfonylurea users were weighted so that their distribution of covariates resembled each other and at least a small amount of data is used from each subject. Our weighting procedure down-weighted metformin patients for whom very few similar sulfonylurea users existed (**Figure S2**). When used to facilitate a weighted cohort, the success of the model is determined by the ability to include all patients and the achievement of covariate balance in the weighted cohort. **Figure S3** demonstrates the standardized mean difference (SMD) before and after weighting. **Table 1** in the paper demonstrates that all SMD after weighting have an absolute value < 0.1, indicating good balance between groups. Matching weights yield approximately equal weighted sample sizes and a pseudo-matched cohort. Summaries of the matching weights, by group demonstrate that among sulfonylurea users the median weight is 1.0, mean weight is 0.86 and 90^{th} percentile is 1.0. Among metformin users the median weight is 0.25, mean weight is 0.36 and 90^{th} percentile is 0.95.

Table S3. Risk of heart failure hospitalization in subgroups stratified by history of cardiovascular disease, heart failure, race, and age.

	Metformin	Sulfonylurea	*P value for Interaction*
No Cardiovascular disease (N in weighted cohort)	16887	16935	
HF Hospitalization Events	313	408	
Person-Years	32373	33391	
Unadjusted Rate/1000 person-years (95% CI)	9.7 (8.7, 10.8)	12.2 (11.1, 13.5)	
Adjusted Hazard Ratio * (95% CI)	**0.79 (0.69, 0.90)**	**Reference**	*p = 0.252*
Cardiovascular Disease (N in weighted cohort)	7798	7869	
HF Hospitalization Events	462	584	
Person-Years	13493	14492	
Unadjusted Rate/1000 person-years (95% CI)	34.2 (31.3, 37.4)	40.2 (37.2, 43.6)	
Adjusted Hazard Ratio * (95% CI)	**0.89 (0.80, 0.99)**	**Reference**	
No history of CHF (N in weighted cohort)	21697	21794	
HF Hospitalization Events	379	464	
Person-Years	41959	43383	
Unadjusted Rate/1000 person-years (95% CI)	9.0 (8.2, 10.0)	10.7 (9.7, 11.7)	
Adjusted Hazard Ratio * (95% CI)	**0.87 (0.77, 0.98)**	**Reference**	*p = 0.765*
History of CHF (N in weighted cohort)	2988	3010	
HF Hospitalization Events	396	528	
Person-Years	3906	4499	
Unadjusted Rate/1000 person-years (95% CI)	101.4 (92.3, 111.2)	117.5 (108.4, 127.2)	
Adjusted Hazard Ratio *(95% CI)	**0.85 (0.75, 0.96)**	**Reference**	
Non-Black race (N in weighted cohort)	20649	20756	
HF Hospitalization Events	676	840	
Person-Years	40599	41232	
Unadjusted Rate/1000 person-years (95% CI)	16.6 (15.4, 17.9)	20.4 (19.0, 21.8)	
Adjusted Hazard Ratio* (95% CI)	**0.86 (0.78, 0.94)**	**Reference**	
Black race (N in weighted cohort)	4036	4048	*p = 0.720*
HF Hospitalization Events	99	152	
Person-Years	5266	6650	
Unadjusted Rate/1000 person-years (95% CI)	18.8 (15.5, 22.8)	22.9 (19.6, 26.8)	
Adjusted Hazard Ratio† (95% CI)	0.79 (0.63, 1.01)	**Reference**	
Age younger than 65 years (N in weighted cohort)	7885	8036	
HF Hospitalization Events	136	208	
Person-Years	12843	13579	
Unadjusted Rate/1000 person-years (95% CI)	10.6 (8.9, 12.5)	15.3 (13.4, 17.5)	
Adjusted Hazard Ratio †(95% CI)	0.86 (0.70, 1.06)	**Reference**	*P = 0.717*
Age 65 years and older (N in weighted cohort)	16800	16768	
HF Hospitalization Events	639	784	
Person-Years	3022	34304	
Unadjusted Rate/1000 person-years (95% CI)	19.4 (17.9, 20.9)	22.8 (21.3, 24.5)	
Adjusted Hazard Ratio * (95% CI)	**0.86 (0.78, 0.94)**	**Reference**	

* Cox Proportional Hazards model for time to event. Adjusted for demographics, clinical information derived from the electronic health record, comorbidities, use of medications and health care utilization (see Supplemental table 1). All continuous variables were modeled as restricted cubic splines. † Reduced model to allow for convergence All covariates in above model except VISN of care regrouped into regions and model excluded comorbidities with small numbers (HIV, history of Kidney disease, Osteomyelitis, Osteoporosis, Falls, Sepsis, Parkinson's, Amputation and Retinopathy)

Figure S1. Study Design Schematic

Main analysis: Comparison of metformin versus sulfonylurea initiators who reached the kidney threshold, and continued their original regimen, persistent exposure on the original regimen is required to remain in follow-up. Gaps (red bars) of up to 90 days are allowed for medication refill after reaching kidney threshold. Patients begin follow-up at the kidney threshold and are censored at addition of another diabetes treatment or no medication refill for 90 days.

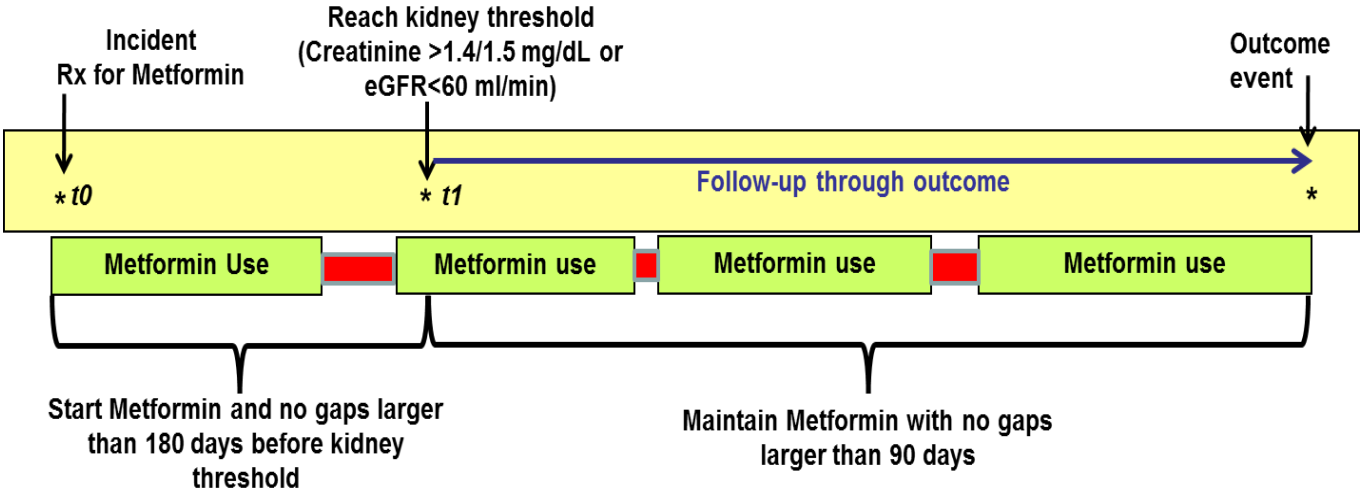

Figure S2. Distribution of logit of propensity scores by drug.

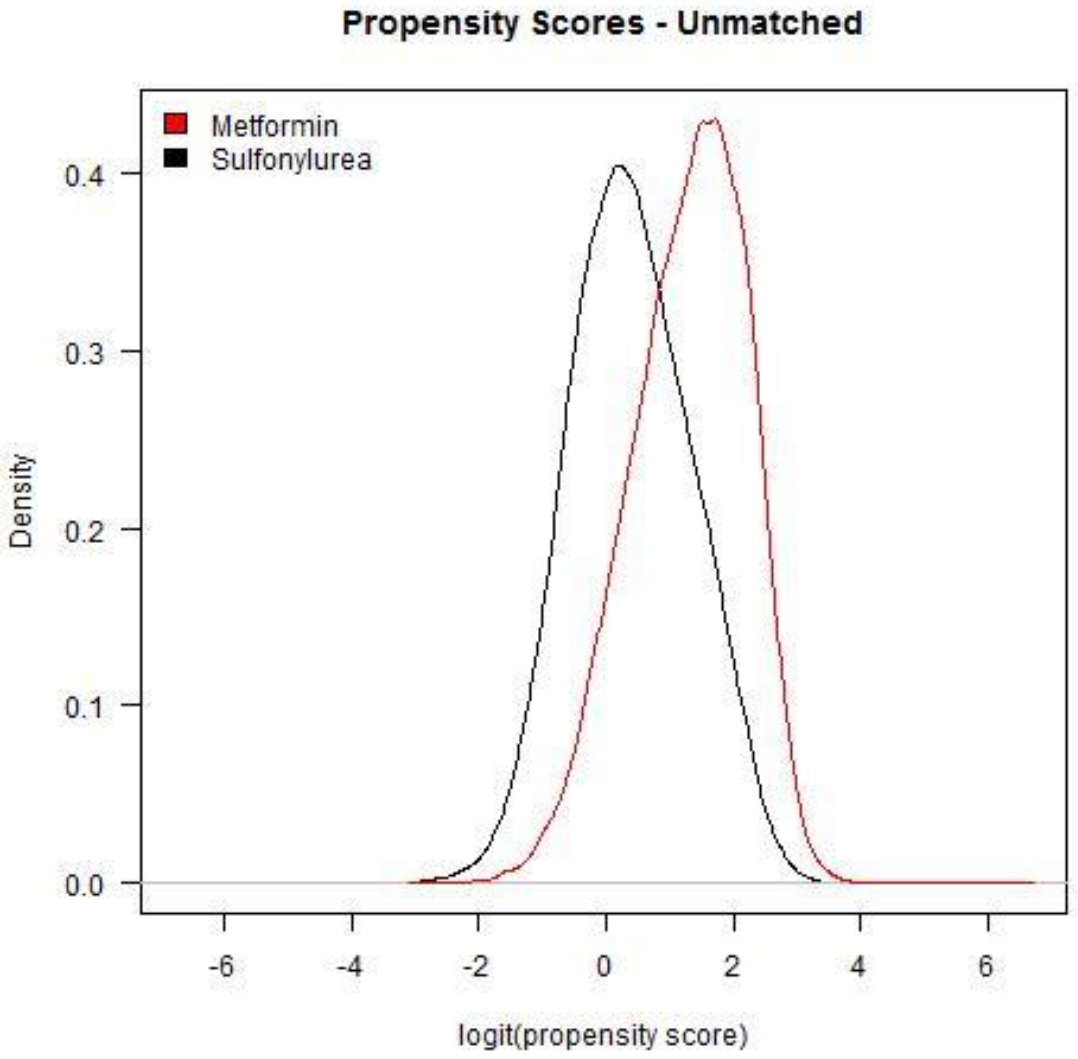

Figure S3. Mean standardized differences comparing metformin versus sulfonylurea before and after weighting the cohort.

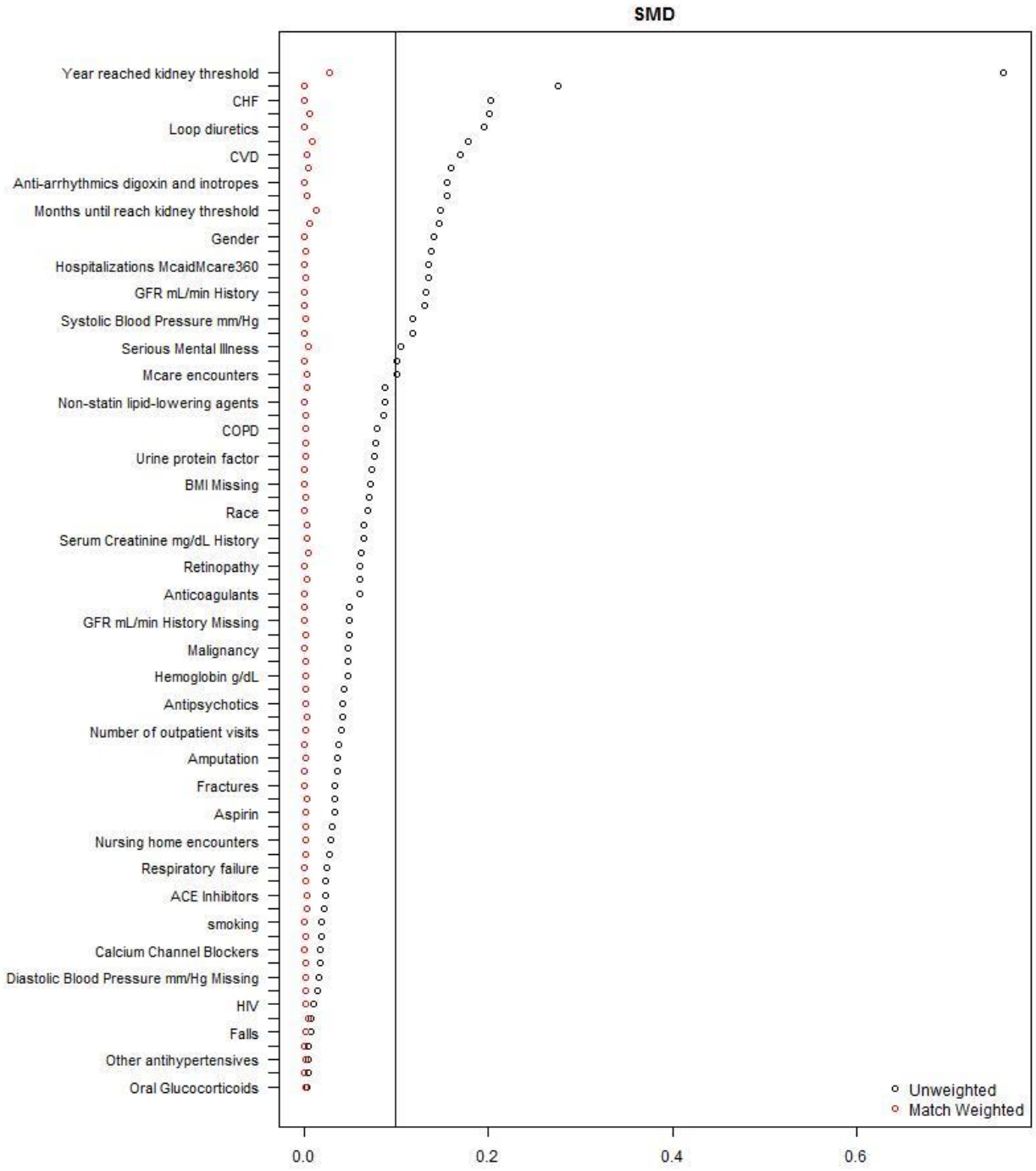

Figure S4. Aalen–Johansen cumulative incidence demonstrating Major adverse cardiovascular events with the competing risks of non-persistence and death from non-cardiovascular cause in weighted cohort.