Comparative Safety of Sulfonylurea and Metformin Monotherapy on the Risk of Heart Failure: A Cohort Study

Christianne L. Roumie, MD, MPH; Jea Young Min, PharmD, MPH; Lucy D'Agostino McGowan, MS; Caroline Presley, MD;
Carlos G. Grijalva, MD, MPH; Amber J. Hackstadt, PhD; Adriana M. Hung, MD, MPH; Robert A. Greevy, PhD; Tom Elasy, MD, MPH;
Marie R. Griffin, MD, MPH

Background—Medications that impact insulin sensitivity or cause weight gain may increase heart failure risk. Our aim was to compare heart failure and cardiovascular death outcomes among patients initiating sulfonylureas for diabetes mellitus treatment versus metformin.

Methods and Results—National Veterans Health Administration databases were linked to Medicare, Medicaid, and National Death Index data. Veterans aged ≥18 years who initiated metformin or sulfonylureas between 2001 and 2011 and whose creatinine was <1.4 (females) or 1.5 mg/dL (males) were included. Each metformin patient was propensity score-matched to a sulfonylurea initiator. The outcome was hospitalization for acute decompensated heart failure as the primary reason for admission or a cardiovascular death. There were 126 867 and 79 192 new users of metformin and sulfonylurea, respectively. Propensity score matching yielded 65 986 per group. Median age was 66 years, and 97% of patients were male; hemoglobin A_{1c} 6.9% (6.3, 7.7); body mass index 30.7 kg/m^2 (27.4, 34.6); and 6% had heart failure history. There were 1236 events (1184 heart failure hospitalizations and 52 cardiovascular deaths) among sulfonylurea initiators and 1078 events (1043 heart failure hospitalizations and 35 cardiovascular deaths) among metformin initiators. There were 12.4 versus 8.9 events per 1000 person-years of use (adjusted hazard ratio 1.32, 95%CI 1.21, 1.43). The rate difference was 4 heart failure hospitalizations or cardiovascular deaths per 1000 users of sulfonylureas versus metformin annually.

Conclusions—Predominantly male patients initiating treatment for diabetes mellitus with sulfonylurea had a higher risk of heart failure and cardiovascular death compared to similar patients initiating metformin. (*J Am Heart Assoc*. 2017;6:e005379. DOI: 10.1161/JAHA.116.005379.)

Key Words: acute heart failure • comparative effectiveness • diabetes mellitus • pharmacoepidemiology

Patients with underlying heart disease and diabetes mellitus have metabolic disturbances including hyperinsulinemia and insulin resistance that can influence heart failure incidence and progression.[1-3] It has been hypothesized that medications that improve insulin sensitivity and limit the potential for weight gain, such as metformin, could prevent heart failure,[1,4] whereas medications that increase endogenous hyperinsulinemia[5] and facilitate weight gain may increase heart failure risk.[1,6-8]

The theory that insulin sensitization may also improve cardiovascular outcomes compared to insulin provision prompted the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial.[9] That trial used a factorial design to randomize patients with diabetes mellitus and cardiovascular disease to either early revascularization or intensive medical therapy. Medical therapy was further randomized as insulin sensitization (metformin and/or a thiazolidinedione) or insulin provision (sulfonylurea and/or insulin). Heart failure was considered an adverse outcome and occurred in 22.6% of those randomized to insulin sensitization compared with 20.0% of those randomized to insulin provision (P=0.13). The effects of metformin and thiazolidinedione could not be separated, and by 3 years 75% of patients in the insulin-sensitizing group were taking thiazolidinedione and more than

25% had also added insulin and/or a sulfonylurea. Although randomized trials are ideal for assessing efficacy, they often lack the ability to assess whether treatments work under real-world conditions with a broader set of participants.[10]

A recent statement by the American Heart Association reported that metformin remains concerning for patients with established heart failure (level C evidence) because of the risk of lactic acidosis that was described with its predecessor, phenformin. Sulfonylureas were not considered in their report of drugs associated with heart failure, which focused on more frequently described associations including thiazolidinediones and saxagliptin.[11] It remains uncertain if common initial diabetes mellitus medications such as sulfonylurea differ from metformin on heart failure outcomes because heart failure has been an infrequent primary outcome in clinical trials.[12] Our aim was to test the hypothesis that heart failure outcomes would be higher among patients initiating sulfonylurea for diabetes mellitus treatment compared to metformin because of the potential for more weight gain.

Methods

Study Design and Data Sources

We assembled a retrospective cohort of Veterans Health Administration (VHA) patients.[13] Pharmacy data included dispensed prescriptions, date filled, days supplied, and number of pills. Demographic, diagnostic, and procedure information identified inpatient and outpatient encounters. We collected laboratory results and vital signs data from clinical sources. For Medicare or Medicaid enrollees, we obtained enrollment, claims files, and prescription (Part D) data.[14–17] We obtained dates and cause of death from vital status and the National Death Index files.[18] The institutional review board of Tennessee Valley Healthcare System approved this study with a waiver of informed consent.

Study Population

The population was made up of veterans aged ≥18 years who received regular VHA care at least once every 365 days for 2 or more years. New users of oral hypoglycemics were identified as patients who filled a first hypoglycemic prescription from October 2001 through December 2011 with ≥730 days of baseline data available and without any diabetic drug fill in the 180 days prior to that first fill (Figure S1). The date of first new use was termed the index date. We selected those who were adherent by including patients who refilled their incident medication at least once in the 180 days after the index date. This prevented the inclusion of those with early nonadherence and those who switched to alternate regimens. We excluded patients receiving hospice care. We also excluded patients with evidence of chronic kidney disease including females with creatinine >1.4 mg/dL and males with a creatinine >1.5 mg/dL on the index date because during this time in the United States metformin was not recommended for these patients.[19]

Exposures

The exposures were metformin and a sulfonylurea (glyburide, glipizide, or glimepiride). Follow-up began at 180 days after the incident prescription and continued through an outcome (described below) or censoring event. Patients were censored on the 181st day without medical contact (inpatient, outpatient, or pharmacy use) or nonpersistence, defined as the 91st day without the hypoglycemic therapy or addition of a second hypoglycemic drug, reaching the previously described creatinine threshold, death, or study end (December 31, 2011). Seventy percent of our population received 90-day prescriptions, and 93% and 94% of metformin and sulfonylurea users, respectively, refilled their prescriptions within 90 days.[20]

Outcome

The primary outcome was a composite of either hospitalization for a diagnosis of heart failure or cardiovascular death. The secondary outcomes evaluated each component separately, and the composite primary outcome also included emergency department visits for heart failure that did not result in hospitalization.

We defined heart failure hospitalization by adapting the validated definitions used in the Mini-Sentinel to identify heart failure outcomes.[21] Events were defined as a primary discharge diagnosis of heart failure (ICD9-CM: 425.X; 428.X; 404.01, 404.03, 404.11, 404.13, 398.91, 402.01, 402.11, 402.91, 404.91, 404.93) or a diagnosis-related group (DRG) code for heart failure (DRG 127 before fiscal year 2008; and 291-293 after fiscal year 2008). Cardiovascular deaths were identified based on death certificates with an ICD-10 coded underlying cause of death including I00-I78 (cardiovascular deaths) or R98, R99, R960, R961 (unattended deaths), excluding I30.X (diseases of the pericardium). This definition was derived from the Centers for Disease Control and Prevention and validated strategies for identification of sudden cardiac deaths.[22]

Emergency department visits for heart failure were included if there was a coded visit (CPT code 99281, 99282, 99283, 99284, 99285) and a primary heart failure diagnosis (listed above) on the same day. Any emergency department visit that resulted in hospitalization within a 48-hour time frame was considered a single hospitalization event.

Covariates

Study covariates were measured during the 730 days before the index date and included age, sex, race (white, black, other), fiscal year, healthcare utilization (hospitalization, nursing home, number of outpatient visits or medications, Medicare or Medicaid use in past year), and physiologic variables (body mass index [BMI], blood pressure, hemoglobin [Hb]A_{1c}, low-density lipoprotein levels, presence of protein-uria, and creatinine), which were used to calculate estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation,[23] selected medications, smoking, and comorbidities (Table S1). Missing covariates were handled with multiple imputations using predictive mean matching with bootstrapping.[24] All covariates from the primary analysis as well as an indicator for each Veterans Integrated Service Networks were included in 20 imputation models to compute final estimates.

Statistical Analyses

The primary analysis compared the hazard of heart failure hospitalization or cardiovascular death between exposure groups in a propensity score–matched cohort. The propensity score modeled the probability of sulfonylurea given covariates and VHA medical center. The 1:1 matching was performed on the log odds of the propensity scores using an 8:1 digit matching algorithm (Table S2, Figure S2).[25,26] Cox proportional hazards models were used to compare outcomes for sulfonylurea versus metformin (referent) in the matched cohort adjusted for covariates. The proportional hazards assumptions were verified through examination of log-log plots.

Evaluation of a Positive Control: Sensitivity and Subgroup Analyses

We conducted planned sensitivity analyses. First, we used the initial regimen that defined exposure and ignored subsequent regimen changes or the 90-day refill requirement (persistent exposure not required). This analysis is akin to intention-to-treat analysis in clinical trials; however, although it increases follow-up time and events, it allows for exposure time misclassification due to patient non-adherence. Second, because the main analysis included a matched subset of the population, we conducted an inverse probability of treatment weighted analysis to include all patients. For these analyses, we used the previously described propensity score and weighted the sulfonylurea users to resemble the metformin population and approximate a balanced cohort. For this analysis we also included new users of thiazolidinedione (a small, select group[27]) as a positive control group because of

the well-described association of thiazolidinediones with heart failure outcomes.[28,29] Third, in the cohort construction we were interested in long-term outcomes; therefore, follow-up began 180 days post–treatment initiation to minimize the inclusion of those with early nonadherence and regimen switching. To evaluate early outcome differences between groups, we performed an alternate weighted analysis with a new-user design in which follow-up began at the index date and continued through the first 180 days.[30,31] For this analysis we also included thiazolidinedione users. We conducted subgroup analyses, stratifying by history of heart failure diagnosis (yes, no), age (≥65, <65 years), and race (black, white). Finally, we explored the sensitivity of our main analysis to potential unmeasured confounding.[32] For this we assessed the strength of the association of an unmeasured binary confounder and its hypothetical distribution between exposure groups that would be required to explain our findings. Analyses were conducted using R (http://www.r-project.org) and SAS for Windows 9.2. (SAS Institute Cary, North Carolina).

Results

Study Cohort and Patient Characteristics

There were 407 145 patients who started an antidiabetic medication (no hypoglycemics filled in the previous 180 days). Of these, 102 457 initiated regimens other than metformin or a sulfonylurea; 142 were excluded for data errors; 21 474 were excluded for elevated creatinine or hospice care; 23 207 died or were censored during the 6-month lag time, and 53 806 were not persistent on their initial regimen at the start of follow-up (early stoppers N=33 363; early intensifiers N=20 443). Thus, there were 126 867 metformin initiators and 79 192 sulfonylurea initiators (46.2% glipizide, 53.1% glyburide, and 0.7% glimepiride; Figure 1). After 1:1 propensity score matching, our study included 65 986 patients in each group, and baseline characteristics were similar (Table 1, Figure S3). Characteristics of patients excluded from the PS match are shown in Table S3. Characteristics of patients included in the weighted analysis (including 6945 thiazolidinedione new users as a positive control group) are listed in Table S4.

In the primary analysis, the median (interquartile range [IQR]) follow-up prior to censoring or reaching an outcome was 1.1 (0.4, 2.7) years among metformin users and 0.9 (0.4, 2.1) year among sulfonylurea users. Reasons for censoring were nonpersistence (49% metformin versus 46% sulfony-lurea); additional therapy (24% versus 28%); no healthcare contact (5% versus 5%); reaching creatinine threshold (10% versus 11%); study end (9% versus 5%); or death (2% versus 2%). In the sensitivity analysis in which regimen persistence
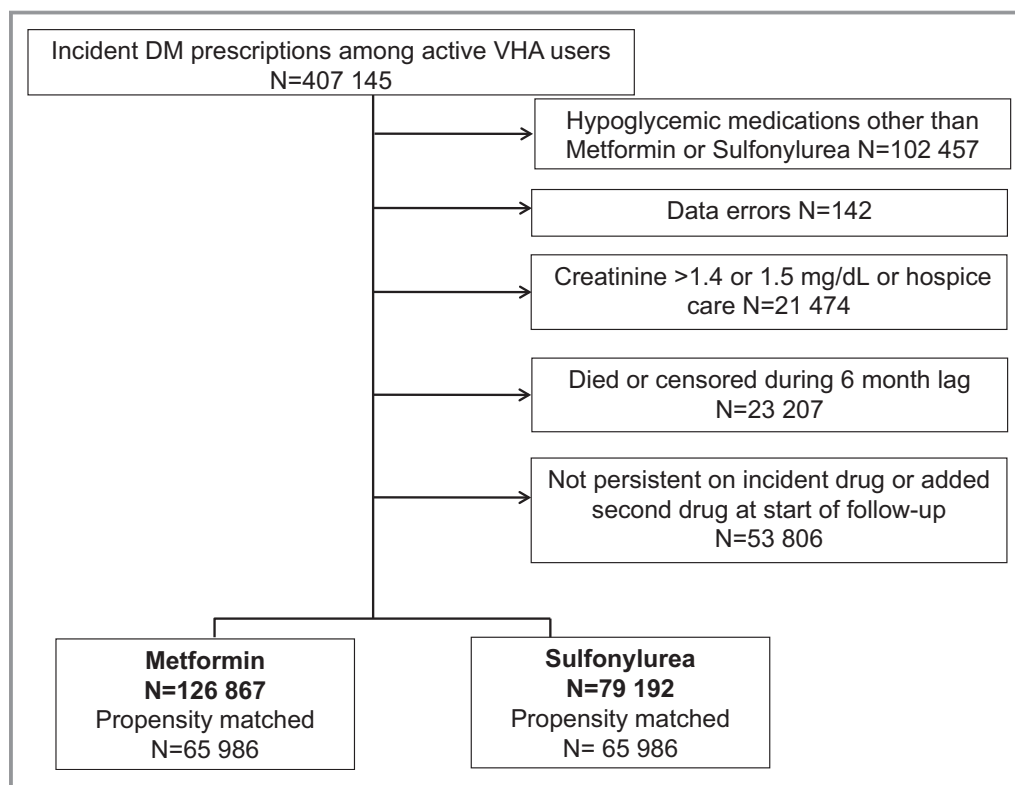
Figure 1. Flow of eligible patients included.

was not required, the median follow-up time was 5.1 (3.6, 6.6) versus 5.0 (3.0, 6.5) years among metformin and sulfonylurea users, respectively.

Time to Heart Failure Events or Cardiovascular Death

There were 1236 events (1184 heart failure hospitalizations and 52 cardiovascular deaths) among sulfonylurea initiators and 1078 events (1043 heart failure hospitalizations and 35 cardiovascular deaths) among metformin initiators, yielding 12.4 versus 8.9 events per 1000 person-years of use, respectively (adjusted hazard ratio [aHR] 1.32, 95%CI [1.21, 1.43]) (Table 2, Figure 2). Event rates for heart failure hospitalization alone comprised the majority of the outcomes and were 11.9 and 8.6 per 1000 person-years among sulfonylurea and metformin users (aHR 1.30 [1.20, 1.42]). Event rates for cardiovascular death alone were 5.2 and 2.9 per 10 000 person years among sulfonylurea and metformin users (aHR 1.76 [1.14, 2.71]). The secondary outcome that added emergency room visits yielded event rates of 15.1 versus 11.0 per 1000 person-years among sulfonylurea and metformin users (aHR 1.30 [1.20, 1.40]).

We assessed median [interquartile range] HbA_{1c} and BMI on the index date and over time for the matched cohort. Baseline HbA_{1c} was 6.9% (51.9 mmol/mol) in both groups,

and declined to 6.4% [6.0, 6.9] (46.4 mmol/mol [42.1, 51.9]) and 6.5% [6.0, 7.1] (47.5 mmol/mol [42.1, 54.1]) in metformin and sulfonylurea initiators, respectively, by 1.5 years after drug initiation. The HbA_{1c} difference of 0.1% (1.1 mmol/mol) was maintained between groups over follow-up. Median BMI declined rapidly in metformin initiators, yielding a maximum difference of 0.9 BMI units between groups by 1.5 years. This difference narrowed to 0.5 BMI unit difference at 7.5 years (Figure 3).

Sensitivity and Subgroup Analyses

In sensitivity analyses in which patients remained in their original exposure group, (persistent exposure not required), there were 4573 events (4366 heart failure hospitalizations, 207 cardiovascular deaths) among sulfonylurea initiators and 4007 events (3830 heart failure hospitalizations, 177 cardiovascular deaths) among metformin initiators, yielding 14.7 and 12.4 events per 1000 person-years (aHR 1.21 [1.16, 1.27]) (Table 2).

In analyses in which sulfonylurea users were weighted to resemble metformin users, there were 1699 and 1499 events among sulfonylurea and metformin users, yielding 8.9 and 6.2 events per 1000 person-years (aHR 1.43, [1.32, 1.55]) (Table 2). As a positive control, thiazolidinedione users were compared to weighted metformin users; there were 141 and

Table 1. Characteristics of Patients in the Unmatched and Matched Cohorts

Characteristics	Full Cohort		Propensity-Matched Cohort		
	Sulfonylurea (N=79 192)	Metformin (N=126 867)	Sulfonylurea (N=65 986)	Metformin (N=65 986)	Standardized Differences for Matched Cohort*
Age, median (IQR)	68 (58, 77)	62 (56, 72)	66 (57, 75)	66 (58, 75)	0.013
Male, %	97	95	97	97	0.006
Race, %					
White	77	76	77	77	0.002
Black	14	13	13	14	0.003
Hispanic/other	5	4	5	5	0.004
Missing	4	7	5	4	0.008
HbA$_{1c}$, % median (IQR)	6.9 (6.3, 7.8)	6.8 (6.3, 7.5)	6.9 (6.3, 7.7)	6.9 (6.3, 7.6)	0.024
Missing measurement, %	22	19	21	21	0
Low-density lipoprotein, mg/dL, median (IQR)	98 (77, 122)	99 (79, 123)	98 (78, 123)	98 (78, 122)	0.007
Missing measurement, %	31	25	29	29	0.002
Creatinine mg/dL, median (IQR)	1.1 (0.9, 1.2)	1.0 (0.9, 1.1)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	0.029
Glomerular filtration rate mL/min, median (IQR)	77 (64, 94)	84 (71, 99)	80 (67, 97)	79 (67, 96)	0.019
Missing measurement, %	18	14	17	17	0
Proteinuria, (%) negative	47	51	48	48	0.001
Urine protein trace or 1+	11	10	11	11	0.001
Proteinuria present at 2+	2	1	2	2	0
Proteinuria present at 3+	0.41	0.27	0	0	0
Proteinuria present at 4+	0.05	0.02	0	0	0
Missing measurement, %	40	39	40	39	0.002
Systolic blood pressure, mm Hg, median (IQR)	136 (124, 148)	135 (124, 146)	136 (124, 148)	136 (124, 148)	0.001
Diastolic blood pressure, mm Hg, median (IQR)	76 (68, 83)	77 (70, 84)	76 (68, 84)	76 (68, 84)	0.006
Missing measurement, %	2.6	1.9	2	2	0.001
Body mass index, kg/m^2, median (IQR)	30.2 (26.9, 34.1)	31.8 (28.4, 36.0)	30.7 (27.4, 34.6)	30.7 (27.4, 34.6)	0.003
Missing measurement, %	4.3	2.9	4	4	0.002
Baseline comorbidities, %[†]					
Malignancy	7	5	6	6	0.002
Liver/respiratory failure	2	1	1	1	0.005
HIV	0.6	0.4	1	0	0.004
Congestive heart failure	10	4	6	6	0.003
Cardiovascular disease	28	22	27	27	0.001
Serious mental illness	16	17	17	17	0
Smoking	11	12	11	11	0.001
Chronic obstructive pulmonary disease	15	12	13	13	0
Cardiac valve disease	2	1	2	2	0.001
Arrhythmia	11	7	9	9	0.002
Parkinson	0.8	0.5	1	1	0.002

Table 1. Continued

Characteristics	Full Cohort		Propensity-Matched Cohort		
	Sulfonylurea (N=79 192)	Metformin (N=126 867)	Sulfonylurea (N=65 986)	Metformin (N=65 986)	Standardized Differences for Matched Cohort*
Use of medications, %					
Angiotensin-converting enzyme inhibitors	53	53	53	53	0.003
Angiotensin II receptor blockers	7	8	7	7	0.003
β-Blockers	44	40	42	42	0.005
Calcium channel blockers	26	24	26	26	0.002
Thiazide and potassium-sparing diuretics	31	33	31	31	0.006
Nonselective α blockers	16	14	15	16	0.009
Loop diuretics	18	10	14	14	0.003
Other antihypertensive medications	26	24	25	25	0.002
Statin lipid-lowering drugs	58	64	60	60	0.002
Nonstatin lipid-lowering drugs	15	18	16	16	0.001
Antiarrhythmics, digoxin, and inotropes	2	2	2	2	0.005
Anticoagulants, platelet inhibitors	8	5	7	7	0.001
Nitrates	15	11	14	14	0.004
Aspirin	18	17	18	18	0
Antipsychotics	7	8	8	8	0.002
Oral glucocorticoids	12	11	12	12	0.001
Indicators of health care utilization, %					
Hospitalized in last year (Veterans Health)	9	6	8	8	0.007
Hospitalized in last year (Medicare/Medicaid)	11	6	8	8	0
Hospitalized within 30 days (Veterans Health)	4	3	3	3	0.003
Hospitalized within 30 days (Medicare/Medicaid)	3	1	2	2	0.004
Days from prior heart failure hospitalization to incident diabetes mellitus drug, median (IQR)	218 (65, 427)	266 (97, 456)	268 (81, 476)	257 (95, 440)	0.032
Nursing home encounter in last year	0.07	0.05	0	0	0.001
Number medications	10 (7, 14)	9 (6, 14)	10 (6, 14)	10 (6, 14)	0.003
Outpatient visits in past year	5 (3, 9)	5 (3, 9)	5 (3, 9)	5 (3, 9)]	0.003
Medicare use in last year	34	26	32	32	0.002
Medicaid use in last year	15	9	12	12	0.001

IQR indicates interquartile range.

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

†Definitions of comorbidities included in Table S1.

154 events, yielding 16.5 (14.0, 19.4) and 10.5 (8.9, 12.2) events per 1000 person-years (aHR 1.44, [1.20, 1.74]).

In the primary analyses, follow-up began 6 months after the index date to minimize early nonadherence and regimen switching. The alternate weighted analysis of new users evaluating this first 6-month period found sulfonylurea (N=163 995) versus metformin (N=166 397) had 11.7 (11.0, 12.5) versus 7.8 (7.2, 8.4) events per 1000 person-

years (aHR 1.50 [1.35, 1.66]). Those who initiated thiazolidinedione (N=10 164) versus metformin (N=10 200) had 25.7 (21.6, 30.6) versus 14.9 (11.9, 18.7) events per 1000 person-years (aHR 1.72 [1.36, 2.18]) (Table S5). Subgroup analyses demonstrated consistent results including patients both with and without a prior history of heart failure. There was no evidence of effect modification (Figure 4).

Table 2. Rates and Adjusted Hazard Ratios for Risk of Congestive Heart Failure Events or Cardiovascular Deaths Among Those Who Initiate Metformin vs Sulfonylurea Among Propensity Score–Matched and Weighted Cohort

	Metformin	Sulfonylurea
Persistent exposure required*		
N at risk	65 986	65 986
Composite heart failure hospitalization or cardiovascular death	1078	1236
Person-years	121 406	99 872
Unadjusted rate/1000 person-years	8.9 (8.4, 9.4)	12.4 (11.7, 13.1)
Adjusted hazard ratio[†] (95%CI)	Reference	1.32 (1.21, 1.43)
Heart failure hospitalization alone	1043	1184
Unadjusted rate/1000 person-years	8.6 (8.1, 9.1)	11.9 (11.2, 12.5)
Adjusted hazard ratio[†] (95%CI)	Reference	1.30 (1.20, 1.42)
Cardiovascular death alone	35	52
Unadjusted rate/10 000 person-years	2.9 (2.1, 4.0)	5.2 (3.9, 6.8)
Adjusted hazard ratio[†] (95%CI)	Reference	1.76 (1.14, 2.71)
Composite heart failure emergency department visit, hospitalization, or cardiovascular death	1334	1449
Person-years	121 147	99 600
Unadjusted rate/1000 person-years	11.0 (10.4, 11.6)	15.1 (14.3, 15.8)
Adjusted hazard ratio[†] (95%CI)	Reference	1.30 (1.20, 1.40)
Persistent exposure not required[‡]		
N at risk	65 986	65 986
Composite heart failure hospitalization or cardiovascular death	4007	4573
Person-years	323 268	311 040
Unadjusted rate/1000 person-years	12.4 (12.0, 12.8)	14.7 (14.3, 15.1)
Adjusted hazard ratio[†] (95%CI)	Reference	1.21 (1.16, 1.27)
Weighted analysis of full cohort		
N at risk (weighted)	126 867	125 362
Composite heart failure hospitalization or cardiovascular death	1499	1699
Person-years	240 948	190 773
Unadjusted rate/1000 person-years	6.2 (5.9, 6.5)	8.9 (8.5, 9.3)
Adjusted hazard ratio[†] (95%CI)	Reference	1.43 (1.32, 1.55)

*Primary analysis considers patients persistent on incident regimen until they do not have oral antidiabetic medications for 90 days.

[†]Cox proportional hazards model for time to event. Adjusted for age, sex, race, fiscal year of cohort entry, number of medications, number of outpatient visits, baseline HbA$_{1c}$, body mass index, estimated glomerular filtration rate, low-density lipoprotein cholesterol, blood pressure, use of medications and health care utilization (see Table S1), smoking-related illness, cardiovascular disease, serious liver/respiratory disease, cancer, Parkinson disease, mental illness, arrhythmia, cardiac valve disease, asthma/obstructive pulmonary disease, procedures for carotid/peripheral artery revascularization or bypass or lower extremity amputation. All continuous variables were modeled as restricted cubic splines.

[‡]Persistent exposure not required analysis in which patients remain in their exposure group, regardless of persistence on drug therapy, until outcome or end of the study.

Our finding of increased hazard for the composite outcome among sulfonylurea users could in theory have resulted from an unmeasured covariate that is associated with heart failure and was more prevalent among sulfonylurea than metformin users. For example, we observed heart failure history to have a HR of 2.3 for our outcome. An unmeasured confounder of this strength would need to be at least 17% more prevalent among sulfonylurea users. For comparison in the unmatched cohort, baseline heart failure history was only 5% more prevalent. Thus, if an unmeasured confounder comparable to heart failure history existed, it would not change this paper's main conclusions (Table S6).

Discussion

Type 2 diabetes mellitus is linked to obesity and is an independent risk factor for cardiomyopathy.[33,34] Patients with type 2 diabetes mellitus have abnormalities in carbohydrate
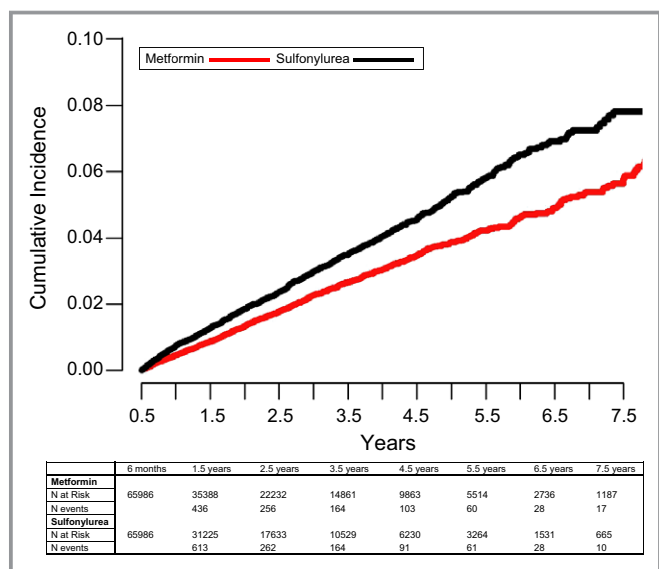
Figure 2. Cumulative incidence of heart failure hospitalization or cardiovascular death over time.

sensitivity and limit weight gain, such as metformin, may be more beneficial than medications that increase endogenous insulin and result in weight gain, such as sulfonylureas. Many hypoglycemics have not been rigorously evaluated for the risk of heart failure.[12,38] Clinical trials of diabetes mellitus medications, including the United Kingdom Prospective Diabetes Study, excluded patients with heart failure. The associations reported between heart failure and thiazolidinediones or saxagliptin have been the subject of much debate, in part because these associations were identified as adverse event reports, not as prespecified outcomes in clinical trials that had other surrogate or cardiovascular events as outcomes.[7,8,39]

In this national cohort of veterans who initiated either metformin or a sulfonylurea for first-line diabetes mellitus treatment, we found that sulfonylurea initiation was associated with an increased risk of heart failure hospitalization and cardiovascular death compared with metformin initiation. Our comparison groups were carefully matched on important covariates including BMI and HbA_{1c} at therapy initiation. Interestingly, among patients who remained at risk by 1.5 years after initiation, metformin users had on average almost 1 BMI unit lower weight than patients prescribed a

metabolism (insulin resistance) and elevated insulin levels (hyperinsulinemia), which contribute to the development of heart failure.[4,35-37] Medications that improve insulin
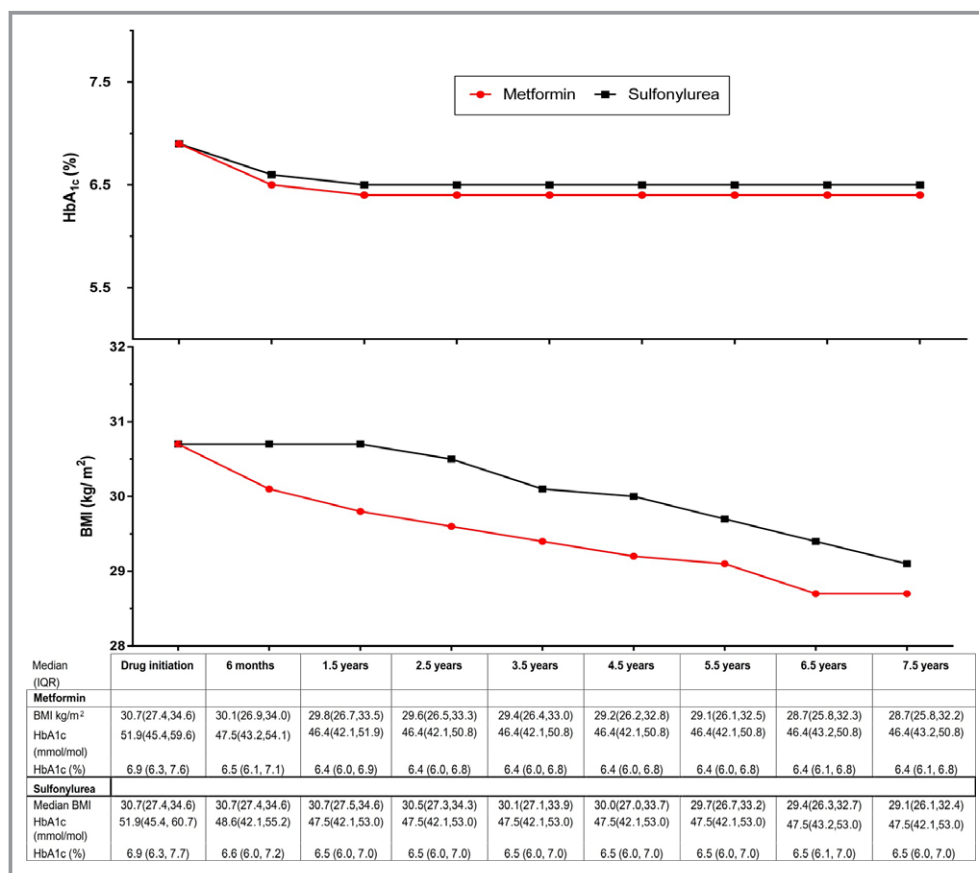

Figure 3. Median (interquartile range) glycated hemoglobin (HbA_{1c}) and body mass index (BMI) of at-risk patients over time.
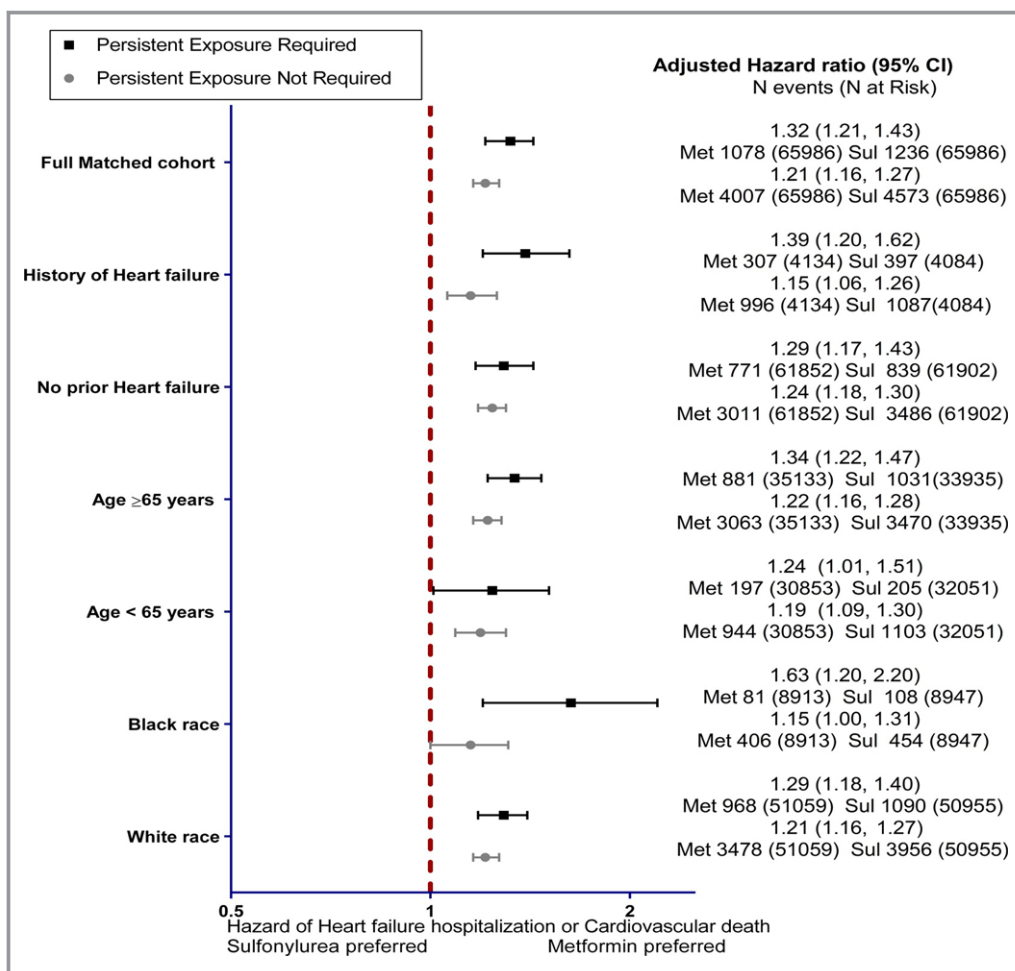
Figure 4. Adjusted hazard ratio and 95%CIs of subgroups. Two medication adherence requirements tested: persistence to medication required with 90-day gaps or persistence not required. Sul indicates sulfonylurea; Met, metformin.

sulfonylurea (≈2.9 kg for an average 5 foot 10 inch male) and a 0.1% lower HbA$_{1c}$. The weight differences largely persisted for the study duration. These weight differences are also consistent with findings from the systematic review and a recent network meta- analysis.[12,40] Bennett reported a pooled 2.5-kg relative difference in weight for monotherapy between metformin and a sulfonylurea with a high strength of evidence. The network meta-analysis by Palmer et al[12] reported a standardized mean difference of 0.19-kg higher weight for sulfonylurea monotherapy users compared with those taking metformin. Nevertheless, it remains unclear to what extent the degree of glycemic control or changes in weight affected the heart failure risk in our study.

Several lines of evidence suggest that weight changes during diabetes mellitus management are associated with heart failure. A meta-analysis and metaregression[41] combined information from multiple trials to investigate whether glucose-lowering drugs (predominantly thiazolidinedione or dipeptidyl peptidase-4 inhibitors) or management strategies

(standard versus intensive control) were associated with heart failure. There were 95 502 patients included from 14 trials. The meta-analysis demonstrated that, compared with standard glucose control, heart failure risk increased with intensive control (risk ratio 1.14 [1.01, 1.30]) and was also associated with weight gain (P=0.02 for meta-regression). Each 1.0 kg increase in weight was associated with a 7.1% (95%CI 1.0–13.6) relative increase in heart failure risk. Conversely, weight loss was associated with a decreased heart failure risk [risk ratio 0.80 (0.62, 1.04)]. Another recent observational cohort followed more than 10 000 patients in a United Kingdom diabetes registry for more than 10 years.[42] The risk of incident heart failure was 2 times higher among obese patients (BMI ≥30 kg/m^2) in all age tertiles compared with patients whose BMI was between 18.5 and 24.9 kg/m^2.

Possible explanations for our findings include differential medication effects on BMI, as evident in our cohort and others,[42,43] and/or differential effects on insulin levels or insulin resistance.[36,37] Our study is not mechanistic and cannot

establish a causal relationship or distinguish among these hypotheses. However, the BMI difference observed between metformin and sulfonylurea users is consistent with a differential risk of heart failure. We also verified the expected increased association of heart failure with thiazolidinediones versus metformin. This finding and consistent results using different methodologic approaches lend credence to the increased risk observed with sulfonylureas versus metformin. Our results are consistent with the United Kingdom Prospective Diabetes Study and a large cohort within the Clinical Practice Research Database, which found beneficial effects of metformin on heart failure but no benefit from sulfonylurea.[44,45] The study by Tzoulaki in the Clinical Practice Research Database found that sulfonylurea was associated with a higher risk of heart failure than metformin, but confidence intervals were wide in fully adjusted models, most likely due to a smaller number of outcome events than in our current study. We estimated sulfonylurea users to have an average of 4 excess heart failure hospitalizations or cardiovascular deaths per 1000 users annually compared to the metformin users.

Our study does have limitations. First, although we utilized multiple strategies to address confounding by indication and disease severity including exclusions, propensity score matching, and covariate adjustment, residual confounding from unmeasured factors, such as patient frailty, remains possible. Our findings were robust when we assessed sensitivity to unmeasured confounders. A hypothetical unmeasured confounder resembling the baseline heart failure history prevalence in prematching imbalance and with a similar strength of association with the outcome would not explain the statistically significant results from our primary analysis (Table S6). Second, veterans may not receive all their care or medications at veteran facilities,[15,16] resulting in missing outcomes or medications, which we partially addressed through supplementation with Medicare/Medicaid information. Third, we did not account for time-varying nonadherence to other medications, such as diuretics, which may lead to heart failure exacerbations. Our groups were matched on baseline characteristics, including medications and comorbidities associated with heart failure risk, and consistent associations were also observed among patients without a history of heart failure. Fourth, to reduce exposure misclassification, follow-up started 180 days after initiation, and because we required persistence on drug for our primary analysis, the median follow-up time was short, ≈1 year. Although this approach excluded the initial exposure period, separate evaluations examined the first 6 months and also allowed for nonpersistence and increased follow-up to an average of 5 years. Both sensitivity analyses produced consistent results. Finally, our population reflects a typical veteran population, predominantly male; therefore, caution is warranted when extrapolating to other settings and to females.

At age 40, the lifetime risk of developing heart failure is 1 in 5. It remains the primary reason for hospital admission among both VHA and Medicare beneficiaries and a major contributor to the $37.2 billion in heart failure costs in the United States. We found that using sulfonylurea as an initial therapy for diabetes mellitus was associated with more heart failure outcomes than initiation of metformin. Metformin is already the preferred first-line medical therapy for diabetes mellitus and now can be used safely in another insulin-resistant state, mild to moderate kidney disease.[46] Despite the recommendation to use metformin, sulfonylurea remains an initial choice for diabetes mellitus treatment in 20%[47] to 30%[27] of the insured and VHA populations, respectively, because of physician preference, relative ease of initiation and titration, and lack of gastrointestinal side effects. Given the clinically important increase in heart failure and other cardiovascular risk associated with sulfonylureas compared with metformin,[13,44] it is urgent to determine whether other drugs should be preferred over sulfonylureas for those intolerant to metformin.

Author Contributions

Drs Roumie, Greevy, Grijalva, Hung, Elasy, and Griffin designed the study. Drs Roumie, Min, Presley, Greevy, and Griffin conducted the study and collected data. Analysis was done by Drs D'Agostino McGowan, Hackstadt, and Greevy. The manuscript was drafted by Dr Roumie, and critical revision of the manuscript was performed by Drs Roumie, Min, Presley, Hung, D'Agostino McGowan, Hackstadt, Greevy, Grijalva, Elasy, and Griffin. Drs Roumie and Greevy had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

None.

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Supplemental Material

Table S1. Definitions of comorbid conditions and medications, on the basis of codes and prescriptions in 730 days before treatment intensification

Covariate Condition	Inclusive conditions	Definition*
Malignancy	Cancer excluding non melanoma skin cancer	ICD 9- CM diagnosis codes:140.X-208.X (exclude 173)
Liver/ Respiratory failure	1. End stage liver disease	ICD 9- CM diagnosis codes: 570.X- 573.X
	2. Respiratory failure	ICD 9- CM diagnosis codes: 518.81, 518.83, 518.84, 799.1, 415.X, 416.X
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, 425.X
Cardiovascular disease	1. MI	ICD 9- CM diagnosis codes:410.X, 412.X, 429.7X
	2. Obstructive coronary disease	ICD 9- CM diagnosis codes:411.X, 413.X, 414.X 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. TIA	ICD 9- CM diagnosis codes: 435.X
	4. Stroke	ICD 9- CM diagnosis codes: 430.X, 431.X. 434.X, 436.X
	5. Peripheral artery disease revascularization or amputation	ICD 9- CM diagnosis codes:440.2X, 442.2, 443.1, 443.9, 445.0X 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; 84.10-84.17 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
	6. 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 HCPCS procedure code: S2211
	7. Pentoxifylline & related drugs	Medications: Pentoxifylline, Cilostazol, Cyclandelate, Ethaverine HCL, Nicotinyl Alcohol Tartate, Papaverine, Tolazolin
Serious Mental illness	1. Dementia	ICD 9- CM diagnosis codes: 290.X, 291.2, 292.82, 294.1X, 331.0-331.1X, 331.82 Medications: Donepezil, Rivastigmine, Galantamine, Tacrine, Memantine
	2. Depression,	ICD 9- CM diagnosis codes: 311, 300.4, 296.2, 296.3, V79.0
	3. Schizophrenia,	ICD 9- CM diagnosis codes: 295.X
	4. Bipolar disorder	ICD 9- CM diagnosis codes: 296.0, 296.4X, 296.5X, 296.6X, 296.7, 296.80, 296.89
	5. Post traumatic stress disorder	ICD 9- CM diagnosis codes: 309.81
Cardiac valve disease		ICD 9- CM diagnosis codes: 394.X, 395.X, 396.X, 424.0, 424.1
Arrhythmia	1. Atrial fibrillation/flutter	ICD 9- CM diagnosis codes: 427.3X
	2. Arrhythmia and conduction disorder	ICD 9- CM diagnosis codes: 426.X, 427.X
Smoking		ICD 9- CM diagnosis codes:305.1, V15.82, 989.84 Medications: Varenicline tartrate, Nicotine Replacement therapy (gum, patch, lozenge)
COPD/ Asthma		ICD 9- CM diagnosis codes:491.X, 492.X, 493.X, 496.X, V17.5, V81.3
HIV		ICD 9- CM diagnosis codes: 042, 079.53, 795.71, V08 Medications: Zidovudine, Didanosine, Zalcitabine, Stavudine, Indinavir, Ritonavir, Saquinavir, Nevirapine, Nelfinavir, Delavirdine, Delavirdine, Abacavir, Amprenavir, Efavirenz, Lamivudine-Zidovudine, Ritonavir-Lopinavir, Abacavir-Lamivudine-Zidovudine
Parkinson's Disease		ICD 9- CM diagnosis codes: 332 Medications: Apokyn, Apomorphine, Carbidopa/levodopa, Entacapone, Pergolide, Pramipexole, Ropinirole, Rotigotine, Selegiline, Tolcapone, Zelapar, Azilect/Rasagiline, Emsam, Isocarboxazid, Phenelzine, Tranylcypromine
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
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

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, Iloprost, 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; 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 in the 730 days before treatment intensification.

Table S2. Details for the construction of the propensity score model
The pre-matching cohort was composed of all eligible persons who initiated metformin or sulfonylurea for diabetes and met the study's inclusion criteria. The matched cohort was formed by matching metformin users to sulfonylurea users with similar propensity scores. The propensity score (PS) is defined as the probability of sulfonylurea use, given a particular pattern of baseline covariates (Table 2). We estimated the PS using a logistic regression model in which the dependent variable was 1 for patients who used sulfonylurea and 0 for metformin users and used restricted cubic splines (3 knots) for continuous covariates in the model. The PS model is designed to be non-parsimonious and highly flexible to capture all observable confounding by indication. Indicator variables denoting missingness were included in the PS model, allowing the PS to balance missingness patterns between the exposures and control for potentially informative missingness.   Multiply imputed PS model coefficients were aggregated using Rubin's rules and the aggregated model used to generate PS values. The PS model is displayed in Appendix Table 2. The PS model yielded a C statistic of 0.71. When used to facilitate matching, the success of the PS model is determined by the covariate balance achieved in the matched cohort. Table S1 and Figures S2 and S3 demonstrate the mean standardized differences before and after propensity score matching. Indicating good balance after matching, all standardized differences have an absolute value $\leq$ 0.1. An important condition for propensity score methods is that every cohort member have a nontrivial probability of having received either of the study therapies (positivity). Our matching procedure excluded sulfonylurea patients for whom very few similar metformin users existed. Unmatched sulfonylurea patients primarily were older, had higher number of co-morbidities and had a higher serum creatinine at the time of drug initiation (See Table S3 for characteristics of unmatched patients). The matching was performed on the log odds of the propensity scores using an 8:1 digit greedy match algorithm.

Logistic regression model for the probability of initiating Sulfonylurea (N=65,986 matches)

Characteristic	Odds Ratio	95% Confidence Intervals	
Comorbidities			
Malignancy	1.06	1.02	1.11
Liver/ respiratory failure	2.12	1.94	2.31
Congestive heart failure	1.60	1.53	1.67
Cardiovascular disease	1.02	0.99	1.04
Serious mental illness	0.98	0.95	1.01
Cardiac valve disease	1.04	0.96	1.12
Arrhythmia	1.02	0.98	1.06
Smoking	1.01	0.98	1.05
Chronic Obstructive Pulmonary Disease/ Asthma	1.01	0.98	1.05
HIV	1.66	1.45	1.91
Parkinsons	1.02	0.90	1.15
Indicators of health care utilization			
Hospitalized in last year (VA)	1.12	1.07	1.18
Hospitalized in last year (Medicare)	1.05	0.98	1.12
Hospitalized in last year (Medicaid)	0.92	0.72	1.17
Hospitalized in month of incident diabetes prescription (VA)	1.12	1.05	1.20
Hospitalized in month of incident diabetes prescription (Medicare)	1.21	1.11	1.31
Hospitalized in month of incident diabetes prescription (Medicaid)	1.11	0.76	1.61
Nursing Home encounter in last year	0.90	0.61	1.33
Number of medications	1.12	1.09	1.15
Outpatient Visits in past year	1.00	0.98	1.02
Medicare encounters in last year	0.92	0.90	0.94
Medicaid encounters in last year	1.11	1.05	1.17
Demographics			
Race Black	1.19	1.15	1.23
Race Other	1.11	1.06	1.17
Gender Female	0.54	0.50	0.57
Age	1.35	1.32	1.39
Incident therapy date	0.65	0.64	0.66
Clinical and laboratory			
HbA1c	1.09	1.08	1.11
Systolic Blood pressure	1.06	1.04	1.07

4

Diastolic Blood pressure	0.99	0.97	1.00
Body Mass Index	0.76	0.74	0.77
Low Density Lipoprotein	1.02	1.01	1.03
Creatinine	1.11	1.06	1.15
Estimated Glomerular Filtration Rate	0.80	0.77	0.83
Urine Protein negative	1.07	1.02	1.11
Urine Protein Trace or 1+	1.21	1.15	1.26
Proteinuria present at 2+,	1.26	1.17	1.36
Proteinuria present at 3+,	1.29	1.09	1.52
Proteinuria present at 4+	2.00	1.17	3.43
Medications			
ACE Inhibitors	0.98	0.96	1.00
ARBs	0.92	0.89	0.96
Calcium Channel Blockers	0.99	0.97	1.02
Beta Blockers	1.04	1.02	1.06
Thiazide and k sparing	0.97	0.95	0.99
Other Anti hypertensive medications	0.96	0.94	0.99
Statin lipid lowering agents	0.75	0.73	0.76
Non-statin lipid lowering agents	0.90	0.88	0.93
Anti-arrhythmics, digoxin and inotropes	1.15	1.07	1.23
Anticoagulant	1.05	1.01	1.10
Nitrates	1.12	1.09	1.16
Aspirin	0.97	0.95	1.00
Loop Diuretics	1.44	1.40	1.49
Antipsychotics	1.06	1.02	1.11
Oral glucocorticoids	1.03	0.99	1.06
Indicators of Missing covariates imputed			
HbA1c missing	0.97	0.94	1.00
LDL missing	1.08	1.05	1.11
Glomerular filtration rate missing	1.25	1.21	1.30
Blood pressure missing	0.93	0.85	1.03
BMI missing	1.23	1.14	1.33
Race missing	0.92	0.87	0.96
Urine protein testing missing	0.97	0.94	0.99
Location of care versus station 589			
Station 402	0.85	0.75	0.97
Station 405	0.84	0.71	1.00
Station 436	0.90	0.77	1.05
Station 437	1.83	1.59	2.12
Station 438	1.15	1.00	1.32
Station 442	0.72	0.58	0.89
Station 459	1.21	1.00	1.46
Station 460	1.00	0.87	1.16
Station 463	0.48	0.38	0.60
Station 501	0.92	0.81	1.04
Station 502	1.42	1.26	1.60
Station 503	1.30	1.13	1.49
Station 504	1.43	1.22	1.67
Station 506	0.98	0.85	1.14
Station 508	2.30	2.05	2.57
Station 509	1.12	0.97	1.30
Station 512	1.46	1.29	1.64
Station 515	1.16	1.00	1.34
Station 516	0.87	0.79	0.96
Station 517	1.12	0.94	1.33
Station 518	0.90	0.73	1.10
Station 519	1.82	1.53	2.16
Station 520	0.91	0.81	1.02
Station 521	0.63	0.56	0.72
Station 523	1.23	1.09	1.40
Station 526	1.04	0.88	1.25
Station 528	1.07	0.98	1.17
Station 529	2.30	1.93	2.74
Station 531	0.51	0.42	0.61
Station 534	0.75	0.66	0.86
Station 537	1.58	1.39	1.78
Station 538	2.27	1.94	2.66
Station 539	0.79	0.69	0.92

Station 540	1.26	1.09	1.45
Station 541	0.95	0.87	1.05
Station 542	1.03	0.87	1.22
Station 544	1.61	1.45	1.79
Station 546	1.16	1.03	1.31
Station 548	3.19	2.87	3.55
Station 549	1.74	1.59	1.91
Station 550	1.73	1.51	1.98
Station 552	0.78	0.68	0.89
Station 553	1.48	1.29	1.71
Station 554	1.37	1.22	1.55
Station 556	0.88	0.74	1.04
Station 557	1.52	1.32	1.77
Station 558	0.89	0.78	1.01
Station 561	1.51	1.36	1.68
Station 562	2.10	1.79	2.46
Station 564	1.20	1.07	1.36
Station 565	1.03	0.91	1.16
Station 568	1.71	1.46	2.02
Station 570	2.91	2.55	3.33
Station 573	1.28	1.17	1.40
Station 575	1.02	0.80	1.29
Station 578	1.25	1.11	1.40
Station 580	1.25	1.14	1.38
Station 581	1.45	1.28	1.64
Station 583	0.80	0.70	0.90
Station 585	1.08	0.92	1.27
Station 586	1.57	1.40	1.75
Station 590	1.32	1.14	1.53
Station 593	1.70	1.50	1.92
Station 595	0.87	0.77	0.99
Station 596	0.79	0.68	0.90
Station 598	1.54	1.38	1.72
Station 600	0.80	0.70	0.92
Station 603	1.41	1.24	1.61
Station 605	1.67	1.49	1.87
Station 607	1.02	0.88	1.17
Station 608	0.86	0.72	1.02
Station 610	1.09	0.97	1.23
Station 612	1.95	1.76	2.17
Station 613	1.70	1.49	1.92
Station 614	1.27	1.13	1.43
Station 618	1.24	1.11	1.38
Station 619	1.67	1.47	1.90
Station 620	1.76	1.51	2.04
Station 621	0.89	0.78	1.01
Station 623	0.83	0.72	0.94
Station 626	1.06	0.97	1.17
Station 629	1.21	1.06	1.38
Station 630	0.81	0.71	0.93
Station 631	1.37	1.11	1.69
Station 632	0.95	0.82	1.09
Station 635	1.39	1.24	1.55
Station 636	1.08	0.98	1.18
Station 637	0.94	0.82	1.08
Station 640	1.02	0.91	1.16
Station 642	1.14	1.02	1.28
Station 644	1.84	1.64	2.06
Station 646	1.47	1.31	1.65
Station 648	2.11	1.88	2.36
Station 649	1.49	1.28	1.73
Station 650	0.66	0.56	0.77
Station 652	0.71	0.62	0.82
Station 653	1.09	0.92	1.29
Station 654	0.72	0.61	0.86
Station 655	0.92	0.78	1.07
Station 656	0.96	0.82	1.12
Station 657	1.50	1.37	1.64
Station 658	1.47	1.29	1.68
Station 659	1.61	1.44	1.81

Station 660	0.59	0.51	0.69
Station 662	0.80	0.68	0.95
Station 663	1.85	1.66	2.06
Station 664	0.53	0.46	0.61
Station 666	0.85	0.66	1.09
Station 667	0.84	0.74	0.95
Station 668	1.40	1.19	1.64
Station 671	0.94	0.85	1.04
Station 672	1.62	1.47	1.79
Station 673	1.62	1.48	1.77
Station 674	0.84	0.75	0.93
Station 675	2.08	1.73	2.50
Station 676	1.18	0.99	1.39
Station 678	2.02	1.78	2.29
Station 679	1.03	0.84	1.25
Station 687	0.70	0.58	0.85
Station 688	1.46	1.29	1.65
Station 689	1.05	0.94	1.18
Station 691	1.32	1.19	1.47
Station 692	0.40	0.31	0.50
Station 693	1.57	1.39	1.76
Station 695	1.11	0.99	1.26
Station 740	0	0	infinity
Station 756	0.61	0.52	0.72
Station 757	1.71	1.48	1.97

Table S3. Characteristics of patients who did not match in 1 to 1 Propensity score matching

Characteristics of patients Excluded after PS matching	Sulfonylurea N=13,206	Metformin N=60,881
Age, median (IQR)	77 (69, 82)	60 (55, 67)
Male (%)	99	93
Race, (%)		
White	78	76
Black	14	11
Hispanic/ Other	5	4
Missing	0.7	10
HbA1c, % median (IQR)	7.0 (6.3, 8.0)	6.8 (6.2, 7.4)
Missing measurement, (%)	25	17
Low Density Lipoprotein mg/dL, median (IQR)	93 (74, 118)	100 (80, 124)
Missing measurement, (%)	40	20
Creatinine mg/dL, median (IQR)	1.2 (1.0, 1.4)	1.0 (0.9, 1.1)
Glomerular filtration rate ml/min, median (IQR)	62 (53, 77)	87 (76, 100)
Missing measurement, (%)	24	10
Proteinuria, (%) negative	41	53
Urine Protein Trace or 1+	13	8
Proteinuria present at 2+,	3	0.9
Proteinuria present at 3+,	0.7	0.2
Proteinuria present at 4+	0.1	0
Missing measurement, (%)	42	38
Systolic Blood pressure mm/Hg, median (IQR)	136 (122,150)	134 (124,144)
Diastolic Blood pressure mm/Hg, median (IQR)	72 (64, 80)	78 (70, 84)
Missing measurement, (%)	4	1
Body Mass Index (kg/meter^2), median (IQR)	27.9 (25.0, 31.2)	33.1 (29.7,37.4)
Missing measurement, (%)	6	2
Baseline Co-morbidities(%)‡		
Malignancy	9	4
Liver/ respiratory failure	4	0.3
HIV	1	0.1
Congestive heart failure	27	1
Cardiovascular disease	41	18
Serious mental illness	15	18
Smoking	10	12
Chronic Obstructive Pulmonary Disease	22	10
Cardiac valve disease	6	1
Arrhythmia	23	4
Parkinson's	1	0.3
Year N (%)		
2002-03	40	11
2004	22	15
2005	17	22
2006	12	26
2007	6	20
2008-2011 †	3	6
Use of Medications N (%)		
Angiotensin Converting Enzyme Inhibitors	55	53
Angiotensin II Receptor Blockers	7	8
Beta Blockers	52	37
Calcium Channel Blockers	30	22
Thiazide and potassium sparing diuretics	30	35
Non Selective alpha Blockers	19	13
Loop Diuretics	39	6
Other Anti hypertensive medications	28	22
Statin lipid lowering medications	49	69
Non Stain Lipid lowering medications	10	20
Anti-arrhythmics, digoxin and inotropes	5	1
Anticoagulants, platelet inhibitors	15	4
Nitrates	24	9
Aspirin	21	17
Antipsychotics	6	8
Oral Glucocorticoids	16	9
Indicators of health care utilization N (%)		
Hospitalized in last year (Veterans Health)	14	5
Hospitalized in last year (Medicare/Medicaid)	24	3
Hospitalized within 30 days (Veterans Health)	7	2
Hospitalized within 30 days (Medicare/Medicaid)	7	0.5

Nursing Home encounter in last year	0.1	0.03
Outpatient Visits in past year	6 (3, 10)	5 (3, 8)
Number Medications	11 (8,16)	9 (6, 14)
Medicare use in last year	48	20
Medicaid use in last year	29	5

Table S4. Description and Characteristics of the weighted analysis cohort

The weighted analyses were performed using inverse probability of treatment weights (IPTW). As opposed to a matched analysis which balances the baseline covariate distributions by selecting a subset of patients from each exposure, a weighted analysis balances the covariate distributions by assigning various weights to the patients in one exposure such that the weighted group now resembles the other group. When comparing metformin and sulfonylurea users, the sulfonylurea users were weighted so that their distribution of covariates resembled that of the metformin users. This was achieved by using stabilized IPTW such that metformin users receive a weight of 1 and sulfonylurea users a weight of $e_i/(1-e_i)$, where e_i is the probability of patient i receiving metformin given their covariates. This creates a pseudo-cohort that uses all of the eligible patients. In simple terms, the older, less healthy sulfonylurea users (who are over-abundant relative to metformin) are down-weighted to match the metformin distribution and the younger, healthier sulfonyurea users are up-weighted to match the metformin population. The sum of the metformin users' weights will equal the number of metformin users because they each received a weight of 1. The sum of the sulfonylurea users' weights will approximate the number of metformin users because the sulfonylurea users are being weighted to approximate that group. The sum will not equal the number of metformin users exactly because the IPTW rely on modeling the exposure and thus provide an approximate solution. Like with matching, the success of the weighting in achieving a well-balanced pseudo-cohort can be seen in the table of patient characteristics and plot of standardized differences. Also like matching, the weighted analysis may be used with or without additional direct covariate adjustment. The analysis that does not use additional covariate adjustment estimates the average sulfonylurea versus metformin effect in a population of metformin users - our control group. This is referred to as the average treatment effect among controls (ATC). In the metformin versus thiazolidinedione comparison, the smaller thiazolidinedione group could not be easily up-weighted to approximate the much larger metformin group; however, the metformin group could be easily down-weighted to approximate the thiazolidinedione users. Hence, we used the thiazolidinedione users as the stabilizing population and estimated the average treatment effect among the treated population (ATT).

Characteristics	Weighted Cohort primary exposure		Weighted Cohort with positive control	
	Sulfonylurea Weighted N=125,362	Metformin N=126,867	Metformin Weighted N=6967	Thiazolidinedione N=6945
Age, median (IQR)	62 (56, 71)	62 (56, 71)	68 (59, 75)	67 (59, 75)
Male (%)	95	95	97	97
Race, (%)				
White	76	76	80	80
Black	12	13	10	10
Hispanic/ Other	4	4	7	7
Missing	7	7	3	3
HbA1c, % median (IQR)	6.9 (6.3, 7.6)	6.8 (6.3, 7.5)	6.6 (6.1, 7.3)	6.6 (6.0, 7.2)
Missing measurement, (%)	19	19	35	34
Low Density Lipoprotein mg/dL, median (IQR)	99 (79, 123)	99 (79, 123)	96 (77, 119)	97 (78, 121)
Missing measurement, (%)	25	25	37	36
Creatinine mg/dL, median (IQR)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	1.10 (0.9, 1.20)	1.10 (0.9, 1.20)
Glomerular filtration rate ml/min, median (IQR)	83.7 (71, 98)	83.7 (71, 99)	77 (64, 92)	76 (62, 91)
Missing measurement, (%)	14	14	28	28
Proteinuria, (%) negative	51	51	47	47
Urine Protein Trace or 1+	10	10	8	8
Proteinuria present at 2+,	1	1	1	1
Proteinuria present at 3+,	0	0	0	0
Proteinuria present at 4+	0	0	0	0
Missing measurement, (%)	38	39	43	43
Systolic Blood pressure mm/Hg, median (IQR)	135 (124,146)	135 (124, 146)	134 (123,145)	133 (122, 144)
Diastolic Blood pressure mm/Hg, median (IQR)	77 (70, 84)	77 (70, 84)	73 (66, 80)	73 (66, 80)
Missing measurement, (%)	2	2	6	5

Body Mass Index (kg/meter^2), median (IQR)	31.9 (28.5, 36.2)	32.0 (28.6, 36.2)	30.4 (27.2, 34.3)	30.5 (27.3, 34.0)
Missing measurement, (%)	3	3	7	6
Baseline Co-morbidities(%)‡				
Malignancy	5	5	6	6
Liver/ respiratory failure	1	1	1	1
HIV	0	0	0	0
Congestive heart failure	4	4	6	7
Cardiovascular disease	23	22	30	30
Serious mental illness	17	17	15	15
Smoking	12	12	8	8
Chronic Obstructive Pulmonary Disease	12	12	12	12
Cardiac valve disease	1	1	2	2
Arrhythmia	7	6	10	10
Parkinson's	1	0	1	1
Use of Medications N (%)				
Angiotensin Converting Enzyme Inhibitors	53	53	49	49
Angiotensin II Receptor Blockers	8	8	12	12
Beta Blockers	40	40	40	40
Calcium Channel Blockers	24	24	27	27
Thiazide and potassium sparing diuretics	32	33	28	28
Non Selective alpha Blockers	14	14	16	15
Loop Diuretics	10	10	16	16
Other Anti hypertensive medications	24	24	25	25
Statin Lipid lowering agents	64	64	64	64
Non Statin lipid Lowering agents	18	18	17	17
Anti-arrhythmics, digoxin and inotropes	2	1	3	2
Anticoagulants, platelet inhibitors	5	5	7	7
Nitrates	11	11	14	14
Aspirin	17	17	14	14
Antipsychotics	8	8	6	6
Oral Glucocorticoids	11	11	10	10
Indicators of health care utilization N (%)				
Hospitalized in last year (Veterans Health)	6	6	4	4
Hospitalized in last year (Medicare/Medicaid)	6	6	13	13
Hospitalized within 30 days (Veterans Health)	3	3	2	2
Hospitalized within 30 days (Medicare/ Medicaid)	1	1	2	2
Nursing Home encounter in last year	0	0	0	0
Outpatient Visits in past year	6 (3, 9)	6 (3, 9)	5 (3, 9)	5 (3, 9)
Number Medications	10 (7,14)	10 (7, 15)	10 (7, 14)	10 (7, 14)
Medicare use in last year	24	23	37	38
Medicaid use in last year	8	8	13	13

Table S5. Sensitivity Analyses evaluating the hazard of heart failure in first 180 days of use of Sulfonylurea versus Metformin and Thiazolidinedione versus Metformin, using new-user design and inverse probability treatment weighted analysis

Weighted Analysis	Metformin	Sulfonylurea Weighted*	Metformin Weighted*	Thiazolidinedione
N at risk†	166397	163995	10200	10164
Heart failure hospitalization or cardiovascular death	624	915.9	72.7	125
Person Years	80031.8	78299.2	4881.9	4872.4
Unadjusted Rate/1000 person-years	7.8 (7.2, 8.4)	11.7 (11.0, 12.5)	14.9 (11.9, 18.7)	25.7 (21.6, 30.6)
Adjusted Hazard Ratio (95% CI)	**Reference**	**1.50 (1.35, 1.66)**	**Reference**	**1.72 (1.36, 2.18)**
Heart failure emergency department visit, hospitalization or cardiovascular death	769	1138.3	88.7	141
Person Years	79994.7	78240.8	4877.3	4869.8
Unadjusted Rate/1000 person-years	9.6 (9.0, 10.3)	14.5 (13.7, 15.4)	18.2 (14.8, 22.3)	29 (24.6, 34.0)
Adjusted Hazard Ratio (95% CI)	**Reference**	**1.51 (1.37, 1.66)**	**Reference**	**1.59 (1.28, 1.98)**

*For the weighted analysis comparing sulfonylurea to metformin, the sulfonylurea population is weighted by their characteristics to more closely resemble the younger and healthier metformin population. For the weighted analysis comparing thiazolidinedione to metformin, the metformin population is weighted by their characteristics to more closely resemble the older population. Refer to Table S4 for details.

† The N at risk for the analysis of the first 180 days is larger then for the primary analysis cohort because it includes all patients from the primary unmatched cohort and also includes people who were excluded during the 180 day lag period for being non persistent; not having a full 180 days of follow-up; those who died; or were censored for reaching the threshold creatinine.

Table S6. Analysis of sensitivity to unmeasured confounding[1]

We evaluated the risk of heart failure in the presence of an unobserved confounder with a relative hazard of 2.3 for heart failure risk, and various prevalence levels of the confounder by exposure group. The primary analysis yielded a greater risk of heart failure with sulfonylurea use over metformin use; HR (95% CI): 1.32 (1.21, 1.43). The bolded numbers correspond to the necessary differential prevalence of such a confounder between exposure groups that could account for study results being the result of such confounding.

		Prevalence of unmeasured confounder in metformin users					
		0.0	0.1	0.2	0.3	0.4	0.5
Prevalence of unmeasured confounder in Sulfonylurea users	0	1.32	1.49	1.66	1.84	2.01	2.17
		(1.21,1.43)	(1.37,1.62)	(1.53,1.80)	(1.68,1.99)	(1.84,2.17)	(2.00,2.36)
	0.1	1.17	1.32	1.47	1.62	1.78	1.93
		(1.07,1.27)	(1.21,1.43)	(1.35,1.60)	(1.49,1.76)	(1.63,1.92)	(1.77,2.09)
	0.2	**1.05**	1.18	1.32	1.46	1.59	1.73
		(0.96,1.14)	(1.09,1.28)	(1.21,1.43)	(1.34,1.58)	(1.46,1.73)	(1.59,1.87)
	0.3	**0.95**	**1.07**	1.2	1.32	1.44	1.57
		(0.87,1.03)	**(0.98,1.16)**	(1.10,1.30)	(1.21,1.43)	(1.32,1.56)	(1.44,1.70)
	0.4	**0.87**	**0.98**	1.09	1.21	1.32	1.43
		(0.80,0.94)	**(0.90,1.06)**	(1.00,1.19)	(1.11,1.31)	(1.21,1.43)	(1.31,1.55)
	0.5	**0.80**	**0.90**	**1.01**	1.11	1.22	1.32
		(0.73,0.87)	**(0.83,0.98)**	**(0.92,1.09)**	(1.02,1.21)	(1.12,1.32)	(1.21,1.43)

The observed risk of prior heart failure history with the primary outcome was an HR of 2.3. For an unmeasured confounder of this strength to tip the primary finding of this paper into statistical non-significance, it would need to be independent of the observed covariates and 17% more prevalent among sulfonylurea users if the prevalence among metformin users was 0%. If the prevalence in metformin users was between 20-50%, it would need to be 21-27% **more** prevalent. If the prevalence in metformin users was 70%, an unmeasured confounder of this strength could not tip the analysis into statistical non-significance. Due to the heterogeneous prescribing practices in the VHA during the study period, selection bias of this degree was not observed. There were no differences in prevalence of this magnitude among the observed covariates in the full (pre-matching) cohort (Table 1).

Figure S1. Study Design Schematic

Below is an example patient who initiated Metformin after having 180 days free of any antidiabetic drug. Sulfonylurea and Thiazolidinedione person time are tracked in the same manner.
Main analysis:
Persistent exposure required: Gaps (red bars) of up to 90 days are allowed in order to refill the regimen. Patients are censored at addition of another drug or no medication refills within 90 days.
Sensitivity analyses:
Persistent exposure not required: In this approach patients are analyzed as users of their incident prescribed regimen regardless of switching, stopping or additions (akin to intent to treat analysis)
First 180 days: This person time has a high likelihood of exposure misclassification and was excluded in above two analyses. This analysis of the first 180 days includes both those that do and don't refill their prescriptions as well as those who make other regimen changes, such as switching regimens and stopping medications. The resultant exposure misclassification, if non-differential would make it harder to show differences between treatment regimens.
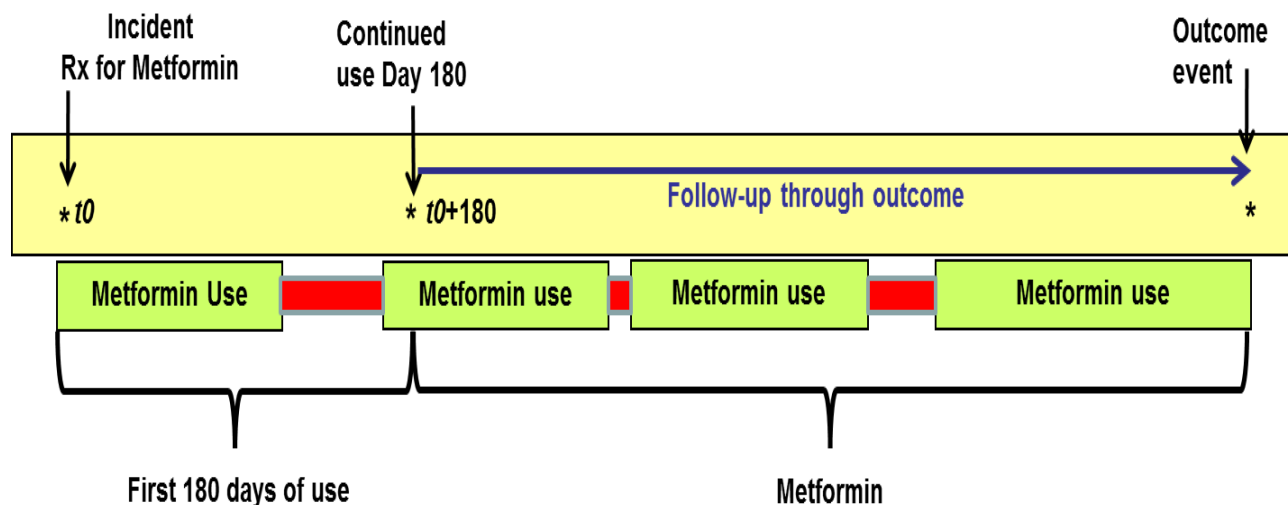
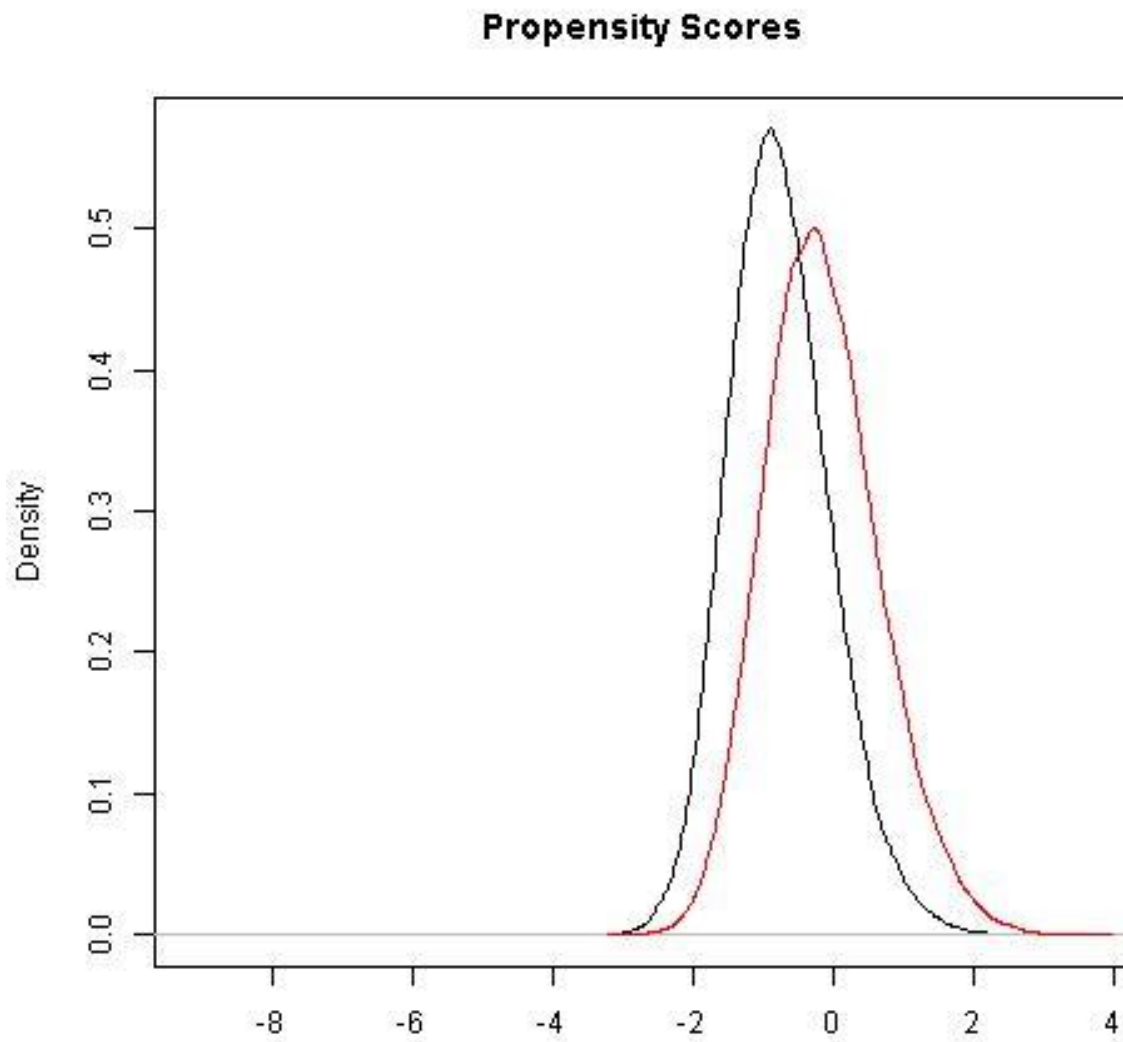**Figure S2. Distribution of Propensity Scores by drug**

Propensity Scores

Figure S3. Mean Standardized difference plot comparing metformin versus sulfonylurea

Supplemental References:

1. Schneeweiss S, Glynn RJ, Tsai EH, Avorn J, Solomon DH. Adjusting for unmeasured confounders in pharmacoepidemiologic claims data using external information: the example of COX2 inhibitors and myocardial infarction. *Epidemiology*. 2005;16:17-24.

2. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res*. 2011;46:399-424.

3. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661-79.