Annals of Internal Medicine | ORIGINAL RESEARCH

Comparative Effectiveness of Sulfonylurea and Metformin Monotherapy on Cardiovascular Events in Type 2 Diabetes Mellitus

A Cohort Study

Christianne L. Roumie, MD, MPH; Adriana M. Hung, MD, MPH; Robert A. Greevy, PhD; Carlos G. Grijalva, MD, MPH; Xulei Liu, MD, MS; Harvey J. Murff, MD, MPH; Tom A. Elasy, MD, MPH; and Marie R. Griffin, MD, MPH

Background: The effects of sulfonylureas and metformin on outcomes of cardiovascular disease (CVD) in type 2 diabetes are not well-characterized.

Objective: To compare the effects of sulfonylureas and metformin on CVD outcomes (acute myocardial infarction and stroke) or death.

Design: Retrospective cohort study.

Setting: National Veterans Health Administration databases linked to Medicare files.

Patients: Veterans who initiated metformin or sulfonylurea therapy for diabetes. Patients with chronic kidney disease or serious medical illness were excluded.

Measurements: Composite outcome of hospitalization for acute myocardial infarction or stroke, or death, adjusted for baseline demographic characteristics; medications; cholesterol, hemoglobin A_{1c}, and serum creatinine levels; blood pressure; body mass index; health care utilization; and comorbid conditions.

Results: Among 253 690 patients initiating treatment (98 665 with sulfonylurea therapy and 155 025 with metformin therapy), crude rates of the composite outcome were 18.2 per 1000 person-years in sulfonylurea users and 10.4 per 1000 person-years in metformin users (adjusted incidence rate difference, 2.2 [95% CI, 1.4 to 3.0] more CVD events with sulfonylureas per 1000 person-years; adjusted hazard ratio [aHR], 1.21 [CI, 1.13 to 1.30]). Results were consistent for both glyburide (aHR, 1.26 [CI, 1.16 to 1.37]) and glipizide (aHR, 1.15 [CI, 1.06 to 1.26]) in subgroups by CVD history, age, body mass index, and albuminuria; in a propensity score–matched cohort analysis; and in sensitivity analyses.

Limitation: Most of the veterans in the study population were white men; data on women and minority groups were limited but reflective of the Veterans Health Administration population.

Conclusion: Use of sulfonylureas compared with metformin for initial treatment of diabetes was associated with an increased hazard of CVD events or death.

Primary Funding Source: Agency for Healthcare Research and Quality and the U.S. Department of Health and Human Services.

Ann Intern Med. 2012;157:601-610. www.annals.org
For author affiliations, see end of text.

Cardiovascular disease (CVD) accounts for most deaths in patients with diabetes mellitus (1–3). Randomized trials have evaluated CVD risk associated with selected thresholds of glycemic control (4, 5), but how specific antidiabetic drugs contribute to CVD risk is less clear. Some studies found that thiazolidinediones increased CVD risk compared with placebo or active comparators (6–8), but the comparative CVD risk associated with the 2 most commonly used drugs, metformin and sulfonylureas, is not well-characterized.

We sought to compare the hazard of CVD outcomes and all-cause mortality in patients who initiated metformin and sulfonylurea therapy by using data from a national cohort that allow for control of important patient characteristics associated with both diabetes treatment and CVD or death (hemoglobin A_{1c} [HbA_{1c}] level, body mass index [BMI], serum creatinine level, and blood pressure).

METHODS

Study Design and Data Sources

We defined a cohort of patients initiating oral monotherapy for diabetes between 1 October 2001 and 30 September 2008 using data sets from national Veterans Health Administration (VHA) Decision-Support Services: pharmacy data sets for prescription data dispensed by the VHA or a consolidated mail outpatient pharmacy, including medication name, date filled, days supplied, pill number, and dosage (9); medical data sets for patient demographic characteristics and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)–coded diagnostic and procedure information from inpatient and outpatient encounters (10); and laboratory data sets derived from Veterans Health Information Systems and Technology Architecture clinical sources. Data on vital signs included all outpatient measurements of height, weight, and blood pressure. We obtained dates of death from VHA Vital Status File. For Medicare- or Medicaid-eligible veterans, we obtained data on supplemental encounters and race from the Centers for Medicare & Medicaid Services (11).

See also:

Print
Editorial comment. 671
Summary for Patients. I-28

Web-Only
Supplement

Context

Diabetes increases risk for cardiovascular disease, but how metformin and sulfonylureas affect that risk is less clear.

Contribution

In this analysis of a national population of veterans, new use of sulfonylureas seemed to increase incidence of and risk for cardiovascular events and death compared with metformin.

Caution

The findings apply primarily to white men.

Implication

Sulfonylureas seem to increase cardiovascular events and death compared with metformin. Whether sulfonylureas are harmful, metformin is protective, or both is unclear.

—The Editors

The institutional review boards of Vanderbilt University and the VHA Tennessee Valley Healthcare System (Nashville, Tennessee) approved this study.

Study Population

The study population comprised veterans aged 18 years or older who received regular VHA care (a VHA encounter or prescription fill at least once every 180 days) for at least the past 365 days. Incident users with known birth date and sex and with more than 365 days of baseline data preceding their first eligible prescription fill were identified. Patients were eligible if they filled a first prescription for an oral antidiabetic drug after at least 365 days without any oral or injectable diabetic drug fill (new users) (12). We excluded patients with serious medical conditions identified at baseline (heart failure, HIV, cancer except for nonmelanoma skin cancer, organ transplantation, end-stage kidney or liver disease, or respiratory failure), cocaine use, or a baseline serum creatinine level of 133 μmol/L (1.5 mg/dL) or greater, because these may influence the prescription of specific antidiabetic drugs and risk for outcomes.

Exposures

Incident exposures were to metformin and sulfonylureas (glyburide and glipizide). We excluded thiazolidinediones and combination metformin–sulfonylurea prescriptions because they are uncommon incident regimens in the VHA. Using pharmacy information, we calculated "days' supply in hand," accounting for early refills. Follow-up began on the incident prescription date and continued until a switch to or addition of another antidiabetic drug, the 90th day with no drugs in hand, an outcome, or a censoring event—whichever came first. Censoring events comprised reaching a serum creatinine level of 133 μmol/L (1.5 mg/dL) or greater (because metformin use is not recommended in this setting), the 181st day of no contact with any VHA facility (inpatient, outpatient, or pharmacy use) or the end of the study (30 September 2008).

Outcomes: CVD and Death

The primary composite outcome was hospitalization for acute myocardial infarction (AMI) or stroke, or death. We defined "AMI" as an ICD-9-CM primary discharge diagnosis for fatal and nonfatal AMI (ICD-9-CM code 410.x) (positive predictive value, 67% to 97% compared with chart review) (13–15). We defined "stroke" as ischemic stroke (ICD-9-CM code 433.x1, 434 [excluding 434.x0], or 436), intracerebral hemorrhage (ICD-9-CM code 431), and subarachnoid hemorrhage (ICD-9-CM code 430), excluding traumatic brain injury (ICD-9-CM codes 800 to 804 and 850 to 854) (positive predictive value, 97%) (16). We determined mortality using the VHA Vital Status File, which combines information from multiple sources (Medicare, the VHA, the U.S. Social Security Administration, and VHA compensation and pension benefits) to determine date of death (sensitivity, 98.3%; specificity, 99.8%; relative to the National Death Index) (17).

Covariates

Covariates were selected a priori on the basis of clinical significance and included age, sex, race, fiscal year of cohort entry, physiologic variables closest to cohort entry (blood pressure; serum creatinine, HbA_{1c}, and low-density lipoprotein [LDL] cholesterol levels; and BMI), indicators of health care utilization (number of outpatient visits and active medications, hospitalization during baseline [yes or no]), smoking status, selected medications indicative of CVD, and comorbid conditions (MI, obstructive coronary disease or prescription for a long-acting nitrate, stroke or transient ischemic attack, atrial fibrillation or flutter, mitral or aortic or rheumatic heart disease, asthma or chronic obstructive pulmonary disease, or procedures for carotid or peripheral artery revascularization or bypass or lower-extremity amputation [**Appendix Table 1**, available at www.annals.org]).

We initially stratified the population by previous CVD history, defined as diagnoses or procedures for MI, coronary artery disease, transient ischemic attack, stroke, or surgical procedures for repair of peripheral or carotid artery disease during baseline. A formal test of interaction between CVD history and treatment was not statistically significant ($P = 0.98$), so we present overall findings. For patients missing covariates, we conducted multiple imputations using the Markov-chain Monte Carlo method and a noninformative Jeffreys prior (SAS software, version 9.2, SAS Institute, Cary, North Carolina) (18). All covariates, survival time, and a censoring indicator were included in 20 imputation models and used to compute final estimates.

Statistical Analysis

The primary analysis was time to the composite outcome of hospitalization for AMI or stroke, or all-cause

death. A secondary analysis included a composite of AMI and stroke events only, with death as a censoring event rather than an outcome. We used Cox proportional hazards regression models to compare time to composite outcomes for sulfonylureas versus metformin, adjusting for the covariates previously stated.

Except for the first 90 to 180 days, when censoring was high, the proportional hazard assumptions were met through examination of log (log survival) plots (**Appendix Figure 1**, available at www.annals.org). We adjusted for clustering of observations within the VHA facility of care and calculated robust SEs (19). Continuous covariates were modeled with third-degree polynomials to account for nonlinearity (age; BMI; HbA_{1c}, LDL cholesterol, and serum creatinine levels; blood pressure; and number of medications and visits).

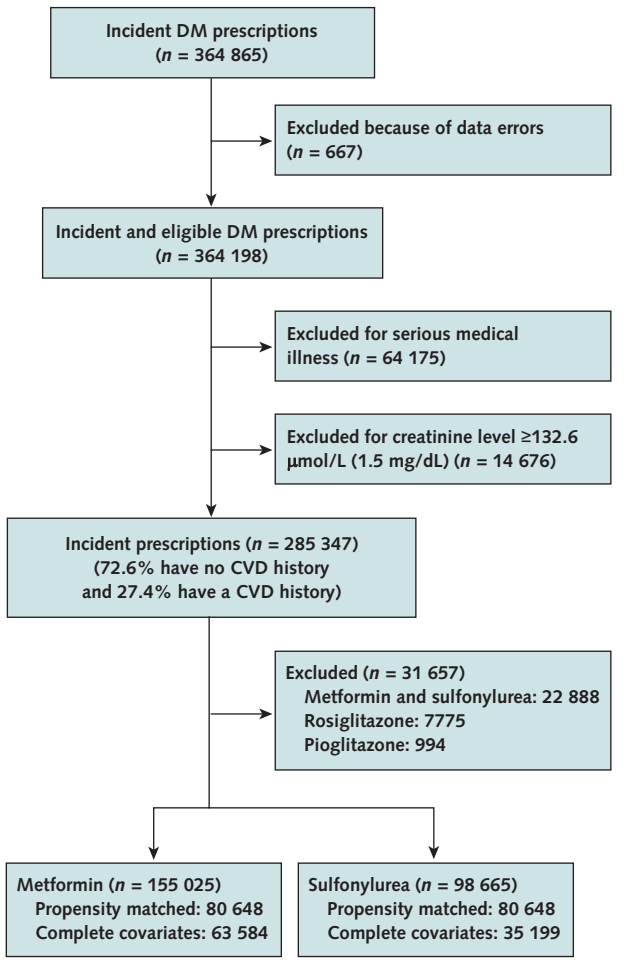
We also performed propensity score–matched analyses. The propensity score modeled the probability of metformin use given all other study covariates and the VHA facility of care (**Appendix** and **Appendix Table 2**, available at www.annals.org, shows additional information and logistic regression model). The visual inspection of the distributions of propensity scores among exposure groups showed good overlap (**Appendix Figure 2**, available at www.annals.org). Sulfonylurea and metformin observations were matched using a 1-to-1 greedy matching algorithm, yielding 80 648 propensity score–matched observations (20, 21).

Sensitivity and Subgroup Analyses

We performed multiple sensitivity and subgroup analyses. In an approach similar to intention-to-treat analyses in clinical trials, we used the incident prescription to define drug exposure and ignored subsequent changes in regimens (persistent exposure not required). We restricted analyses to patients with complete covariates (multiple imputations not used) (22–24). We conducted stratified analyses by CVD history, age (<65 and ≥65 years), and BMI (<30 and ≥30 kg/m^2) in the full cohort and proteinuria in a subset of patients with information on baseline urinary protein–creatinine ratio (36 425 of the 253 690 patients [14.3%]), where "proteinuria" was defined as a urinary protein–creatinine ratio of 30 mg/g or more.

Finally, we quantified the strength of the association of a hypothetical unmeasured binary confounder that would be required to eliminate a statistically significant association (25). We assumed a confounder–outcome association similar to that which we observed among measured covariates (hazard ratio, 1.25) and considered a range of confounder prevalence in sulfonylurea and metformin users; we also considered a stronger confounder–outcome association (hazard ratio, 2.0). Analyses were conducted using R, version X64 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS software, version 9.2 (SAS Institute).

Figure 1. **Study flow diagram.**



CVD = cardiovascular disease; DM = diabetes mellitus.

Role of the Funding Source

The U. S. Department of Health and Human Services and the Agency for Healthcare Research and Quality's Developing Evidence to Inform Decisions about Effectiveness program sponsored this study. The principal investigators and co-investigators had full access to the data and were responsible for the study protocol, statistical analysis plan, progress of the study, analysis, reporting of the study, and the decision to publish. The Agency for Healthcare Research and Quality reviewed the manuscript and had the opportunity to comment before submission.

RESULTS

Study Cohort and Patient Characteristics

Of 364 865 incident prescriptions for oral antidiabetic drugs, 667 (<0.2%) were excluded for missing date of birth, sex, age younger than 18 years, or data errors; 64 175 (17.6%) were excluded for serious medical illness or cocaine use during baseline; and 14 676 (4.0%) were

Table 1. **Patient Characteristics in Full and Propensity Score–Matched Cohorts, by New Exposure to Metformin or Sulfonylureas**

Characteristic	Full Cohort			Propensity Score–Matched Cohort		
	Metformin (*n* = 155 025)	Sulfonylureas (*n* = 98 665)	Standardized Difference*†	Metformin (*n* = 80 648)	Sulfonylureas (*n* = 80 648)	Standardized Difference*‡
Median age (IQR), y	62 (56–71)	67 (57–76)	0.33	65 (57–74)	64 (56–74)	0.03‡
Men, %	95	97	0.12	97	97	0.01
Race, %						
White	74	75	0.04	75	75	0.01
Black	12	13	0.04	13	13	0.00
Hispanic/other	6	6	0.03	6	6	0.00
Available§	91	95	0.13	94	94	0.01
HbA_{1c}						
Median level (IQR), %	7.0 (6.4–7.8)	7.3 (6.6–8.2)	0.17	7.2 (6.5–8.2)	7.2 (6.6–8.2)	0.02
Available§	67	61	0.14	63	63	0.01
LDL cholesterol						
Median level (IQR)						
mmol/L	2.668 (2.098–3.315)	2.616 (2.072–3.239)	0.03	2.641 (2.072–3.239)	2.641 (2.098–3.239)	0.01
mg/dL	103 (81–128)	101 (80–127)	0.03	102 (80–127)	102 (81–127)	0.01
Available§	63	55	0.17	57	57	0.02
Serum creatinine						
Median level (IQR)						
μmol/L	88 (80–97)	97 (80–106)	0.29	97 (80–106)	97 (80–106)	0.03‡
mg/dL	1.0 (0.9–1.1)	1.1 (0.9–1.2)	0.29	1.1 (0.9–1.2)	1.0 (0.9–1.2)	0.03‡
Available§	80	72	0.18	74	74	0.02
Median systolic blood pressure (IQR), *mm/Hg*	134 (124–144)	135 (124–146)	0.08	135 (124–146)	135 (124–146)	0.01
Median diastolic blood pressure (IQR), *mm/Hg*	77 (70–84)	76 (68–83)	0.09	76 (69–83)	76 (69–83)	0.00
Available systolic and diastolic blood pressures§	95	94	0.07	94	94	0.00
BMI						
Median BMI (IQR), kg/m^2	31.9 (28.5–36.2)	30.2 (26.9–34.2)	0.30	30.7 (27.4–34.6)	30.7 (27.5–34.7)	0.02‡
Available§	93	91	0.09	91	91	0.01
Median medications (IQR), *n*	5 (3–7)	5 (3–7)	0.03	5 (3–7)	5 (3–7)	0.00
Median outpatient visits (IQR), *n*	4 (2–7)	3 (2–7)	0.02	4 (2–7)	4 (2–7)	0.00
Patients hospitalized, %	6	7	0.04	7	7	0.00
Baseline comorbid conditions, %‖						
MI/coronary disease	20	23	0.09	22	22	0.01
Stroke/TIA/carotid revascularization	8	9	0.05	9	9	0.00
Peripheral artery disease	3	3	0.05	3	3	0.00
Smoking	10	8	0.07	9	9	0.00
COPD/emphysema	9	9	0.02	9	9	0.00
Atrial fibrillation/flutter	3	4	0.06	3	3	0.01
Fiscal year						
2003	13	19	0.17	18	17	0.02‡
2004	17	22	0.11	21	21	0.01
2005	21	21	0.01	21	21	0.00
2006	24	21	0.07	22	22	0.01
2007	25	17	0.19	18	19	0.02
Use of medications, %						
ACEIs or ARBs	58	57	0.01†	57	58	0.00
β-Blockers	36	38	0.04	37	37	0.00

Continued on following page

Table 1—**Continued**

Characteristic	Full Cohort			Propensity Score–Matched Cohort		
	Metformin (*n* = 155 025)	Sulfonylureas (*n* = 98 665)	Standardized Difference*†	Metformin (*n* = 80 648)	Sulfonylureas (*n* = 80 648)	Standardized Difference*‡
Calcium-channel blockers	23	25	0.06	25	24	0.01
Other antihypertensives	16	18	0.06	17	17	0.01
Statins	61	55	0.12	56	56	0.01
Other lipid-lowering agents	13	11	0.05	11	11	0.00
Antiarrhythmics	1	1	0.06	1	1	0.00
Anticoagulants	4	6	0.08	5	5	0.01
Antipsychotics	7	7	0.01†	7	7	0.01
Digoxin	3	6	0.14	5	5	0.01
Thiazides and other diuretics	33	30	0.05	30	31	0.00
Loop diuretics	9	14	0.17	11	11	0.01‡
Nitrates	11	14	0.09	13	13	0.01
Aspirin	17	17	0.01†	17	17	0.00
Platelet inhibitors	6	8	0.07	8	7	0.01

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; HbA_{1c} = hemoglobin A_{1c}; IQR = interquartile range; LDL = low-density lipoprotein; MI = myocardial infarction; TIA = transient ischemic attack.
* The absolute difference in means or percentages divided by an evenly weighted pooled SD, or the difference between groups in number of SDs.
† All *P* values for the comparison of metformin and sulfonylurea users were significant at $P < 0.001$ except for ACEIs/ARBs, which were significant at $P = 0.059$; antipsychotics at $P = 0.006$; and aspirin at $P = 0.002$.
‡ All *P* values for the comparison of metformin and sulfonylurea users in propensity score–matched cohorts were not significant except for age at $P < 0.001$; serum creatinine level at $P < 0.001$; fiscal year at $P < 0.001$; BMI at $P = 0.003$; and loop diuretics at $P = 0.006$.
§ The proportion of the population that had the covariate available; if it is not reported, no data were missing.
‖ Definitions of comorbid conditions and medications are available in **Appendix Table 1**, available at www.annals.org.

excluded for a serum creatinine level of 133 μmol/L (1.5 mg/dL) or greater. The remaining 285 347 prescriptions were filled by 269 921 patients, approximately 5% of whom met criteria for cohort entry more than once. Our analysis focused on incident prescriptions for metformin (50%) and sulfonylureas (40% [55% glyburide and 45% glipizide]) and excluded combination metformin–sulfonylurea (8%), rosiglitazone (3%), and pioglitazone (<1%) (**Figure 1**). Ninety percent of patients had an ICD-9-CM–coded encounter for diabetes, and 73% had no history of CVD at the time of their incident prescription.

There were a median 1768 prescriptions (interquartile range [IQR], 1131 to 2306; range, 410 to 6544) per facility among 128 VHA facilities (median, 1030 [IQR, 696 to 1554] in the propensity score–matched cohort). Median follow-up was 0.78 years (IQR, 0.25 to 1.71 years; range, 1 day to 5.5 years) for patients taking metformin and 0.61 years (IQR, 0.25 to 1.50 years; range, 1 day to 5.5 years) for sulfonylurea users. Reasons for censoring were discontinuing therapy (73% metformin and 66% sulfonylureas), changing therapy (18% metformin and 21% sulfonylureas), leaving the VHA or ending the study (5% metformin and 7% sulfonylureas), and reaching a serum creatinine level of 133 μmol/L (1.5 mg/dL) (2% metformin and 4% sulfonylureas); proportions for each reason within drug groups were similar in the propensity score–matched cohort. Censoring was the highest in the first year; however, characteristics of patients who remained at risk after 1, 2, and 3 years were similar to baseline characteristics (**Supplement**, available at www.annals.org).

Among the patients, 97% were men and 75% were white (**Table 1**). Median age was 62 years (IQR, 56 to 71 years) among metformin users versus 67 years (IQR, 57 to 76 years) among sulfonylurea users. The HbA_{1c} level was 7.0% (IQR, 6.4% to 7.8%) among those who began metformin therapy and 7.3% (IQR, 6.6% to 8.2%) among those who began sulfonylurea therapy; metformin users were slightly heavier (BMI, 31.9 kg/m^2 vs. 30.2 kg/m^2) and used statins more often (61% vs. 55%) than sulfonylurea users.

Characteristics of the 2 groups were more similar after propensity score matching. Standardized differences, a more meaningful measure of between-group differences in large samples, were small before matching and became negligible after matching. Baseline characteristics of the subset with complete covariates were similar, with no important between-group differences (**Appendix Table 3**, available at www.annals.org).

Cardiovascular Events and Deaths

Unadjusted rates of the composite outcome were 18.2 per 1000 person-years among 98 665 patients starting sulfonylurea therapy and 10.4 per 1000 person-years among 155 025 patients starting metformin therapy (adjusted hazard ratio [aHR], 1.21 [95% CI, 1.13 to 1.30]) (**Table 2**). Results were consistent for glyburide (aHR, 1.26 [CI, 1.16 to 1.37]) and glipizide (aHR, 1.15 [CI, 1.06 to 1.26]). Unadjusted rates of CVD events (AMI and stroke) excluding deaths were 13.5 per 1000 person-years for sulfonylurea users and 8.2 per 1000 person-years for metformin users (aHR, 1.16 [CI, 1.06 to 1.25]). Using adjusted rate differences, we estimated 2.2 (CI, 1.4 to 3.0) more CVD events or deaths and 1.2 (CI, 0.5 to 2.1) more CVD events

Table 2. **Unadjusted Incidence Rates, Adjusted Incidence Rate Difference, and Adjusted Hazard Ratios for Hazard of the Primary Composite Outcome and Secondary Outcome Among Full and Propensity Score–Matched Cohorts of New Users of Sulfonylureas Compared With Metformin***

Variable	Full Cohort		Propensity Score–Matched Cohort	
	Metformin (*n* = 155 025)	Sulfonylureas (*n* = 98 665)	Metformin (*n* = 80 648)	Sulfonylureas (*n* = 80 648)
Persistent exposure required†				
Person-years	179 351	101 125	94 970	83 848
Cardiovascular events or deaths, *n*	1871	1844	1239	1284
Unadjusted rate per 1000 person-years (95% CI)	10.4 (10.0–10.9)	18.2 (17.4–19.1)	13.0 (12.3–13.8)	15.3 (14.5–16.2)
Adjusted incidence rate difference (95% CI)‡	2.2 (1.4–3.0)		2.1 (1.0–3.3)	
Adjusted hazard ratio (95% CI)§	1.00 (reference)	1.21 (1.13–1.29)	1.00 (reference)	1.16 (1.08–1.25)
Cardiovascular events, *n*	1467	1367	958	969
Unadjusted rate per 1000 person-years	8.2 (7.8–8.6)	13.5 (12.8–14.2)	10.1 (9.5–10.7)	11.6 (10.9–12.3)
Adjusted incidence rate difference (95% CI)‡	1.2 (0.5–2.1)		1.3 (0.3–2.4)	
Adjusted hazard ratio (95% CI)§	1.00 (reference)	1.15 (1.06–1.25)	1.00 (reference)	1.13 (1.03–1.24)
Persistent exposure not required‖				
Person-years	361 929	244 804	204 286	198 517
Cardiovascular events or deaths, *n*	4818	5572	3550	3816
Unadjusted rate per 1000 person-years (95% CI)	13.3 (12.9–13.7)	22.8 (22.2–23.4)	17.4 (16.8–18.0)	19.2 (18.6–19.8)
Adjusted incidence rate difference (95% CI)‡	2.8 (2.1–3.6)		3.5 (2.6–4.5)	
Adjusted hazard ratio (95% CI)§	1.00 (reference)	1.21 (1.16–1.27)	1.00 (reference)	1.20 (1.15–1.26)
Cardiovascular events, *n*	3194	3422	2202	2378
Unadjusted rate per 1000 person-years (95% CI)	8.8 (8.5–9.1)	14.0 (13.5–14.5)	10.8 (10.3–11.2)	12.0 (11.5–12.5)
Adjusted incidence rate difference (95% CI)‡	1.2 (0.6–1.8)		1.4 (0.8–2.2)	
Adjusted hazard ratio (95% CI)§	1.00 (reference)	1.14 (1.07–1.20)	1.00 (reference)	1.13 (1.07–1.20)

* Cardiovascular disease or death is the primary composite outcome; cardiovascular events are the secondary outcomes.
† Primary analysis requires patients to be persistent on their medications (they must refill their prescriptions); therefore, patients are censored after 90 d without oral antidiabetic medications.
‡ The excess in the number of events per 1000 person-years of sulfonylurea use compared with that of metformin use. The adjusted rate difference is calculated as the unadjusted incidence rate among metformin users (the adjusted rate difference is calculated as: unadjusted incidence rate among metformin users × [adjusted hazard ratio – 1]).
§ Cox proportional hazards model for time to cardiovascular disease with sandwich variance estimate clustered by facility of care. Adjusted for age, sex, race, fiscal year of cohort entry, physiologic variables closest to cohort entry (blood pressure; levels of serum creatinine, hemoglobin A_{1c}, and low-density lipoprotein cholesterol; and body mass index), indicators of health care utilization (numbers of outpatient visits and active medications and hospitalization during baseline [yes/no]), smoking status, selected medications indicative of cardiovascular disease and comorbid conditions (myocardial infarction, obstructive coronary disease or prescription for a long-acting nitrate, stroke/transient ischemic attack, atrial fibrillation/flutter, mitral/aortic or rheumatic heart disease, asthma/chronic obstructive pulmonary disease, and carotid/peripheral artery revascularization or bypass or lower-extremity amputation [shown in **Appendix Table 1**, available at www.annals.org]). Propensity score–matched models also include facility of care. All continuous variables were modeled as third-degree polynomials.
‖ These analyses are similar to an intention-to-treat analysis in which patients remain in their exposure group, regardless of any changes to drug therapy or lack of persistence, until the outcome or end of the study.

per 1000 person-years of sulfonylurea compared with metformin use.

Results from the propensity score–matched analysis were consistent with those of the full cohort. Among 80 648 patients receiving sulfonylureas and 80 648 patients receiving metformin, the unadjusted rate of the composite outcomes was 15.2 per 1000 person-years for sulfonylurea users and 13.0 for metformin users (aHR, 1.15 [CI, 1.07 to 1.25]) (**Table 2** and **Figure 2** [*top*]). Cardiovascular event rates were 11.6 for sulfonylurea users and 10.1 per 1000 person-years for metformin users (aHR, 1.13 [CI, 1.03 to 1.23]). **Appendix Table 4** (available at www.annals.org) shows unadjusted rates and adjusted incidence rate differences by time in follow-up.

Sensitivity and Subgroup Analyses

Results were similar in analyses where patients remained in their original exposure group even if they changed their regimen (persistent exposure not required) (**Table 2** and **Figure 2** [*bottom*]). Results stratified by CVD history, age, BMI, and proteinuria (in the subset tested for urinary protein levels) were similar to the main findings ($P > 0.60$ for each interaction term) (**Appendix Figure 3** and **Appendix Table 5**, available at www.annals.org), as were results restricted to patients with complete covariates (**Appendix Table 6**, available at www.annals.org).

Our finding of increased hazard for the composite outcome among sulfonylurea users could have resulted from an unmeasured confounder that increased the hazard for this outcome and had a greater prevalence among sulfonylurea users compared with metformin users. Assuming a degree of association similar to that observed among measured covariates, we calculated that an unmeasured binary confounder would need to be at least 53% more prevalent among sulfonylurea users than metformin users to explain our main findings (**Appendix Table 7**, available at www.annals.org). A stronger confounder with a hazard ratio for the composite outcome of 2.0 would need to be 14% more

prevalent in sulfonylurea users than metformin users (**Appendix Table 8**, available at www.annals.org).

DISCUSSION

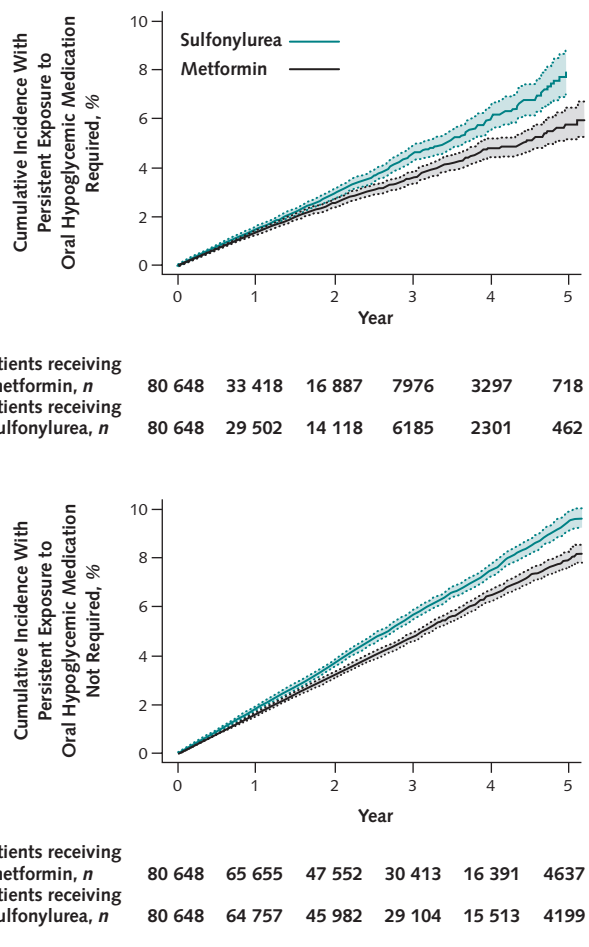
This national cohort study of veterans initiating oral treatments for diabetes mellitus found that sulfonylurea use was associated with an increased hazard of AMI, stroke, or death compared with metformin use. The findings do not clarify whether the difference in CVD risk is due to harm from sulfonylureas, benefit from metformin (26), or both. Recent comparative effectiveness reviews and meta-analyses (4, 5, 27) concluded that metformin was associated with a slightly lower risk for all-cause mortality compared with sulfonylureas, but results were inconsistent and imprecise. This study provides further evidence of a risk difference in CVD outcomes for sulfonylurea and metformin users and quantifies the difference.

Questions about the cardiovascular safety of sulfonylureas date back to 1970. The University Group Diabetes Program reported an increased risk for cardiovascular death with tolbutamide compared with placebo and insulin (28–30), leading to a controversial U.S. Food and Drug Administration–mandated black box warning for all sulfonylureas (30–33). Between 1977 and 1991, the UKPDS (United Kingdom Prospective Diabetes Study) randomly assigned patients newly diagnosed with diabetes to intensive sulfonylurea or insulin treatment or diet. In 1998, this study reported similar between-group diabetes-related and all-cause mortality at 10 years, allaying concerns about an increase in sulfonylurea-associated cardiovascular risk. In a UKPDS subpopulation of overweight patients randomly assigned to metformin ($n = 342$) or diet ($n = 411$), those receiving metformin experienced relative risk reductions of 42% for diabetes-related deaths and 36% for all-cause deaths compared with the diet-alone group, suggesting an advantage of metformin on mortality (26, 34). In the early 2000s, ADOPT (A Diabetes Outcome Prevention Trial) randomly assigned 4360 patients to metformin, rosiglitazone, or glyburide (35) and reported similarly low numbers of cardiovascular events (fatal or nonfatal AMI and stroke) across treatment groups after a median 4 years of treatment.

Compared with metformin, sulfonylureas are associated with increases in weight and lipid levels and greater risk for hypoglycemia but similar glycemic control (4, 36–38). Thus, metformin is recommended as first-line therapy for patients without contraindications (39–41). Nonetheless, sulfonylureas are sometimes preferred because they require little titration and have fewer gastrointestinal adverse effects than metformin. In 2007, more than 10.1 million Americans (approximately 34% of patients with treated diabetes) used a sulfonylurea as part of their diabetes treatment (42).

Our results are consistent with those of several observational studies in diabetic patients. In a smaller propensity score–matched cohort ($n = 8977$), McAfee and colleagues (43) showed a 23% decrease in AMI or revascularization with metformin compared with sulfonylurea (aHR, 0.77 [CI, 0.62 to 0.96]). Using the United Kingdom general practice research database ($n = 91\,000$), Tzoulaki and associates (44) found that, compared with metformin, sulfonylureas were associated with an increase in all-cause mortality (aHR, 1.24 [CI, 1.14 to 1.35]) but not first AMI (aHR, 1.09 [CI, 0.94 to 1.27]). A study by Corrao and coworkers (45) found that patients initiating sulfonylurea therapy had a higher risk for hospitalization (aHR, 1.15 [CI, 1.08 to 1.21]) and death (aHR, 1.37 [CI, 1.26 to 1.49]) than did those initiating metformin therapy. Finally, the VHA Diabetes Epidemiology Cohort reported all-cause mortality of 2.7% in 2988 metformin users compared with 5.3% among 19 053 sulfonylurea users (adjusted odds ratio, 0.87 [CI, 0.68 to 1.10]) (46). Of note in

Figure 2. **Cumulative incidence (95% CIs) of cardiovascular disease or death.**



Top. Propensity score–matched cohort with persistent exposure to oral hypoglycemic medication required. **Bottom.** Propensity score–matched cohort with persistent exposure to oral hypoglycemic medication not required, in which patients remain in their exposure group regardless of persistence with drug therapy.

our study, we were able to measure and adjust for clinical variables, such as HbA_{1c}, cholesterol, and serum creatinine levels; blood pressure; and BMI; both McAfee and colleagues' (43) and Corrao and associates' (45) studies relied on administrative data alone.

The reason for the difference in risk between metformin and sulfonylurea users remains unknown. Our previous studies evaluating the association of oral antidiabetic medications and intermediate outcomes in a regional VHA cohort reported results similar to those of a comparative effectiveness review of "high-quality evidence." In that review, metformin compared with sulfonylureas resulted in decreases of 2.7 kg in weight, 0.259 mmol/L (10 mg/dL) in LDL cholesterol levels, and 0.1 mmol/L (8.6 mg/dL) in triglyceride levels and no difference in HbA_{1c} levels (4). We estimated that after 1 year, those who began metformin therapy compared with sulfonylurea would have decreases of 3.2 kg in weight, 0.130 mmol/L (5 mg/dL) in LDL cholesterol levels (not statistically significant), and 0.1 mmol/L (8.7 mg/dL) in triglyceride levels and no difference in HbA_{1c} levels (36, 37). Our previous studies also found that metformin users compared with sulfonylurea users had a decrease of 1.2 mm Hg in systolic blood pressure and less likelihood of a decline in kidney function (47, 48). Whether the minor advantages in cholesterol level, weight, and blood pressure among metformin users could account for the differences in CVD and death or whether another mechanism accounts for the risk difference observed, such as ischemic preconditioning (49), is currently unknown.

Our study has limitations. Confounding by indication could occur if patients with certain characteristics that increase CVD risk were also more likely to use metformin or sulfonylureas. There were some differences in the 2 groups at baseline; however, our large sample size allowed us to directly control for many baseline variables in our primary analysis, and a propensity score–matched analysis yielded similar results. We included only baseline clinical variables and did not account for time-varying covariates. Furthermore, the laboratory results came from individual VHA facilities, not a central laboratory, which could lead to imprecision in measurement.

We accounted for the decrease in sulfonylurea prescribing over time (42, 50) by controlling for year of study entry in all analyses. Although we could not exclude residual confounding, we estimated that an unmeasured confounder or an underreported confounder, such as smoking, with a risk for CVD or death of 1.25 would need to have a very large prevalence imbalance among exposure groups to explain our findings. A much stronger confounder with a risk for CVD equal to 2.0 would need to be less imbalanced (approximately 14% more common among sulfonylurea users) to explain our results.

Refill data were used as a proxy for medication taking and may result in exposure misclassification. Nevertheless, prescription fills seem to be a good proxy for medication use (51). Our definitions required patients to refill their prescribed medications (persistence) because they were censored for gaps in medication use greater than 90 days or for a change in therapy. Censoring because of stopping or changing medications was high, especially in the first year; however, censoring was similar between groups, and the results of analyses that did not require persistent exposure were consistent with the main findings. In addition, analyses of results for each year of follow-up were similar (**Appendix Table 4** and Supplement).

If persons were admitted to non-VHA facilities for study outcomes, those events could be missed and outcome misclassification could occur. We supplemented our VHA data with national Medicaid or Medicare data to minimize this concern. Furthermore, use of non-VHA facilities is unlikely to be differential by exposure group. Finally, our patients reflect a typical veteran population, with most patients being white and male.

In conclusion, our study suggests a modest but clinically important 21% increased hazard of hospitalization for AMI or stroke or of death associated with initiation of sulfonylurea compared with metformin therapy. This translates into an excess of approximately 2.2 (CI, 1.4 to 3.0) cardiovascular events or deaths per 1000 person-years of sulfonylurea use. These observations support the use of metformin for first-line diabetes therapy and strengthen the evidence about the cardiovascular advantages of metformin compared with sulfonylureas.

From Veterans Health Administration, Tennessee Valley Healthcare System Geriatric Research Education Clinical Center, Health Services Research and Development Center, and Vanderbilt University, Nashville, Tennessee.

Disclaimer: The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality, the U.S. Department of Health and Human Services, or the Department of Veterans Affairs.

Grant Support: This project was funded under contract 290-05-0042 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services, as part of the Developing Evidence to Inform Decisions about Effectiveness program. Drs. Roumie (04-342-2) and Hung (2-031-09S) were supported by Veterans Affairs Career Development Awards. Dr. Roumie was also supported in part by the Vanderbilt Clinical Translational Scientist Award UL1 RR024975-01 from the National Center for Research Resources/National Institutes of Health. Support for Veterans Affairs/Centers for Medicare & Medicaid Services data provided by the Department of Veterans Affairs, Veterans Affairs Health Services Research and Development Service, Veterans Affairs Information Resource Center (project numbers SDR 02-237 and 98-004).

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-0009.

Reproducible Research Statement: *Study protocol and statistical code*: Available from Dr. Roumie (e-mail, christianne.roumie@vanderbilt.edu). *Data set:* Not available.

Requests for Single Reprints: Christianne L. Roumie, MD, MPH, Nashville Veterans Affairs Medical Center, 1310 24th Avenue South, Geriatric Research Education Clinical Center 4A120, Nashville, TN; e-mail, christianne.roumie@vanderbilt.edu.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee.** Executive summary: heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation. 2012;125:188-97. [PMID: 22215894]

2. **Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee.** Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation. 2012;125:e2-e220. [PMID: 22179539]

3. **Centers for Disease Control and Prevention.** National Diabetes Fact Sheet, 2011. 2011. Accessed at www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf on 27 March 2012.

4. **Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, et al.** Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med. 2007;147:386-99. [PMID: 17638715]

5. **Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, et al.** Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med. 2011;154:602-13. [PMID: 21403054]

6. **Lincoff AM, Wolski K, Nicholls SJ, Nissen SE.** Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA. 2007;298:1180-8. [PMID: 17848652]

7. **Nissen SE, Wolski K.** Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356:2457-71. [PMID: 17517853]

8. **Nissen SE, Wolski K.** Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med. 2010;170:1191-1201. [PMID: 20656674]

9. **Arnold N, Hines D, Stroupe K.** VIReC Technical Report 1: Comparison of VA Outpatient Prescriptions in the DSS Datasets and the PBM Database. Hines, IL: VA Information Resource Center; 2006. Accessed at www.virec.research.va.gov/Reports/TR/TR-DSS-PBM-OP-Rx-CY06-ER.pdf on 10 September 2012.

10. International Classification of Diseases, Ninth Revision, Clinical Modification. Hyattsville, MD: National Center for Health Statistics, Centers for Medicare & Medicaid Services; 1988.

11. **Hynes DM, Koelling K, Stroupe K, Arnold N, Mallin K, Sohn MW, et al.** Veterans' access to and use of Medicare and Veterans Affairs health care. Med Care. 2007;45:214-23. [PMID: 17304078]

12. **Ray WA.** Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003;158:915-20. [PMID: 14585769]

13. **Choma NN, Griffin MR, Huang RL, Mitchel EF Jr, Kaltenbach LA, Gideon P, et al.** An algorithm to identify incident myocardial infarction using Medicaid data. Pharmacoepidemiol Drug Saf. 2009;18:1064-71. [PMID: 19718697]

14. **Rosamond WD, Chambless LE, Sorlie PD, Bell EM, Weitzman S, Smith JC, et al.** Trends in the sensitivity, positive predictive value, false-positive rate, and comparability ratio of hospital discharge diagnosis codes for acute myocardial infarction in four US communities, 1987-2000. Am J Epidemiol. 2004;160:1137-46. [PMID: 15583364]

15. **Petersen LA, Wright S, Normand SL, Daley J.** Positive predictive value of the diagnosis of acute myocardial infarction in an administrative database. J Gen Intern Med. 1999;14:555-8. [PMID: 10491245]

16. **Roumie CL, Mitchel E, Gideon PS, Varas-Lorenzo C, Castellsague J, Griffin MR.** Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. Pharmacoepidemiol Drug Saf. 2008;17:20-6. [PMID: 17979142]

17. **Arnold N, Sohn M, Maynard C, DM H.** VIReC Technical Report 2: VA-NDI Mortality Data Merge Project. Hines, IL: VA Information Resource Center; 2006.

18. **Yuan YC.** Multiple Imputation for Missing Data: Concepts and New Development (Version 9.0). Rockville, MD: SAS Institute: 2011.

19. **Lin D, Wei L.** The robust inference for the Cox proportional hazards model. J Am Stat Assoc. 1989;84:1074-8.

20. **Parsons L.** Reducing bias in a propensity score matched-pair sample using greedy matching techniques [Abstract]. In: Proceedings of the Twenty-Sixth Annual SAS Users Group International Conference, Long Beach, California, 22–25 April 2001. Cary, NC: SAS Institute; 2001:214. Abstract 214-26.

21. **D'Agostino R, Rubin D.** Estimating and using propensity scores with partially missing data. J Am Stat Assoc. 2000;95:749-59.

22. **Psaty BM, Koepsell TD, Lin D, Weiss NS, Siscovick DS, Rosendaal FR, et al.** Assessment and control for confounding by indication in observational studies. J Am Geriatr Soc. 1999;47:749-54. [PMID: 10366179]

23. **Schneeweiss S.** Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf. 2006;15:291-303. [PMID: 16447304]

24. **Lin DY, Psaty BM, Kronmal RA.** Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics. 1998;54:948-63. [PMID: 9750244]

25. **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. [PMID: 15613941]

26. **UK Prospective Diabetes Study (UKPDS) Group.** Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854-65. [PMID: 9742977]

27. **Selvin E, Bolen S, Yeh HC, Wiley C, Wilson LM, Marinopoulos SS, et al.** Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. Arch Intern Med. 2008;168:2070-80. [PMID: 18955635]

28. **Goldner MG, Knatterud GL, Prout TE.** Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. 3. Clinical implications of UGDP results. JAMA. 1971;218:1400-10. [PMID: 4941698]

29. **Knatterud GL, Klimt CR, Jacobson ME, Goldner MG.** The UGDP and insulin therapy: a reply [Letter]. Diabetes Care. 1979;2:247-8. [PMID: 520128]

30. **Prout TE, Knatterud GL, Meinert CL, Klimt CR.** The UGDP controversy. Clinical trials versus clinical impressions. Diabetes. 1972;21:1035-40. [PMID: 4561330]

31. **Seltzer HS.** A summary of criticisms of the findings and conclusions of the University Group Diabetes Program (UGDP). Diabetes. 1972;21:976-9. [PMID: 5055722]

32. **Schor SS.** Editorials: Statistical problems in clinical trials: the UGDP study revisited. Am J Med. 1973;55:727-32. [PMID: 4584989]

33. **Bradley RF, Dolger H, Forsham PH, Seltzer H.** "Settling the UGDP controversy"? JAMA. 1975;232:813-7. [PMID: 1091759]

34. **UK Prospective Diabetes Study (UKPDS) Group.** Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837-53. [PMID: 9742976]

35. **Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al; ADOPT Study Group.** Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355:2427-43. [PMID: 17145742]

36. **Roumie CL, Huizinga MM, Liu X, Greevy RA, Grijalva CG, Murff HJ, et al.** The effect of incident antidiabetic regimens on lipid profiles in veterans with type 2 diabetes: a retrospective cohort. Pharmacoepidemiol Drug Saf. 2011;20:36-44. [PMID: 21182152]

37. **Huizinga MM, Roumie CL, Greevy RA, Liu X, Murff HJ, Hung AM, et al.** Glycemic and weight changes after persistent use of incident oral diabetes therapy: a Veterans Administration retrospective cohort study. Pharmacoepidemiol Drug Saf. 2010;19:1108-12. [PMID: 20878643]

38. **Phung OJ, Scholle JM, Talwar M, Coleman CI.** Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA. 2010;303:1410-8. [PMID: 20388897]

39. **American Diabetes Association.** Executive summary: standards of medical care in diabetes—2011. Diabetes Care. 2011;34 Suppl 1:S4-10. [PMID: 21193627]

40. **American Diabetes Association.** Standards of medical care in diabetes—2011. Diabetes Care. 2011;34 Suppl 1:S11-61. [PMID: 21193625]
41. **Cryer DR, Nicholas SP, Henry DH, Mills DJ, Stadel BV.** Comparative outcomes study of metformin intervention versus conventional approach the COSMIC Approach Study. Diabetes Care. 2005;28:539-43. [PMID: 15735184]
42. **Alexander GC, Sehgal NL, Moloney RM, Stafford RS.** National trends in treatment of type 2 diabetes mellitus, 1994-2007. Arch Intern Med. 2008;168: 2088-94. [PMID: 18955637]
43. **McAfee AT, Koro C, Landon J, Ziyadeh N, Walker AM.** Coronary heart disease outcomes in patients receiving antidiabetic agents. Pharmacoepidemiol Drug Saf. 2007;16:711-25. [PMID: 17551989]
44. **Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A, et al.** Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ. 2009;339:b4731. [PMID: 19959591]
45. **Corrao G, Romio SA, Zambon A, Merlino L, Bosi E, Scavini M.** Multiple outcomes associated with the use of metformin and sulphonylureas in type 2 diabetes: a population-based cohort study in Italy. Eur J Clin Pharmacol. 2011; 67:289-99. [PMID: 21088829]
46. **Kahler KH, Rajan M, Rhoads GG, Safford MM, Demissie K, Lu SE, et al.** Impact of oral antihyperglycemic therapy on all-cause mortality among patients with diabetes in the Veterans Health Administration. Diabetes Care. 2007;30: 1689-93. [PMID: 17440170]
47. **Hung AM, Roumie CL, Greevy RA, Liu X, Grijalva CG, Murff HJ, et al.** Comparative effectiveness of incident oral antidiabetic drugs on kidney function. Kidney Int. 2012;81:698-706. [PMID: 22258320]
48. **Roumie CL, Liu X, Choma NN, Greevy RA, Hung AM, Grijalva CG, et al.** Initiation of sulfonylureas versus metformin is associated with higher blood pressure at one year. Pharmacoepidemiol Drug Saf. 2012;21:515-23. [PMID: 22431419]
49. **Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al.** The risk of overall mortality in patients with type 2 diabetes receiving glipizide, glyburide, or glimepiride monotherapy: a retrospective analysis. Diabetes Care. 2010;33:1224-9. [PMID: 20215447]
50. **Huizinga MM, Roumie CL, Elasy TA, Murff HJ, Greevy R, Liu X, et al.** Changing incident diabetes regimens: a Veterans Administration cohort study from 2000 to 2005 [Letter]. Diabetes Care. 2007;30:e85. [PMID: 17855270]
51. **Grymonpre R, Cheang M, Fraser M, Metge C, Sitar DS.** Validity of a prescription claims database to estimate medication adherence in older persons. Med Care. 2006;44:471-7. [PMID: 16641666]

Current Author Addresses: Drs. Roumie and Liu: Veterans Affairs Tennessee Valley Healthcare System, 1310 24th Avenue South, Geriatric Research Education Clinical Center, Nashville, TN 37212.
Dr. Hung: Vanderbilt University Medical Center, 1161 21st Avenue South, Garland Division of Nephrology, S-3223 Medical Center North, Nashville, TN 37232.
Dr. Greevy: Vanderbilt University School of Medicine, Department of Biostatistics, 1161 21st Avenue South, S-2323 Medical Center North, Nashville, TN 37232.
Dr. Grijalva: Department of Preventive Medicine, 1500 21st Avenue South, The Village at Vanderbilt, Suite 2650, Nashville, TN 37212.
Dr. Murff: Vanderbilt Institute for Medicine and Public Health, 2525 West End Avenue, Sixth Floor, Nashville, TN 37203-1738.
Dr. Elasy: Vanderbilt University Medical Center, Medical Center East, North Tower, Suite 6000, 1215 21st Avenue South, Nashville, TN 37232-8300.
Dr. Griffin: Department of Preventive Medicine, 1500 21st Avenue South, The Village at Vanderbilt, Suite 2600, Nashville, TN 37212.

Author Contributions: Conception and design: C.L. Roumie, A.M. Hung, R.A. Greevy, C.G. Grijalva, T.A. Elasy, M.R. Griffin.
Analysis and interpretation of the data: C.L. Roumie, A.M. Hung, R.A. Greevy, C.G. Grijalva, X. Liu, H.J. Murff, T.A. Elasy, M.R. Griffin.
Drafting of the article: C.L. Roumie, R.A. Greevy, T.A. Elasy.
Critical revision of the article for important intellectual content: C.L. Roumie, A.M. Hung, R.A. Greevy, C.G. Grijalva, X. Liu, H.J. Murff, T.A. Elasy, M.R. Griffin.
Final approval of the article: C.L. Roumie, A.M. Hung, R.A. Greevy, C.G. Grijalva, H.J. Murff, T.A. Elasy, M.R. Griffin.
Statistical expertise: R.A. Greevy.
Obtaining of funding: C.L. Roumie, R.A. Greevy, C.G. Grijalva, M.R. Griffin.
Administrative, technical, or logistic support: C.L. Roumie, T.A. Elasy.
Collection and assembly of data: C.L. Roumie, R.A. Greevy.

Appendix: Propensity Score

We analyzed 2 cohorts. The first cohort comprised all eligible persons who initiated either metformin or sulfonylurea monotherapy after 365 days with no exposure to medications for diabetes. The second cohort is a subset of the first and used propensity scores to match eligible metformin users to sulfonylurea users. The propensity score is defined as the probability of metformin use, given a particular pattern of baseline covariates. We estimated the propensity score by using a logistic regression model in which the dependent variable was 1 for patients who used metformin at baseline and 0 for sulfonylurea users. The model was simple logistic regression, with a third-degree polynomial term for continuous covariates and facility of care in the model.

Appendix Table 1 and **Table 1** list baseline covariates included. **Appendix Table 2** shows the model for the probability of being a metformin user. Two variables were strongly related to metformin initiation. Metformin use increased relative to sulfonylurea use over time as reflected by odds ratios for fiscal years 2004 to 2007. Initiation of metformin therapy decreased with increasing baseline serum creatinine levels as reflected by odds ratios for 0.54. **Table 1** shows the *P* values for patients who initiated metformin and sulfonylurea therapy before and after propensity score matching; after matching, few standardized differences are statistically significant, indicating good balance.

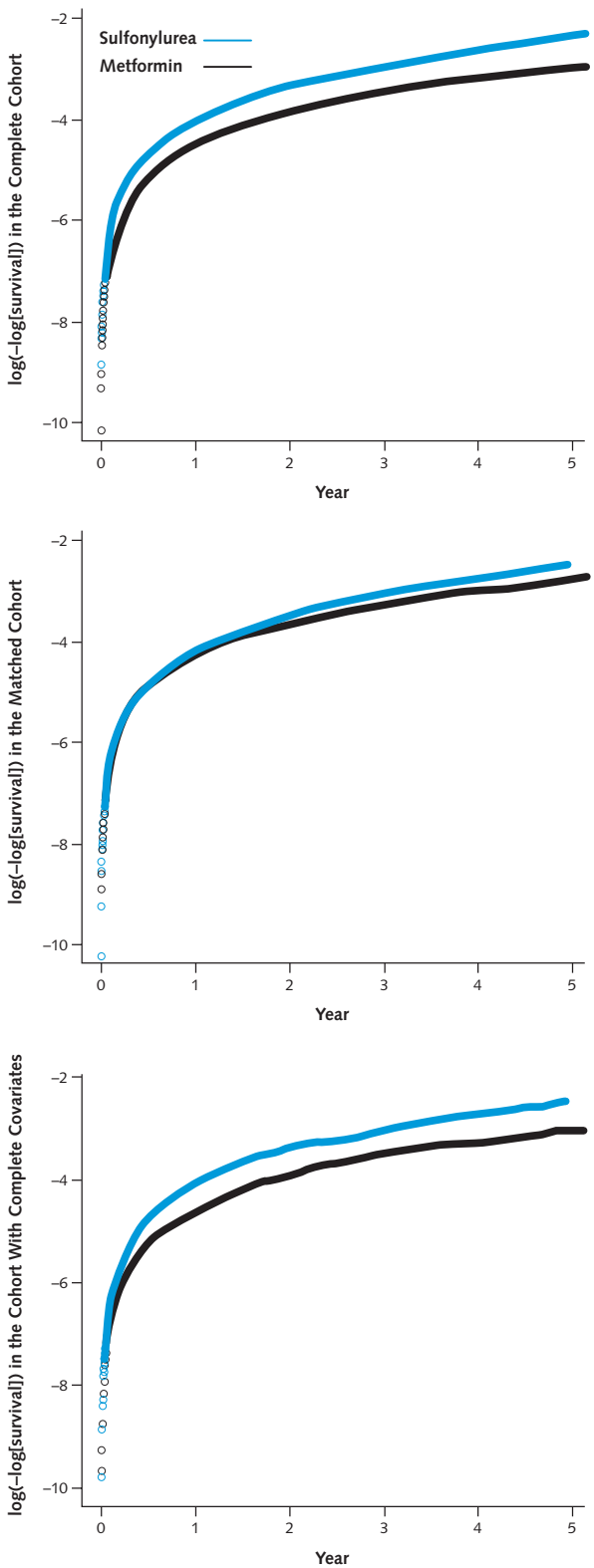
Another important assumption for propensity score methods is that every cohort member has a nonzero probability of being either a sulfonylurea user or a metformin user. Any cohort members who must always receive a sulfonylurea or who could never receive a sulfonylurea would be excluded, because the relevant comparison is between persons who are eligible for either drug but may or may not actually receive one of them. We tested this assumption by reviewing the overlap in the distribution of the propensity scores in patients who initiated sulfonylurea and metformin therapy. As **Appendix Figure 1** shows, this distribution differed slightly for users of metformin and sulfonylureas, but the overlap was nearly complete. The model yielded a c-statistic of 0.71.

Appendix Table 1. **Definitions of Comorbid Conditions and Medications, on the Basis of Codes and Prescriptions in 365 Days Before Exposure***

Condition or Drug Class	Definition†
MI	ICD-9-CM diagnosis codes: 410 (acute MI), 412 (old MI), 429.7 (MI sequela)
Obstructive coronary artery disease	ICD-9-CM diagnosis codes: 411, 413 or 414.xx (angina) ICD-9-CM procedure codes associated with a hospital discharge: 36.01, 36.02, 36.03, 36.05, 36.09, 36.10–36.19 CPT codes: 33533–33536, 33510–33523, 33530, 92980–92982, 92984, 92995, 92996 (coronary artery revascularization procedure) or prescription for a long-acting nitrate
TIA or cerebrovascular disease/stroke or carotid revascularization procedure	ICD-9-CM diagnosis codes: 435, 430.X, 431.X, 433.x1, 434 (excluding 434.x0), or 436, 433.1 ICD-9-CM procedure codes: 38.12, 38.11, 00.61, 00.63, 39.28
Peripheral artery disease/ revascularization/amputation	ICD- 9 diagnosis codes: 440.2, 443.1, 443.9, 442.2, 445.0 ICD-9-CM procedure codes: 38.08, 38.09, 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 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, 34802–34805 or prescription for pentoxifylline or cilostazol
Rheumatic/aortic/mitral valve disease	ICD-9-CM diagnosis codes: 394, 395, 396, 424.0, 424.1
Atrial fibrillation/flutter	ICD-9-CM diagnosis code: 427.3
Smoking	ICD-9-CM diagnosis codes: 305.1, V15.82, 989.84 or prescription for varenicline tartrate or nicotine replacement therapy
COPD/emphysema/asthma	ICD-9-CM diagnosis codes: 496, 491.2, 491.21, 493.2, 492, 492.8, v81.3, 493, 493.1, 493.9, 493.8, V17.5, 493.82
ACEIs or ARBs	Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Antiarrhythmics	Amiodarone, flecainide, ibutilide, procainamide, propafenone, quinidine disopyramide, dofetilide, mexiletine, moricizine, tocainide
Anticoagulants	Warfarin, argatroban, bivalirudin, dalteparin, enoxaparin, eptifibatide, fondaparinux, heparin, lepirudin, tirofiban, tinzaparin
Antipsychotic medications	Lithium, clozapine, haloperidol, loxapine, molindone, olanzapine, paliperidone, quetiapine fumarate, risperidone, aripiprazole, ziprasidone, chlorpromazine, fluphenazine, fluphenazine decanoate, mesoridazine, perphenazine, thioridazine, thiothixene, trifluoperazine, triflupromazine
β-Blockers	Acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol tartrate, metoprolol succinate, propranolol, penbutolol, pindolol, nadolol, sotalol, timolol
Calcium-channel blockers	Amlodipine, isradipine, felodipine, nifedipine, nicardipine; diltiazem (regular and sustained release), verapamil (regular and sustained release), nimodipine, nisoldipine, bepridil, amlodipine–atorvastatin
Digoxin	Digoxin
Statins	Atorvastatin, fluvastatin, lovastatin, simvastatin, rosuvastatin, lovastatin–niacin, ezetimibe–simvastatin
Other lipid-lowering agents	Cholestyramine, colesevelam, clofibrate, colestipol, niacin, niacinamide, fish oil concentrate, ω-3 fatty acids, gemfibrozil, fenofibrate, dextrothyroxine, fenofibric acid, ezetimibe
Thiazides and other diuretics, alone or in combination	Chlorothiazide, chlorthalidone, hydrochlorothiazide, methyclothiazide, trichlormethiazide, metolazone, indapamide, eplerenone, amiloride, spironolactone, triamterene, hydrochlorothiazide–triamterene, hydrochlorothiazide–spironolactone
Nitrates	Amyl nitrate, isosorbide dinitrate, isosorbide mononitrate, nitroglycerin (all forms [sustained action, patch, sublingual, ointment, aerosol spray]), ranolazine
Aspirin	Aspirin, aspirin–dipyridamole
Loop diuretics	Furosemide, ethacrynic acid, bumetanide, torsemide
Other antihypertensives	Doxazosin, prazosin, terazosin, clonidine, guanabenz, guanfacine, hydralazine, methyldopa, metyrosine, reserpine, minoxidil
Platelet inhibitors, not aspirin	Clopidogrel, ticlopidine, aspirin–dipyridamole, dipyridamole alone

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, Clinical Modification; MI = myocardial infarction; TIA = transient ischemic attack.
* For the medications listed, the definition includes obtaining a prescription for a particular drug within the past 365 d.
† Each comorbid condition was defined as present if there was 1 specified inpatient or 2 specified outpatient codes separated by 30 d, or 1 specified procedure code or prescription for a medication defining that comorbid condition in the 365 d before initiating oral antidiabetic drug therapy.

Appendix Figure 1. **Examination of the proportional hazards assumption using log(log survival) plots.**



Appendix Table 2. **Odds of Receiving Metformin Compared With Sulfonylureas***

Variable	Odds Ratio (95% CI)
Comorbid conditions	
Coronary disease or AMI	0.995 (0.988–1.002)
TIA, stroke, or carotid disease	0.901 (0.892–0.910)
Peripheral artery disease	0.931 (0.921–0.942)
Rheumatic/aortic/mitral valve disease	1.055 (1.030–1.081)
Atrial fibrillation/flutter	1.032 (1.019–1.046)
Smoking	1.014 (1.007–1.021)
COPD/emphysema/asthma	1.053 (1.043–1.064)
Medications	
Aspirin	1.041 (1.035–1.047)
ACEIs/ARBs	1.023 (1.019–1.027)
Antiarrhythmics	0.825 (0.809–0.842)
Anticoagulants	0.946 (0.936–0.956)
Antipsychotics	0.938 (0.931–0.945)
β-Blockers	0.980 (0.976–0.985)
Calcium-channel blockers	0.992 (0.987–0.997)
Digoxin	0.875 (0.866–0.884)
Statins	1.312 (1.306–1.317)
Other lipid-lowering medications	1.069 (1.063–1.076)
Thiazides and other diuretics	1.070 (1.065–1.075)
Nitrates	0.895 (0.888–0.903)
Loop diuretics	0.696 (0.691–0.701)
Other antihypertensives	0.995 (0.990–1.001)
Platelet inhibitors (nonaspirin)	0.941 (0.934–0.949)
Demographic characteristics	
Mean centered age	0.991 (0.991–0.991)
Mean centered age^2	0.999 (0.999–0.999)
Mean centered age^3	1.000 (1.000–1.000)
Women	1.335 (1.321–1.350)
Race	
Black	0.947 (0.941–0.953)
Hispanic	0.829 (0.818–0.841)
Other	0.910 (0.901–0.918)
Fiscal year	
2004	1.135 (1.128–1.142)
2005	1.349 (1.340–1.358)
2006	1.608 (1.597–1.618)
2007	2.020 (2.007–2.034)
Clinical and laboratory indicators	
Mean centered HbA_{1c} level	0.855 (0.854–0.857)
Mean centered HbA_{1c} level^2	1.000 (1.000–1.001)
Mean centered HbA_{1c} level^3	1.001 (1.001–1.001)
Mean centered LDL cholesterol level	1.000 (1.000–1.000)
Mean centered LDL cholesterol level^2	1.000 (1.000–1.000)
Mean centered LDL cholesterol level^3	1.000 (1.000–1.000)
Mean centered serum creatinine level	0.537 (0.528–0.546)
Mean centered serum creatinine level^2	0.022 (0.021–0.023)
Mean centered serum creatinine level^3	0.004 (0.004–0.005)
Mean centered systolic blood pressure	0.996 (0.996–0.996)
Mean centered systolic blood pressure^2	1.000 (1.000–1.000)
Mean centered systolic blood pressure^3	1.000 (1.000–1.000)
Mean centered diastolic blood pressure	1.002 (1.001–1.002)
Mean centered diastolic blood pressure^2	1.000 (1.000–1.000)
Mean centered diastolic blood pressure^3	1.000 (1.000–1.000)
Mean centered BMI	1.040 (1.040–1.040)
Mean centered BMI^2	0.999 (0.999–0.999)
Mean centered BMI^3	1.000 (1.000–1.000)
Indicators of health care utilization	
Mean centered outpatient medications	0.986 (0.985–0.987)
Mean centered outpatient medications^2	0.999 (0.999–0.999)
Mean centered outpatient medications^3	1.000 (1.000–1.000)

Continued on following page

Appendix Table 2—Continued

Variable	Odds Ratio (95% CI)
Mean centered outpatient visits	1.001 (1.000–1.001)
Mean centered outpatient visits^2	1.000 (1.000–1.000)
Mean centered outpatient visits^3	1.000 (1.000–1.000)
Hospitalized in the past year	0.854 (0.847–0.861)
Indicators of missing clinical variables	
BMI missing	0.855 (0.845–0.865)
Serum creatinine level missing	0.774 (0.770–0.779)
Diastolic blood pressure missing	0.415 (0.343–0.502)
HbA_{1c} level missing	0.945 (0.940–0.949)
LDL cholesterol level missing	0.914 (0.910–0.918)
Systolic blood pressure missing	2.747 (2.270–3.324)
Race missing	1.157 (1.147–1.167)
VHA medical center: VA station	
402 vs. 757	2.103 (2.030–2.179)
405 vs. 757	1.953 (1.875–2.035)
436 vs. 757	1.619 (1.558–1.682)
437 vs. 757	0.908 (0.875–0.943)
438 vs. 757	1.317 (1.269–1.366)
442 vs. 757	1.858 (1.771–1.950)
459 vs. 757	1.213 (1.164–1.265)
460 vs. 757	1.592 (1.535–1.650)
463 vs. 757	3.508 (3.338–3.686)
501 vs. 757	1.771 (1.712–1.833)
502 vs. 757	1.091 (1.055–1.128)
503 vs. 757	1.422 (1.371–1.475)
504 vs. 757	1.185 (1.141–1.232)
506 vs. 757	1.564 (1.507–1.624)
508 vs. 757	0.770 (0.746–0.795)
509 vs. 757	1.395 (1.344–1.448)
512 vs. 757	0.983 (0.951–1.017)
515 vs. 757	1.367 (1.318–1.418)
516 vs. 757	1.784 (1.731–1.839)
517 vs. 757	1.557 (1.493–1.623)
518 vs. 757	1.716 (1.638–1.798)
519 vs. 757	0.835 (0.802–0.871)
520 vs. 757	1.787 (1.731–1.846)
521 vs. 757	2.533 (2.449–2.621)
523 vs. 757	1.400 (1.353–1.449)
526 vs. 757	1.389 (1.331–1.449)
528 vs. 757	1.505 (1.462–1.548)
529 vs. 757	0.595 (0.571–0.620)
531 vs. 757	2.937 (2.815–3.064)
534 vs. 757	2.362 (2.280–2.446)
537 vs. 757	1.042 (1.007–1.077)
538 vs. 757	0.629 (0.605–0.654)
539 vs. 757	1.907 (1.838–1.979)
540 vs. 757	1.377 (1.327–1.429)
541 vs. 757	1.519 (1.474–1.564)
542 vs. 757	1.623 (1.557–1.692)
544 vs. 757	0.971 (0.941–1.001)
546 vs. 757	1.309 (1.267–1.353)
548 vs. 757	0.440 (0.426–0.453)
549 vs. 757	0.848 (0.824–0.873)
550 vs. 757	0.944 (0.911–0.978)
552 vs. 757	1.846 (1.781–1.913)
553 vs. 757	0.999 (0.962–1.036)
554 vs. 757	1.041 (1.008–1.076)
556 vs. 757	1.967 (1.887–2.050)
557 vs. 757	1.186 (1.142–1.231)
558 vs. 757	1.597 (1.543–1.653)
561 vs. 757	1.010 (0.979–1.042)
562 vs. 757	0.728 (0.700–0.757)
564 vs. 757	1.477 (1.429–1.526)
565 vs. 757	1.535 (1.486–1.586)

Continued

Appendix Table 2—Continued

Variable	Odds Ratio (95% CI)
568 vs. 757	0.896 (0.861–0.932)
570 vs. 757	0.622 (0.601–0.644)
573 vs. 757	1.227 (1.192–1.263)
575 vs. 757	1.648 (1.561–1.740)
578 vs. 757	1.296 (1.254–1.339)
580 vs. 757	1.400 (1.360–1.442)
581 vs. 757	1.010 (0.976–1.045)
583 vs. 757	1.934 (1.870–2.000)
585 vs. 757	1.334 (1.282–1.387)
586 vs. 757	1.182 (1.145–1.219)
589 vs. 757	1.494 (1.452–1.537)
590 vs. 757	1.243 (1.198–1.289)
593 vs. 757	0.841 (0.814–0.869)
595 vs. 757	1.954 (1.887–2.024)
596 vs. 757	2.140 (2.061–2.221)
598 vs. 757	1.009 (0.978–1.042)
600 vs. 757	1.788 (1.727–1.850)
603 vs. 757	1.278 (1.234–1.323)
605 vs. 757	0.961 (0.930–0.991)
607 vs. 757	1.543 (1.488–1.600)
608 vs. 757	1.761 (1.688–1.838)
610 vs. 757	1.496 (1.447–1.547)
612 vs. 757	0.655 (0.636–0.674)
613 vs. 757	0.959 (0.927–0.993)
614 vs. 757	1.193 (1.155–1.233)
618 vs. 757	1.371 (1.328–1.414)
619 vs. 757	1.061 (1.026–1.098)
620 vs. 757	0.965 (0.929–1.002)
621 vs. 757	2.083 (2.010–2.158)
623 vs. 757	1.924 (1.858–1.993)
626 vs. 757	1.457 (1.413–1.501)
629 vs. 757	1.390 (1.342–1.439)
630 vs. 757	1.683 (1.625–1.742)
631 vs. 757	1.085 (1.035–1.137)
632 vs. 757	1.896 (1.826–1.969)
635 vs. 757	1.073 (1.040–1.108)
636 vs. 757	1.556 (1.511–1.603)
637 vs. 757	1.740 (1.678–1.804)
640 vs. 757	1.593 (1.541–1.647)
642 vs. 757	1.260 (1.220–1.302)
644 vs. 757	0.802 (0.777–0.828)
646 vs. 757	1.037 (1.005–1.071)
648 vs. 757	0.723 (0.700–0.746)
649 vs. 757	1.016 (0.979–1.055)
650 vs. 757	2.548 (2.446–2.654)
652 vs. 757	2.189 (2.112–2.268)
653 vs. 757	1.420 (1.364–1.478)
654 vs. 757	1.909 (1.829–1.992)
655 vs. 757	1.703 (1.637–1.771)
656 vs. 757	1.580 (1.519–1.644)
657 vs. 757	1.109 (1.077–1.142)
658 vs. 757	1.104 (1.066–1.143)
659 vs. 757	1.057 (1.024–1.092)
660 vs. 757	2.693 (2.594–2.796)
662 vs. 757	1.767 (1.698–1.839)
663 vs. 757	0.660 (0.640–0.680)
664 vs. 757	2.227 (2.150–2.307)
666 vs. 757	2.071 (1.959–2.188)
667 vs. 757	1.714 (1.656–1.773)
668 vs. 757	1.075 (1.033–1.118)
671 vs. 757	1.779 (1.726–1.834)
672 vs. 757	1.028 (0.997–1.060)
673 vs. 757	0.963 (0.935–0.991)
674 vs. 757	1.881 (1.823–1.942)
675 vs. 757	0.671 (0.640–0.703)
676 vs. 757	1.181 (1.135–1.229)

Continued on following page

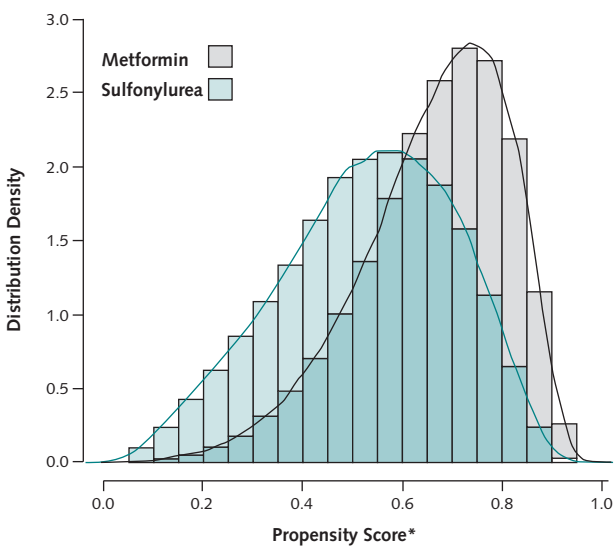
Appendix Table 2—Continued

Variable	Odds Ratio (95% CI)
678 vs. 757	0.700 (0.676–0.724)
679 vs. 757	1.552 (1.480–1.627)
687 vs. 757	2.065 (1.975–2.159)
688 vs. 757	1.303 (1.261–1.346)
689 vs. 757	1.400 (1.355–1.446)
691 vs. 757	1.107 (1.074–1.141)
692 vs. 757	3.828 (3.630–4.036)
693 vs. 757	0.989 (0.957–1.023)
695 vs. 757	1.378 (1.332–1.425)
756 vs. 757	2.356 (2.265–2.450)

AMI = acute myocardial infarction; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; HbA_{1c} = hemoglobin A_{1c}; LDL = low-density lipoprotein; TIA = transient ischemic attack; VA = Veterans Affairs; VHA = Veterans Health Administration.

* Odds ratios (95% CIs) of initiation of metformin therapy compared with that of sulfonylurea therapy, controlling for all variables in the table.

Appendix Figure 2. Distribution of propensity scores, by drug.



* Probability of using metformin.

Appendix Table 3. Baseline Characteristics of Patients With Complete Covariates, by Antidiabetic Drug

Characteristic	Metformin (*n* = 63 584)	Sulfonylureas (*n* = 35 199)	Standardized Difference*
Median age (IQR), *y*	63 (56–71)	67 (58–76)	0.30
Men, %	95	97	0.09
Race, %			
White	81	80	0.01
Black	13	13	0.00
Hispanic/other	6	6	0.01
Median HbA_{1c} level (IQR), %	7.0 (6.4–7.8)	7.2 (6.6–8.1)	0.16
Median LDL cholesterol level (IQR)			
mmol/L	2.64 (2.10–3.29)	2.61 (2.07–3.26)	0.03
mg/dL	102 (81–127)	101 (80–126)	0.03
Median serum creatinine level (IQR)			
μmol/L	88 (79–106)	97 (79–115)	
mg/dL	1.0 (0.9–1.2)	1.1 (0.9–1.3)	0.32
Median systolic blood pressure (IQR), *mm Hg*	134 (124–144)	135 (124–145)	0.06
Median diastolic blood pressure (IQR), *mm Hg*	76 (70–83)	75 (6882)	0.09
Median BMI (IQR), kg/m^2	32.0 (28.5–36.2)	30.4 (27.2–34.4)	0.27
Median medications (IQR), *n*	5 (3–8)	5 (3–8)	0.04
Median outpatient visits (IQR), *n*	5 (3–8)	5 (3–8)	0.00
Hospitalized, %	7	8	0.04
Baseline comorbid conditions, %†			
MI/coronary disease	22	26	0.10
Stroke/TIA or carotid revascularization	9	11	0.07
Peripheral artery disease	3	4	0.05
Smoking	11	10	0.07
COPD/emphysema	9	10	0.03
Atrial fibrillation/flutter	3	5	0.08
Fiscal year			
2003	11	16	0.13
2004	17	21	0.11
2005	21	23	0.04
2006	25	22	0.07
2007	26	18	0.19
Use of medications, %†			
ACEIs or ARBs	61	62	0.01
β-Blockers	39	40	0.04
Calcium-channel blockers	24	26	0.06
Other antihypertensives	16	19	0.06
Statins	66	62	0.09
Other lipid-lowering medications	14	13	0.03
Antiarrhythmics	1	1	0.05
Anticoagulants	5	6	0.07
Antipsychotic medications	8	7	0.02
Digoxin	3	5	0.12
Thiazides and other diuretics	34	32	0.03
Loop diuretics	9	13	0.13
Nitrates	12	15	0.09
Aspirin	19	20	0.01
Platelet inhibitors	7	9	0.07

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; HbA_{1c} = hemoglobin A_{1c}; IQR = interquartile range; LDL = low-density lipoprotein; MI = myocardial infarction; TIA = transient ischemic attack.

* The absolute difference in means or percentages divided by an evenly weighted pooled SD, or the difference between groups in number of SDs. All *P* values for the comparison of metformin and sulfonylurea users were significant at $P < 0.001$, except outpatient visits, which were $P = 0.016$; ACEIs/ARBs, $P = 0.08$; and aspirin use, $P = 0.15$.

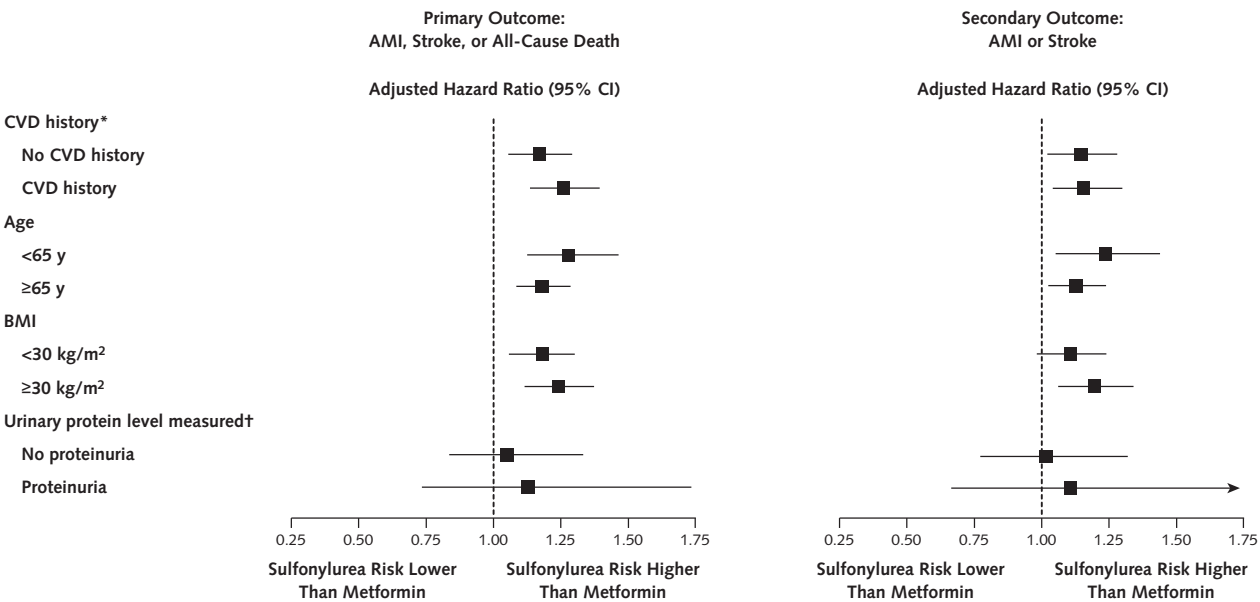
† Definitions of comorbid conditions and medications are available in **Appendix Table 1**.

Appendix Table 4. **Yearly Unadjusted Incidence Rates and Unadjusted and Adjusted Incidence Rate Differences for the Primary Composite Outcome Among a Propensity Score–Matched Cohort of New Users of Sulfonylureas Compared With Metformin***

Variable	Year 1		Year 2		Year 3		Year 4		Year 5	
	Metformin	Sulfonylureas	Metformin	Sulfonylureas	Metformin	Sulfonylureas	Metformin	Sulfonylureas	Metformin	Sulfonylureas
Persistent exposure required†										
At risk, *n*	80 648	80 648	33 418	29 502	16 887	14 118	7976	6185	3297	2301
Person-years	51 344	47 979	24 248	20 848	11 966	9658	5381	3984	1857	1272
Cardiovascular events or deaths, *n*	726	739	296	305	129	159	69	56	16	25
Unadjusted rate per 1000 person-years (95% CI)	14.1 (13.2 to 15.2)	15.4 (14.3 to 16.5)	12.2 (10.9 to 13.7)	14.6 (13.1 to 16.4)	10.8 (9.1 to 12.8)	16.4 (14.1 to 19.2)	12.8 (10.1 to 16.2)	14.0 (10.8 to 18.2)	8.6 (5.3 to 14.0)	19.7 (13.3 to 28.9)
Unadjusted incidence rate difference (95% CI)	1.3 (−0.2 to 2.8)		2.4 (0.3 to 4.6)		5.7 (2.6 to 8.9)		1.2 (−3.4 to 6.2)		11.0 (2.8 to 20.8)	
Adjusted incidence rate difference (95% CI)‡	2.3 (1.1 to 3.5)		1.9 (1.0 to 3.0)		1.7 (0.9 to 2.7)		2.1 (1.0 to 3.2)		1.4 (0.7 to 2.2)	
Persistent exposure not required§										
At risk, *n*	80 648	80 648	65 655	64 757	47 552	45 982	30 413	29 104	16 391	15 513
Person-years	74 364	73 730	56 584	55 155	38 755	37 097	23 273	22 070	10 189	9523
Cardiovascular events or deaths, *n*	1199	1379	916	1023	629	760	415	419	167	212
Unadjusted rate per 1000 person-years (95% CI)	16.1 (15.2 to 17.0)	18.7 (17.7 to 19.6)	16.2 (15.2 to 17.3)	18.5 (17.5 to 19.7)	16.2 (15.0 to 17.5)	20.5 (19.1 to 22.0)	17.8 (16.2 to 19.6)	19.0 (17.3 to 20.9)	16.4 (14.1 to 19.0)	22.2 (19.5 to 25.4)
Unadjusted rate difference (95% CI)	2.6 (1.2 to 3.9)		2.4 (0.8 to 3.9)		4.3 (2.3 to 6.2)		1.2 (−1.3 to 3.6)		5.9 (2.0 to 9.8)	
Adjusted incidence rate difference (95% CI)‡	3.2 (2.4 to 4.2)		3.2 (2.4 to 4.2)		3.3 (2.4 to 4.2)		3.6 (2.7 to 4.6)		3.3 (2.5 to 4.3)	

* Cardiovascular disease or death is the primary composite outcome.
† Primary analysis requires patients to be persistent on their medications (they refill their prescriptions); therefore, patients are censored after 90 d without oral antidiabetic medications.
‡ The excess in the number of events per 1000 person-years of sulfonylurea use compared with that of metformin use. The adjusted rate difference is calculated as [unadjusted incidence rate among metformin users × (adjusted hazard ratio − 1)]. The hazard ratios used in each calculation are derived from the respective models shown in **Table 2**.
§ These analyses are similar to an intention-to-treat analysis in which patients remain in their exposure group, regardless of any changes to drug therapy or lack of persistence, until the outcome or end of the study.

Appendix Figure 3. **Adjusted hazard ratios for the primary composite outcome (CVD or death) and secondary outcome (CVD alone), stratified by CVD history, age, and BMI.**



AMI = acute myocardial infarction; BMI = body mass index; CVD = cardiovascular disease.
* CVD defined by diagnoses or procedure codes for MI, coronary artery disease, transient ischemic attack, stroke, or surgical procedures for repair of peripheral or carotid artery disease in the baseline period.
† Results are also presented for a sample of patients (14.3%) tested for proteinuria and found positive or negative.

Appendix Table 5. **Incidence Rates and Adjusted Hazard Ratios for Risk for the Primary Composite Outcome and Secondary Outcome Among the Full Cohort of New Users of Sulfonylureas Compared With Metformin, Stratified by CVD History, Age, and BMI***

Variable	Oral Antidiabetic Medication	
	Metformin	Sulfonylureas
History of CVD†		
Sample size, *n*	40 577	30 366
Cardiovascular or death rate per 1000 person-years (95% CI)	17.1 (16.0–18.3)	28.7 (27.0–30.6)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.26 (1.14–1.39)
Cardiovascular event rate per 1000 person-years (95% CI)	13.7 (12.7–14.8)	20.8 (19.3–22.4)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.16 (1.05–1.30)
No history of CVD†		
Sample size, *n*	114 448	68 299
Cardiovascular or death rate per 1000 person-years (95% CI)	7.9 (7.5–8.4)	13.3 (12.5–14.2)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.17 (1.06–1.29)
Cardiovascular event rate per 1000 person-years (95% CI)	6.1 (5.7–6.6)	10.0 (9.4–10.9)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.15 (1.03–1.28)
Age ≥65 y		
Sample size, *n*	64 009	54 005
Cardiovascular or death rate per 1000 person-years (95% CI)	15.9 (15.0–16.8)	24.6 (23.4–25.9)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.18 (1.09–1.28)
Cardiovascular event rate per 1000 person-years (95% CI)	12.9 (12.1–13.7)	18.5 (17.5–19.6)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.13 (1.03–1.24)
Age <65 y		
Sample size, *n*	91 016	44 610
Cardiovascular or death rate per 1000 person-years (95% CI)	6.1 (5.6–6.6)	9.4 (8.5–10.3)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.28 (1.13–1.46)
Cardiovascular event rate per 1000 person-years (95% CI)	4.4 (4.0–4.8)	6.6 (5.8–7.4)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.24 (1.06–1.44)
BMI ≥30 kg/m²		
Sample size, *n*	92 429	46 033
Cardiovascular or death rate per 1000 person-years (95% CI)	8.3 (7.8–8.9)	13.6 (12.6–14.7)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.24 (1.12–1.37)
Cardiovascular event rate per 1000 person-years (95% CI)	6.4 (6.0–6.9)	10.5 (9.6–11.4)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.20 (1.07–1.34)
BMI <30 kg/m²		
Sample size, *n*	62 596	2 632
Cardiovascular or death rate per 1000 person-years (95% CI)	13.6 (12.8–14.5)	22.6 (21.3–23.8)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.18 (1.06–1.30)
Cardiovascular event rate per 1000 person-years (95% CI)	10.8 (10.1–11.6)	16.3 (15.3–17.4)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.11 (0.99–1.24)
Tested positive for proteinuria (urinary protein–creatinine ratio >30 mg/g)		
Sample size, *n*	4580	2979
Cardiovascular or death rate per 1000 person-years (95% CI)	13.8 (10.8–17.7)	20.0 (15.2–26.2)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.13 (0.74–1.73)
Cardiovascular event rate per 1000 person-years (95% CI)	10.0 (7.5–13.4)	15.6 (11.4–21.2)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.11 (0.67–1.83)
Tested negative for proteinuria (urinary protein–creatinine ratio <30 mg/g)		
Sample size, *n*	19 302	9564
Cardiovascular or death rate per 1000 person-years (95% CI)	8.3 (7.2–9.6)	12.7 (10.7–15.1)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.05 (0.84–1.33)
Cardiovascular event rate per 1000 person-years (95% CI)	7.0 (6.0–8.2)	10.3 (8.4–12.4)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.02 (0.78–1.32)

BMI = body mass index; CVD = cardiovascular disease.

* Similar analyses for sample of patients (14.3%) with urinary protein measurement, by proteinuria status. CVD or death is the primary composite outcome; cardiovascular events are the secondary outcomes. Primary analysis requires patients to be persistent on their medications (that is, that patients refill their prescribed medications); therefore, patients are censored after 90 d without oral antidiabetic medications.

† CVD is defined by diagnoses or procedure codes for myocardial infarction, coronary artery disease, transient ischemic attack, stroke, or surgical procedures for repair of peripheral or carotid artery disease in the baseline period.

‡ Cox proportional hazards model for time to CVD with sandwich variance estimate clustered by facility of care. Adjusted for age, sex, race, fiscal year of cohort entry, physiologic variables closest to cohort entry (blood pressure; levels of serum creatinine, hemoglobin A_{1c}, and low-density lipoprotein cholesterol; and BMI), indicators of health care utilization (numbers of outpatient visits and active medications and hospitalization during baseline [yes/no]), smoking status, selected medications indicative of CVD, and comorbid conditions (myocardial infarction, obstructive coronary disease or prescription for a long-acting nitrate, stroke/transient ischemic attack, atrial fibrillation/flutter, mitral/aortic or rheumatic heart disease, asthma/chronic obstructive pulmonary disease, and carotid/peripheral artery revascularization or bypass or lower-extremity amputation [shown in **Appendix Table 1**]). All continuous variables were modeled as third-degree polynomials.

Appendix Table 6. **Rates and Adjusted Hazard Ratios for Risk for the Primary Composite Outcome and Secondary Outcome Among Those With Complete Covariates Who Were New Users of Sulfonylureas Compared With Metformin***

Variable	Metformin (*n* = 63 584)	Sulfonylureas (*n* = 35 199)
Persistent exposure required†		
Person-years	75 137	37 791
Cardiovascular events or deaths, *n*	755	626
Rate per 1000 person-years (95% CI)	10.0 (9.4–10.8)	16.6 (15.3–17.9)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.19 (1.07–1.34)
Cardiovascular events, *n*	602	493
Rate per 1000 person-years (95% CI)	8.0 (7.4–8.7)	13.0 (11.9–14.2)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.18 (1.03–1.33)
Persistent exposure not required§		
Person-years	147 331	87 740
Cardiovascular events or deaths, *n*	1919	1865
Rate per 1000 person-years (95% CI)	13.0 (12.5–13.6)	21.3 (20.3–22.2)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.19 (1.11–1.27)
Cardiovascular events, *n*	1293	1191
Rate per 1000 person-years (95% CI)	8.8 (8.3–9.3)	13.6 (12.8–14.4)
Adjusted hazard ratio (95% CI)‡	1.00 (reference)	1.14 (1.05–1.24)

* Cardiovascular disease or death is the primary composite outcome; cardiovascular events are the secondary outcomes.
† Primary analysis requires patients to be persistent on their medications (that is, that patients refill their prescribed medications); therefore, patients are censored after 90 d without oral antidiabetic medications.
‡ Cox proportional hazards model for time to cardiovascular disease with sandwich variance estimate. Adjusted for age, sex, race, fiscal year of cohort entry, physiologic variables closest to cohort entry (blood pressure; levels of serum creatinine, hemoglobin A_{1c}, and low-density lipoprotein cholesterol; and body mass index), indicators of health care utilization (numbers of outpatient visits and active medications and hospitalization during baseline [yes/no]), smoking status, selected medications indicative of cardiovascular disease, and comorbid conditions (myocardial infarction, obstructive coronary disease or prescription for a long-acting nitrate, stroke/transient ischemic attack, atrial fibrillation/flutter, mitral/aortic or rheumatic heart disease, asthma/chronic obstructive pulmonary disease, and carotid/peripheral artery revascularization or bypass or lower-extremity amputation [shown in **Appendix Table 1**]). All continuous variables were modeled as third-degree polynomials.
§ These analyses are similar to an intention-to-treat analysis in which patients remain in their exposure group, regardless of any changes to drug therapy or lack of persistence, until the outcome or end of the study.

Appendix Table 7. **Risk for CVD in the Presence of an Unmeasured Confounder With a Hazard Ratio of 1.25 for CVD and Various Prevalence Levels of the Confounder, by Exposure Group***

Prevalence of Unmeasured Confounder in Sulfonylurea Users*	Prevalence of Unmeasured Confounder in Metformin Users					
	0.0	0.1	0.2	0.3	0.4	0.5
0.0	1.21 (1.13–1.30)	1.24 (1.16–1.33)	1.27 (1.19–1.37)	1.30 (1.22–1.40)	1.33 (1.24–1.43)	1.36 (1.27–1.46)
0.1	1.18 (1.10–1.27)	1.21 (1.13–1.30)	1.24 (1.16–1.33)	1.27 (1.19–1.36)	1.30 (1.21–1.40)	1.33 (1.24–1.43)
0.2	1.15 (1.08–1.24)	1.18 (1.10–1.27)	1.21 (1.13–1.30)	1.24 (1.16–1.33)	1.27 (1.18–1.36)	1.30 (1.21–1.39)
0.3	1.13 (1.05–1.21)	1.15 (1.08–1.24)	1.18 (1.10–1.27)	1.21 (1.13–1.30)	1.24 (1.16–1.33)	1.27 (1.18–1.36)
0.4	1.10 (1.03–1.18)	1.13 (1.05–1.21)	1.15 (1.08–1.24)	1.18 (1.10–1.27)	1.21 (1.13–1.30)	1.24 (1.16–1.33)
0.5	1.08 (1.00–1.16)	1.10 (1.03–1.18)	1.13 (1.06–1.21)	1.16 (1.08–1.24)	1.18 (1.11–1.27)	1.21 (1.13–1.30)
0.6	**1.05 (0.98–1.13)**	1.08 (1.01–1.16)	1.10 (1.03–1.19)	1.13 (1.06–1.22)	1.16 (1.08–1.24)	1.18 (1.11–1.27)
0.7	**1.03 (0.96–1.11)**	**1.056 (0.99–1.13)**	1.08 (1.01–1.16)	1.11 (1.03–1.19)	1.13 (1.06–1.22)	1.16 (1.08–1.24)
0.8	**1.01 (0.94–1.08)**	**1.034 (0.97–1.11)**	**1.06 (0.99–1.14)**	1.08 (1.01–1.16)	1.11 (1.04–1.19)	1.13 (1.06–1.22)
0.9	**0.99 (0.92–1.06)**	**1.012 (0.95–1.09)**	**1.04 (0.97–1.11)**	**1.06 (0.99–1.14)**	1.09 (1.02–1.17)	1.11 (1.04–1.19)
1.0	**0.97 (0.90–1.04)**	**0.99 (0.93–1.07)**	**1.02 (0.95–1.09)**	**1.04 (0.97–1.12)**	**1.06 (0.99–1.14)**	1.09 (1.02–1.17)

CVD = cardiovascular disease.
* Values reported are hazards ratios (95% CIs). The bolded data indicate the hazard ratios (95% CIs) that correspond to the necessary differential prevalence of such a confounder, by exposure group, that could account for study results being the result of such confounding. An unmeasured confounder could be a proposed confounder that was not included in our models or a confounder that was probably underreported in our cohort, such as tobacco use. The shaded boxes represent the hazard ratio of the Cox proportional hazards model if a potential unmeasured confounder was equally prevalent among both metformin and sulfonylurea users.

Appendix Table 8. **Risk for CVD in the Presence of an Unmeasured Confounder With a Hazard Ratio of 2.0 for CVD and Various Prevalence Levels of the Confounder, by Exposure Group***

Prevalence of Unmeasured Confounder in Sulfonylurea Users*	Prevalence of Unmeasured Confounder in Metformin Users					
	0.0	0.1	0.2	0.3	0.4	0.5
0.0	1.21 (1.13–1.30)	1.331 (1.24–1.43)	1.452 (1.36–1.56)	1.573 (1.47–1.69)	1.694 (1.58–1.82)	1.815 (1.70–1.95)
0.1	1.10 (1.03–1.18)	1.21 (1.13–1.30)	1.32 (1.23–1.42)	1.43 (1.34–1.54)	1.54 (1.44–1.66)	1.65 (1.54–1.77)
0.2	**1.01 (0.94–1.08)**	1.109 (1.04–1.19)	1.21 (1.13–1.30)	1.31 (1.22–1.41)	1.412 (1.32–1.52)	1.512 (1.41–1.63)
0.3	0.931 (0.87–1.00)	**1.024 (0.96–1.10)**	1.117 (1.04–1.20)	1.21 (1.13–1.30)	1.303 (1.22–1.40)	1.396 (1.30–1.50)
0.4	0.86 (0.81–0.93)	**0.95 (0.89–1.02)**	**1.04 (0.97–1.11)**	1.12 (1.05–1.21)	1.21 (1.13–1.30)	1.30 (1.21–1.39)
0.5	0.81 (0.75–0.87)	0.89 (0.83–0.95)	**0.97 (0.90–1.04)**	**1.05 (0.98–1.13)**	1.13 (1.06–1.21)	1.21 (1.13–1.30)
0.6	0.76 (0.71–0.81)	0.83 (0.78–0.89)	0.91 (0.85–0.98)	**0.98 (0.92–1.06)**	**1.06 (0.99–1.14)**	1.13 (1.06–1.22)
0.7	0.71 (0.66–0.77)	0.78 (0.73–0.84)	0.85 (0.80–0.92)	0.93 (0.86–0.99)	**1.00 (0.93–1.07)**	**1.07 (1.00–1.15)**
0.8	0.67 (0.63–0.72)	0.74 (0.69–0.79)	0.81 (0.75–0.87)	0.87 (0.82–0.94)	**0.94 (0.88–1.01)**	**1.01 (0.94–1.08)**
0.9	0.64 (0.59–0.68)	0.70 (0.65–0.75)	0.76 (0.71–0.82)	0.83 (0.77–0.89)	0.89 (0.83–0.96)	**0.96 (0.89–1.03)**
1.0	0.61 (0.56–0.65)	0.67 (0.62–0.72)	0.73 (0.68–0.78)	0.79 (0.74–0.85)	0.85 (0.79–0.91)	0.91 (0.85–0.98)

CVD = cardiovascular disease.
* Values reported are hazards ratios (95% CIs). The bolded data indicate the hazard ratios (95% CIs) that correspond to the necessary differential prevalence of such a confounder, by exposure group, that could account for study results being the result of such confounding. An unmeasured confounder could be a proposed confounder that was not included in our models or a confounder that was probably underreported in our cohort, such as tobacco use. The shaded boxes represent the hazard ratio of the Cox proportional hazards model if a potential unmeasured confounder was equally prevalent among both metformin and sulfonylurea users.