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Research

Comparative effectiveness of metformin versus sulfonylureas on kidney function decline or death among patients with reduced kidney function: a retrospective cohort study

Adriana M. Hung MD MPH, Amber J. Hackstadt PhD, Marie R. Griffin MD MPH, Carlos G. Grijalva MD MPH, Robert A. Greevy Jr. PhD, Christianne L. Roumie MD MPH

Abstract

Background: Diabetes often causes kidney disease. In this study, we sought to evaluate if metformin use was associated with death or kidney events in patients with diabetes and concurrent reduced kidney function.

Methods: We used data from the Veterans Health Administration, Medicare and National Death Index databases to assemble a national retrospective cohort of veterans who were using metformin or sulfonylureas from 2001 through 2016 and who began follow-up at an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2. The primary composite outcome was a kidney event (i.e., 40% decline in eGFR or end-stage renal disease) or death. The secondary outcome was a kidney event (eGFR decline or end-stage renal disease). We weighted the cohort using propensity scores and used Cox proportional models to estimate the cause-specific hazard of outcomes and of treatment nonpersistence as a competing risk. We stratified follow-up into 2 periods, namely the first 360 days from the start of follow-up, and 361 days and beyond.

Results: In the first 360 days, the propensity score–weighted cohort included 24 883 patients who used metformin and 24 998 who used sulfonylureas. There were 33.5 (95% confidence interval [CI] 30.9–36.3) and 43.0 (95% CI 40.1–46.0) deaths or kidney events per 1000 person-years for patients who used metformin or sulfonylureas, respectively (hazard ratio [HR] 0.78, 95% CI 0.71–0.85). For the secondary outcome of kidney events, the HR was 0.94 (95% CI 0.67–1.33). In the second period from 361 days onward, the primary outcome event rate was 26.5 (95% CI 24.7–28.5) per 1000 person-years for those who used metformin, compared with 36.3 (95% CI 34.2–38.6) per 1000 person-years for those who used sulfonylureas (HR 0.73, 95% CI 0.67–0.79). Results were consistent for kidney events alone (HR 0.73, 95% CI 0.59–0.91).

Interpretation: Metformin use for 361 days or longer after reaching an eGFR of less than 60 mL/min/1.73 m^2 was associated with decreased likelihood of kidney events or death in patients with diabetes, compared with use of sulfonylureas. Metformin provided end-organ protection, in addition to glucose control.

Type 2 diabetes is the most common cause of chronic kidney disease and end-stage renal disease worldwide.[1] Metformin is considered the first-line pharmacologic treatment for type 2 diabetes based on results from the United Kingdom Prospective Diabetes Study, which showed macrovascular benefits of metformin compared with sulfonylureas, but the study was underpowered to report on renal outcomes.[2,3] Metformin reduces glycated hemoglobin (HbA_{1c}), promotes weight loss and insulin sensitivity, and reduces the long-term risk of microvascular and macrovascular complications, compared with sulfonylureas or insulin.[4] Sulfonylureas affect weight change and blood pressure, both known contributors to kidney dysfunction.[5] However, the protective associations between metformin and kidney function appear to be independent of changes in body mass index, blood pressure and glucose control.[6] Whether the beneficial association of metformin in patients

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Correspondence to: Adriana Hung, adriana.hung@vumc.org

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with normal renal function extends to patients with mild-to-moderate kidney disease remains unknown.

We sought to test the hypothesis that persistent metformin use is associated with lower risk of kidney events and death among patients with diabetes and reduced kidney function, compared with use of sulfonylureas.

Methods

Study design

We conducted a retrospective cohort study of veterans who were cared for at the veterans health care system where the study was conducted, who were using metformin or sulfonylureas from 2001 through 2016 and who began follow-up at an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2.

Data sources

The data sources included the United States Veterans Health Administration (VHA), with linkage via a research identifier to data from the Medicare, Medicaid and National Death Index databases from 2001 through 2016. The clinical data warehouse of the VHA includes data derived from the electronic health record, designed for research to include identifiers to link multiple data sources. Pharmacy data included dispensed VHA prescriptions, date filled, days supplied and medication dose. Diagnostic and procedure information identified inpatient and outpatient encounters using structured data from the *International Classification of Diseases, 9th Revision* and *10th Revision*, depending on what data were available for a given year. We collected laboratory and vital signs data from the clinical data warehouse.[7] The Veterans Affairs Information Resource Center assembles Medicare and Medicaid data for veteran enrollees. From these files, we obtained enrolment and prescription (Part D) data. Dates of death were included in the vital statistics and in the National Death Index.

Study population

We assembled a retrospective cohort of patients with new onset diabetes. The underlying cohort included veterans (aged ≥ 18 yr) who received regular VHA care (i.e., a VHA encounter or prescription fill at least once every 180 d) in the 2 years before cohort entry, and who had a new prescription of metformin or a sulfonylurea (including glipizide, glyburide or glimepiride), with no fill of any diabetes medication within the previous 180 days.

We followed patients longitudinally; they were required to remain persistent to their incident diabetes regimen, with medication gaps no larger than 180 days, until they reached the index date. The index date and start of follow-up was when patients reached an eGFR of less than 60 mL/min/1.73 m^2 (Appendix 1, Supplemental Figure 1, available at www.cmajopen.ca/content/11/1/E77/suppl/DC1). We excluded patients who added or switched medications at or before the index date and those who had dialysis, an organ transplant or hospice enrolment within 2 years before the index date. The index date was restricted to dates between Jan. 1, 2002, and Dec. 30, 2016, to allow sufficient collection of baseline data and follow-up.

Study variables

The study exposures were continued use of metformin or sulfonylureas on the index date. Follow-up began at the date of reduced kidney function (eGFR < 60 mL/min/1.73 m^2) and continued until an outcome (as defined below), a competing risk (nonpersistence) or a censoring event.

We used creatinine measures to calculate eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation.[8,9] The primary outcome was a composite of death or kidney event, an outcome used by clinical trials.[10] Kidney events included either a sustained decline in eGFR of 40% for 3–12 months or end-stage renal disease, defined as renal replacement therapy (including dialysis), renal transplantation or an eGFR of less than 15 mL/min/1.73 m^2 (Appendix 1, Supplemental Table 1).[10–12] The secondary outcome was a kidney event. To avoid capturing a single reduced eGFR measure, which may represent acute kidney injury, we used the first confirmed event as the event date.

We considered treatment nonpersistence — defined as 90 days without use of an antidiabetic agent, the addition of a new agent or switch to a different agent — as a competing risk event. All-cause death and treatment nonpersistence were competing risk events for the secondary outcome (kidney event). Censoring events were reaching day 181 of no contact with a VHA facility (inpatient, outpatient or pharmacy use) or study end (Dec. 31, 2016). We included study covariates (Appendix 1, Supplemental Table 2) measured closest to the index date and up to 720 days before the index date. Missing covariates were handled with multiple imputations using 20 iterations of chained imputations. The imputed values are found using predictive mean matching[13] and canonical correlation analysis.[9] We included indicators for missingness to account for potential informative missingness.

Statistical analysis

Propensity scores modelled the probability of metformin continuation, given covariates, Veterans Integrated Services Network and an indicator for imputed covariates. The weighted analysis balances the covariate distributions by assigning weights to patients in both exposure groups such that the weighted groups resemble each other group (average treatment effect in evenly matchable units). Both metformin and sulfonylurea groups were weighted so that their distribution of covariates resembled each other.[14,15] We derived matching weights at the index date and at 361 days. We calculated standardized mean differences as the difference between groups in number of standard deviations. We estimated the cause-specific hazard of the primary composite outcome (kidney event or death) using Cox proportional hazards models between the metformin and sulfonylurea (referent) groups in a propensity score–weighted cohort. For the regression models, we used multiple imputation with predictive mean matching and 20 imputed data sets for the propensity score estimation and the covariate-adjusted Cox proportional hazard models to address missingness in the baseline covariates (Appendix 1, Supplemental Methods).

A plot of Schoenfeld residuals against time indicated that the proportional hazards assumption in the Cox model was not met.[16,17] To meet these assumptions, we divided our study into 2 time periods (index date through the first 360 d, and day 361 onward for patients persistent on their medication). Multistate models for the propensity score–weighted cohort estimated cumulative incidence in the presence of competing risks of medication nonpersistence using the Aalen–Johansen estimator (Appendix 1, Supplemental Methods).[18–21]

We conducted sensitivity analyses adjusted for all covariates in the propensity score–weighted cohort for the evaluation of the primary outcome of death or kidney events. We examined prespecified subgroups in the time period from 361 days onward, including groups by age (≥ 65 yr, < 65 yr), race (Black and non-Black), baseline eGFR at the index date (eGFR ≥ 45 mL/min/1.73 m^2, eGFR < 45 mL/min/1.73 m^2) and the use of renin–angiotensin–aldosterone system (RAAS) inhibitors (yes, no). We conducted analyses using R (http://www.r-project.org).

Ethics approval

The institutional review board of VHA Tennessee Valley Healthcare System approved this study.

Results

We identified 74096 new users of metformin and 28967 new users of sulfonylurea who reached eGFR < 60 mL/min/1.73 m^2 and began the first study period (Figure 1). Table 1 shows the weighted cohort characteristics on the index date and for those who persisted on their regimen on day 361 (Appendix 1, Supplementary Table 3 shows the unweighted cohort characteristics). The weighted cohort included 24883 patients using metformin and 24998 patients using sulfonylureas, including glipizide (n = 2750, 55.0%), glyburide (n = 10999, 44.0%) and glimepiride (n = 250, 1.0%).

On day 361, we identified 12571 patients using metformin and 12637 patients using sulfonylureas in the recalculated propensity score–weighted cohort. Median follow-up in the weighted cohort for the study period beginning at day 361 was 1.5 (interquartile range [IQR] 0.6–3.2) years for patients taking metformin and 1.5 (IQR 0.6–3.2) years for those using sulfonylureas. All standardized mean differences in both weighted cohorts were less than 0.10 (Table 1).

Estimated glomerular filtration rate values

The median historical eGFR before the index date was 69.6 (IQR 64.9–78.1) mL/min/1.73 m^2 and the median difference between the historical and index date eGFR values was 14.6 (IQR 9.6–23.5) mL/min/1.73 m^2 for patients taking metformin and 14.6 (IQR 9.6–23.2) mL/min/1.73 m^2 for those taking sulfonylureas. The median time between eGFR measures was 4.6 (IQR 2.4–7.0) months for patients taking metformin and 5.0 (IQR 2.6–7.5) months for those taking sulfonylureas. The median number of days between the index and follow-up eGFR measures was 112 days, and the median follow-up eGFR was 54 mL/min/1.73 m^2. The median eGFR closest to the 361-day time point was 63.5 (IQR 55.8–72.3) mL/min/1.73 m^2 for patients using metformin and 63.7 (IQR 55.7–72.3) mL/min/1.73 m^2 for those using sulfonylureas.

Outcomes

First 360 days of follow-up

In the first 360 days, 10951 (44.0%) of 24883 patients taking metformin and 9822 (39.3%) of 24998 patients taking sulfonylureas did not persist in treatment. Nonpersistent patients on metformin stopped the drug (n = 6358, 25.6%) or added other drugs (n = 4593, 14.2%). Nonpersistent patients on sulfonylureas stopped the drug (n = 6263, 25.1%) or added other drugs (n = 3559, 14.2%). Among those treated with metformin or sulfonylurea, 265 (1.1%) and 361 (1.5%), respectively, were censored for leaving the VA; 13090 (52.6%) and 14029 (56.1%), respectively, were censored for reaching the end of 360-day study period.

There were 576 events (527 deaths and 49 kidney events, including 41 instances of eGFR decline, 3 eGFR events and 5 instances of end-stage renal disease) for patients treated with metformin and 786 events (730 deaths and 56 kidney events, including 44 instances of eGFR decline, 2 eGFR events and 9 instances of end-stage renal disease) for those treated with sulfonylureas, yielding 33.5 (95% confidence interval [CI] 30.9–36.3) events and 43.0 (95% CI 40.1–46.0) events per 1000 person-years, respectively. The propensity score–weighted, cause-specific hazard ratio (HR) for death and kidney events among patients treated with metformin compared with those treated with sulfonylureas was 0.78 (95% CI 0.71–0.85). Covariate adjustment to the propensity score–weighted model yielded similar results (adjusted HR 0.79, 95% CI 0.72–0.87). When evaluating the secondary outcome of kidney events, with death as a competing risk, there were 2.9 (95% CI 2.2–3.8) events and 3.1 (95% CI 2.4–4.0) events per 1000 person-years for patients treated with metformin or sulfonylurea, respectively, yielding an HR of 0.94 (95% CI 0.67–1.33). When evaluating the secondary outcome of death, there were 30.6 (95% CI 28.2–33.3) events and 40 (95% CI 37.2–42.9) events per 1000 person-years for patients treated with metformin or sulfonylurea, respectively, yielding an HR of 0.76 (95% CI 0.69–0.84) (Table 2). The cumulative incidence plots showing the competing risks are shown in Figure 2A and Figure 2B.

Day 361 of follow-up and onward

Among the 12571 patients who persisted on metformin for at least 361 days after the index date, there were 747 primary composite events (637 deaths and 110 kidney events, including 107 instances of eGFR decline and 3 of end-stage renal disease). Among the 12637 patients who persisted on sulfonylureas, there were 1033 events (884 deaths and 149 kidney events, including 148 with eGFR decline and 1 with end-stage renal disease) (Table 2). Incidence rates were 26.5 (95% CI 24.7–28.5) per 1000 person-years for patients on metformin versus 36.3 (95% CI 34.2–38.6) per 1000 person-years for those on sulfonylureas, yielding an HR of 0.73 (95% CI 0.67–0.79); we observed consistent results after

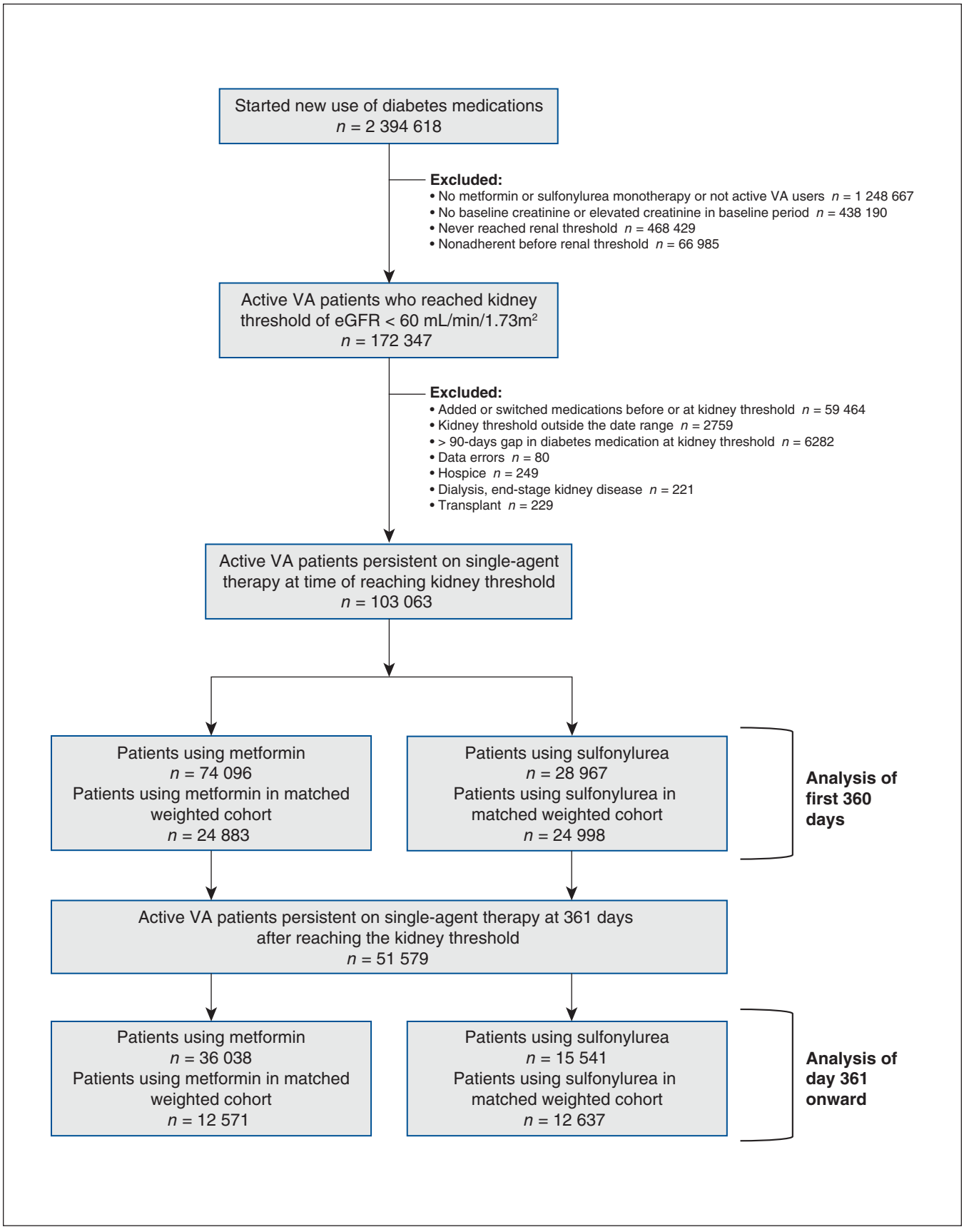

Figure 1: Study flowchart. Note: VA = Veterans Affairs.

Table 1 (part 1 of 3): Patient characteristics on index date of kidney function decline and at 361 days after the index date for persistent patients

Characteristic	No. (%) of patients in propensity score–weighted cohort at index date*			No. (%) of patients in propensity score–weighted cohort at 361 d		
	Metformin *n* = 24 883	Sulfonylureas *n* = 24 998	SMD†	Metformin *n* = 12 571	Sulfonylureas *n* = 12 637	SMD†
Age, yr, median (IQR)	70.7 (63.7–78.1)	70.5 (63.7–78.1)	0.001	72.5 (65.4–79.5)	72.2 (65.3–79.4)	0.003
Sex, male	24 362 (97.9)	24 476 (97.9)	0.001	12 334 (98.1)	12 406 (98.2)	0.004
Race						
White	20 908 (84.0)	21 007 (84.0)	0.002	10 918 (86.9)	10 982 (86.9)	0.002
Black	3503 (14.1)	3512 (14.0)		1424 (11.3)	1430 (11.3)	
Other‡	472 (1.9)	479 (1.9)		229 (1.8)	226 (1.8)	
Time from cohort entry to kidney threshold, mo, median (IQR)	14.2 (5.9–30.7)	14.3 (6.1–30.9)	0.014	28.4 (18.9–45.4)	28.6 (19.0–45.6)	0.009
Year reached kidney threshold						
2002–2003	2815 (11.3)	2808 (11.2)	0.027	1568 (12.5)	1545 (12.2)	0.038
2004–2005	4308 (17.3)	4268 (17.1)		2236 (17.8)	2234 (17.7)	
2006–2007	5005 (10.1)	5216 (20.9)		2722 (21.7)	2853 (22.6)	
2008–2009	3726 (15.0)	3781(15.1)		1983 (15.8)	1999 (15.8)	
2010–2011	3291 (13.2)	3207 (12.8)		1737 (13.8)	1673 (13.2)	
2012–2013	2603 (10.5)	2556 (10.2)		1281(10.2)	1254 (9.9)	
2014–2015	2164 (8.7)	2181 (8.7)		1038 (8.2)	1076 (8.5)	
2016	971 (3.9)	981 (3.9)		5 (0.0)	3 (0.0)	
Laboratory variables						
HbA_{1c}, %, median (IQR)	6.5 (6.1–7.1)	6.5 (6.1–7.2)	0.007	6.5 (6.1–7.0)	6.50 (6.0–7.1)	0.007
Missing HbA_{1C} measure	1011 (4.1)	994 (4.0)	0.004	503 (4.0)	488 (3.9)	
Historical eGFR before kidney threshold, mL/min/1.73 m^2, median (IQR)§	69.3 (64.5–76.6)	69.3 (64.5–76.6)	0.001	–	–	
eGFR at kidney threshold, mL/min/1.73 m^2, median (IQR)	55.6 (51.4–58.0)	55.6 (51.4–58.0)	0.002	55.9 (52.2–58.1)	55.8 (52.2–58.2)	0.003
eGFR at 361 days, mL/min/1.73 m^2, median (IQR)	–	–		63.5 (55.8–72.3)	63.7 (55.7–72.3)	0.007
Missing eGFR	293 (1.2)	296 (1.2)	0.001	964 (7.7)	957 (7.6)	0.004
Hemoglobin, g/dL, median (IQR)	14.0 (13.0–15.1)	14.1 (13.0–15.1)	0.003	13.9 (12.9–14.9)	14.0 (12.9–15.0)	0.004
Missing hemoglobin	1507 (6.1)	1503 (6.0)	0.002	777 (6.2)	792 (6.3)	0.003
Low-density lipoprotein, mmol/L, median (IQR)	2.28 (1.81–2.82)	2.28 (1.81–2.82)	0.002	2.18 (1.76–2.64)	2.18 (1.76–2.67)	0.001
Missing low-density lipoprotein measure	779 (3.1)	781 (3.1)	< 0.001	310 (2.5)	309 (2.4)	0.004
Microalbumin-to-creatinine ratio stage						
Normal (< 30 mg/g)	9616 (38.6)	9670 (38.7)	0.003	5261 (41.9)	5305 (42.0)	0.003
Microalbuminuria (30–300 mg/g)	2775 (11.2)	2771.0 (11.1)		1516 (12.1)	1523 (12.1)	
Macroalbuminuria (> 300 mg/g)	788 (3.2)	781.6 (3.1)		370 (2.9)	373 (3.0)	
Missing microalbumin-to-creatinine ratio	11 703 (47.0)	11 775 (47.1)		5424 (43.1)	5436 (43.0)	

Table 1 (part 2 of 3): Patient characteristics on index date of kidney function decline and at 361 days after the index date for persistent patients

Characteristic	No. (%) of patients in propensity score–weighted cohort at index date*			No. (%) of patients in propensity score–weighted cohort at 361 d		
	Metformin *n* = 24 883	Sulfonylureas *n* = 24 998	SMD†	Metformin *n* = 12 571	Sulfonylureas *n* = 12 637	SMD†
Proteinuria by urinalysis						
Negative	11 736 (47.2)	11 787 (47.2)	0.002	6101 (48.5)	6129 (48.5)	0.002
Urine protein trace or 1+	3533 (14.2)	3561 (14.2)		1700 (13.5)	1711 (13.5)	
Proteinuria present at 2+	831 (3.3)	838 (3.4)		330 (2.6)	330 (2.6)	
Proteinuria present at 3+ or 4+	336 (1.3)	336 (1.3)		127 (1.0)	126 (1.0)	
Unknown urine protein measure	8446 (33.9)	8476 (33.9)		4313 (34.3)	4341 (34.4)	
Clinical variables						
Systolic blood pressure, mm Hg, median (IQR)	131 (119–142)	131 (119–142)	0.002	132 (120–142)	132 (121–142)	0.005
Diastolic blood pressure, mm Hg, median (IQR)	72 (64–80)	72 (64–80)	0.001	72 (64–79)	72 (64–79)	0.001
BMI, median (IQR)	30.3 (27.0–34.4)	30.3 (27.0–34.3)	0.003	30.2 (27.0–34.2)	30.2 (27.0–34.1)	0.001
Missing BMI measure	4688 (18.8)	4719 (18.9)	0.001	2290 (18.2)	2306 (18.3)	0.003
Baseline comorbidities						
Malignant disease¶	2971 (11.9)	2990 (12.0)	0.001	1622 (12.9)	1622 (12.8)	0.002
Liver disease	625 (2.5)	621 (2.5)	0.002	230 (1.8)	229 (1.8)	0.001
HIV	89 (0.4)	90 (0.4)	0.001	39 (0.3)	40 (0.3)	0.001
Congestive heart failure	3051 (12.3)	3071 (12.3)	0.001	1580 (12.6)	1592 (12.6)	0.001
Cardiovascular disease	7935 (31.9)	8006 (32.0)	0.003	3987 (31.7)	4019 (31.8)	0.002
Stroke	831 (3.3)	827 (3.3)	0.002	399 (3.2)	401 (3.2)	< 0.01
Transient ischemic attack	322 (1.3)	332 (1.3)	0.003	155 (1.2)	153 (1.2)	0.002
Serious mental illness**	4957 (19.9)	5035 (20.1)	0.005	2401 (19.1)	2430 (19.2)	0.003
Smoking	3045 (12.2)	3068 (12.3)	0.001	1262 (10.0)	1263 (10.0)	0.002
Chronic obstructive pulmonary disease	4284 (17.2)	4321 (17.3)	0.002	2157 (17.2)	2166 (17.1)	< 0.01
History of respiratory failure	821 (3.3)	821 (3.3)	0.001	543 (4.3)	533 (4.2)	0.005
History of sepsis	406 (1.6)	414 (1.7)	0.002	291 (2.3)	291 (2.3)	0.001
History of pneumonia	1074 (4.3)	1092 (4.4)	0.003	648 (5.2)	640 (5.1)	0.004
Arrhythmia	4387 (17.6)	4418 (17.7)	0.001	2399 (19.1)	2414 (19.1)	< 0.01
Cardiac valve disease	919 (3.7)	929 (3.7)	0.001	497 (4.0)	503 (4.0)	0.002
Parkinson disease	234 (0.9)	237 (0.9)	0.001	162 (1.3)	158 (1.3)	0.003
Urinary tract infection	1055 (4.2)	1067 (4.3)	0.001	640 (5.1)	645 (5.1)	0.001
Osteomyelitis	156 (0.6)	154 (0.6)	0.002	65 (0.5)	64 (0.5)	0.002
Osteoporosis	200 (0.8)	206 (0.8)	0.002	118 (0.9)	115 (0.9)	0.003
Falls	57 (0.2)	59 (0.2)	0.002	59 (0.5)	57 (0.4)	0.003
Fractures	556 (2.2)	556 (2.2)	0.001	315 (2.5)	313 (2.5)	0.002
Amputation	118 (0.5)	123 (0.5)	0.002	55 (0.4)	55 (0.4)	0.001
Retinopathy	286 (1.1)	287 (1.1)	< 0.001	117 (0.9)	121 (1.0)	0.003

Table 1 (part 3 of 3): Patient characteristics on index date of kidney function decline and at 361 days after the index date for persistent patients

Characteristic	No. (%) of patients in propensity score–weighted cohort at index date*			No. (%) of patients in propensity score–weighted cohort at 361 d		
	Metformin *n* = 24 883	Sulfonylureas *n* = 24 998	SMD†	Metformin *n* = 12 571	Sulfonylureas *n* = 12 637	SMD†
Use of medications						
Angiotensin-converting enzyme inhibitors	15 958 (64.1)	16 080 (64.3)	0.004	7623 (60.6)	7690 (60.9)	0.004
Angiotensin II receptor blockers	2904 (11.7)	2904 (11.6)	0.002	1647 (13.1)	1644 (13.0)	0.003
β-blockers	12 699 (51.0)	12 770 (51.1)	0.001	6533 (52.0)	6565 (51.9)	< 0.01
Calcium-channel blockers	7417 (29.8)	7454 (29.8)	< 0.001	3801 (30.2)	3820 (30.2)	< 0.01
Thiazide- and potassium-sparing diuretics	10 072 (40.5)	10 169 (40.7)	0.004	4531 (36.0)	4578 (36.2)	0.004
Loop diuretics	5059 (20.3)	5087 (20.3)	< 0.001	2433 (19.4)	2448 (19.4)	0.001
Other antihypertensive medications	6873 (27.6)	6887 (27.6)	0.002	3834 (30.5)	3834 (30.3)	0.003
Statin lipid-lowering drugs	16 763 (67.4)	16 917 (67.7)	0.007	9059 (72.1)	9119 (72.2)	0.002
Nonstatin lipid-lowering agents	4237 (17.0)	4264 (17.1)	0.001	2275 (18.1)	2280 (18.0)	0.002
Antiarrhythmic drugs, digoxin and inotropes	2313 (9.3)	2321 (9.3)	< 0.001	1072 (8.5)	1078 (8.5)	< 0.01
Anticoagulant drugs and platelet inhibitors	2578 (10.4)	2588 (10.4)	< 0.001	1386 (11.0)	1394 (11.0)	< 0.01
Nitrates	3652 (14.7)	3689 (14.8)	0.002	1716 (13.6)	1739 (13.8)	0.003
ASA	5332 (21.4)	5385 (21.5)	0.003	2533 (20.1)	2570 (20.3)	0.005
Non-ASA platelet inhibitors	2643 (10.6)	2660 (10.6)	0.001	1329 (10.6)	1343 (10.6)	0.002
Antipsychotic drugs	1662 (6.7)	1685 (6.7)	0.003	747 (5.9)	745 (5.9)	0.002
Oral glucocorticoids	1823 (7.3)	1845 (7.4)	0.002	894 (7.1)	892 (7.1)	0.002
Indicators of health care use††						
Admitted to hospital within year (Veterans Health)	3550 (14.3)	3600 (14.4)	0.004	1510 (12.0)	1538 (12.2)	0.005
Admitted to hospital in 30 days (Veterans Health)	934 (3.8)	953 (3.8)	0.003	188 (1.5)	187 (1.5)	0.001
Admitted to hospital within year (Medicare/ Medicaid)	2851 (11.5)	2860 (11.4)	< 0.001	1521 (12.1)	1507 (11.9)	0.005
Admitted to hospital in 30 days (Medicare/ Medicaid)	450 (1.8)	461 (1.8)	0.003	197 (1.6)	198 (1.6)	< 0.01
Medicaid use in previous year	298 (1.2)	307 (1.2)	0.003	143 (1.1)	142 (1.1)	0.001
Medicare use in previous year	9128 (36.7)	9129 (36.5)	0.003	5221 (41.5)	5213 (41.3)	0.006
Nursing home encounter in previous year	97 (0.4)	102 (0.4)	0.003	66 (0.5)	67 (0.5)	< 0.01
Medicare Advantage use	3979 (16.0)	3998 (16.0)	< 0.001	2498 (19.9)	2517 (19.9)	0.001

Note: ASA = acetylsalicylic acid, BMI = body mass index, eGFR = estimated glomerular filtration rate, IQR = interquartile range, SMD = standardized mean difference.
*Unless indicated otherwise.
†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 weighted cohort, all standardized differences were less than 0.01, suggesting there were no important imbalances.
‡Other races include American Indian or Alaska Native, Asian, and Native Hawaiian or Pacific Islander.
§Historical eGFR is the eGFR before the patient met the inclusion criteria of eGFR < 60 mL/min/1.73 m^2; eGFR at kidney threshold indicates the eGFR when the patient met the inclusion criteria of eGFR < 60 mL/min/1.73 m^2.
¶Malignant disease includes all types of cancer except nonmelanoma skin cancer.
**Serious mental illness included schizophrenia, depression, bipolar disorder, dementia and post-traumatic stress disorder.
††The Veterans Health Administration provides health care coverage for those who serve their country through military services. Medicare and Medicaid health services are federal health care programs for eligible people older than 65 years. Medicare Advantage is a Medicare plan offered by private insurers that provides hospital, outpatient and (usually) prescription drug coverage, supplanting benefits under other Medicare plans.

Table 2: Rates and hazard ratios for kidney composite outcomes among patients who persisted on metformin or sulfonylurea in matched weighted cohort in first 360 days and from day 361 onward of reaching reduced kidney function threshold*

	First 360 days		361 days onward	
Outcome	Metformin *n* = 24 883	Sulfonylurea *n* = 24 998	Metformin *n* = 12 571	Sulfonylurea *n* = 12 637
Primary outcome: kidney events or death				
Number of events	576	786	747	1033
Person-time, yr	17 194	18 278	28 191	28 429
Events per 1000 person-years (95% CI)	33.5 (30.9–36.3)	43.0 (40.1–46.0)	26.5 (24.7–28.5)	36.3 (34.2–38.6)
PS-weighted HR, unadjusted (95% CI)	0.78 (0.71–0.85)	Ref.	0.73 (0.67–0.79)	Ref.
PS-weighted HR, adjusted* (95% CI)	0.79 (0.72–0.87)	Ref.	0.76 (0.70–0.83)	Ref.
Secondary outcome: kidney events				
Number of events	49	56	110	149
Person-time, yr	17 194	18 278	28 191	28 429
Events rates per 1000 person-years (95% CI)	2.9 (2.2–3.8)	3.1 (2.4–4.0)	3.9 (3.2–4.7)	5.2 (4.5–6.1)
PS-weighted HR, unadjusted (95% CI)	0.94 (0.67–1.33)	Ref.	0.73 (0.59–0.91)	Ref.
Secondary outcome: death				
Number of events	527	730	642	903
Person-time, yr	17 201	18 300	28 240	28 717
Events rates per 1000 person-years (95% CI)	30.6 (28.2–33.3)	40 (37.2–42.9)	22.7 (21.0–24.5)	31.5 (29.5–33.5)
PS-weighted HR, unadjusted (95% CI)	0.76 (0.69–0.84)	Ref.	0.72 (0.66–0.79)	Ref.

Note: HR = hazard ratio, PS = propensity score, Ref. = reference category.
*Cox Proportional Hazards model for time to event. Adjusted for demographics, clinical information derived from the electronic health record, comorbidities, use of medications and health care utilization (see Appendix 1, Supplemental Table 1, available at www.cmajopen.ca/content/11/1/E77/suppl/DC1). All continuous variables were modelled as restricted cubic splines. All covariates in PS model included in the PS-weighted and adjusted model (see Appendix 1, Supplemental Table 1).

adjusting for covariates (adjusted HR 0.76, 95% CI 0.70–0.83). For the secondary outcome, which evaluated kidney events and treated death as a competing risk, the event rate was 3.9 (95% CI 3.2–4.7) versus 5.2 (95% CI 4.5–6.1) events per 1000 person-years for patients treated with metformin or sulfonylureas, respectively (HR 0.73, 95% CI 0.59–0.91). For the secondary outcome of death, the event rate was 22.7 (95% CI 21.0–24.5) versus 31.5 (95% CI 29.5–33.5) events per 1000 person-years for patients treated with metformin or sulfonylureas, respectively (HR 0.72, 95% CI 0.66–0.79). Figure 3A and Figure 3B show the cumulative probabilities of death and kidney events or of kidney event alone, respectively.

For those patients who persisted on their drug therapy for at least 361 days after reaching reduced kidney function, the cumulative probability of death or kidney event at 3 years was 3.8% for patients on metformin and 6.4% for those on sulfonylureas (risk difference 2.6%). The number needed to treat with metformin is 38.5 patients to prevent 1 death or kidney event. For these same patients who remained on metformin or sulfonylureas, the cumulative probability of reaching a kidney event at 5 years was 0.76% (95% CI 0.64%–0.91%) versus 1.00% (95% CI 0.87%–1.20%), respectively, and was 1.10% (95% CI 0.95%–1.30%) versus 1.50% (95% CI 1.30%–1.70%) at 10 years, respectively.

Subgroup analysis

Results stratified by age (≥ 65 yr v. < 65 yr), race (Black v. non-Black), eGFR (≥ 45 mL/min/1.73 m^2 v. < 45 mL/min/1.73 m^2) and use of RAAS inhibitors (yes v. no) were consistent with the main analysis, but CIs were wide for most subgroups (Figure 4).

Interpretation

Diabetes is the most common condition associated with kidney disease worldwide. In this national evaluation of patients with type 2 diabetes who developed an eGFR of less than 60 mL/min/1.73 m^2, continued use of metformin was associated with a decreased risk of the composite outcome of death or kidney event, compared with use of sulfonylureas. In particular, use of metformin was associated with lower risk of death in the first 360 days. Continued use of metformin past 361 days was associated with lower risk of clinically important kidney outcomes. Accordingly, the risk difference for death or a kidney event for patients treated with metformin versus sulfonylureas was 2.6%; the number needed to treat was 38.5 patients with continued metformin for 3 years to prevent 1 death or kidney event.

Our results are consistent with work that showed metformin was associated with lower rates of kidney events

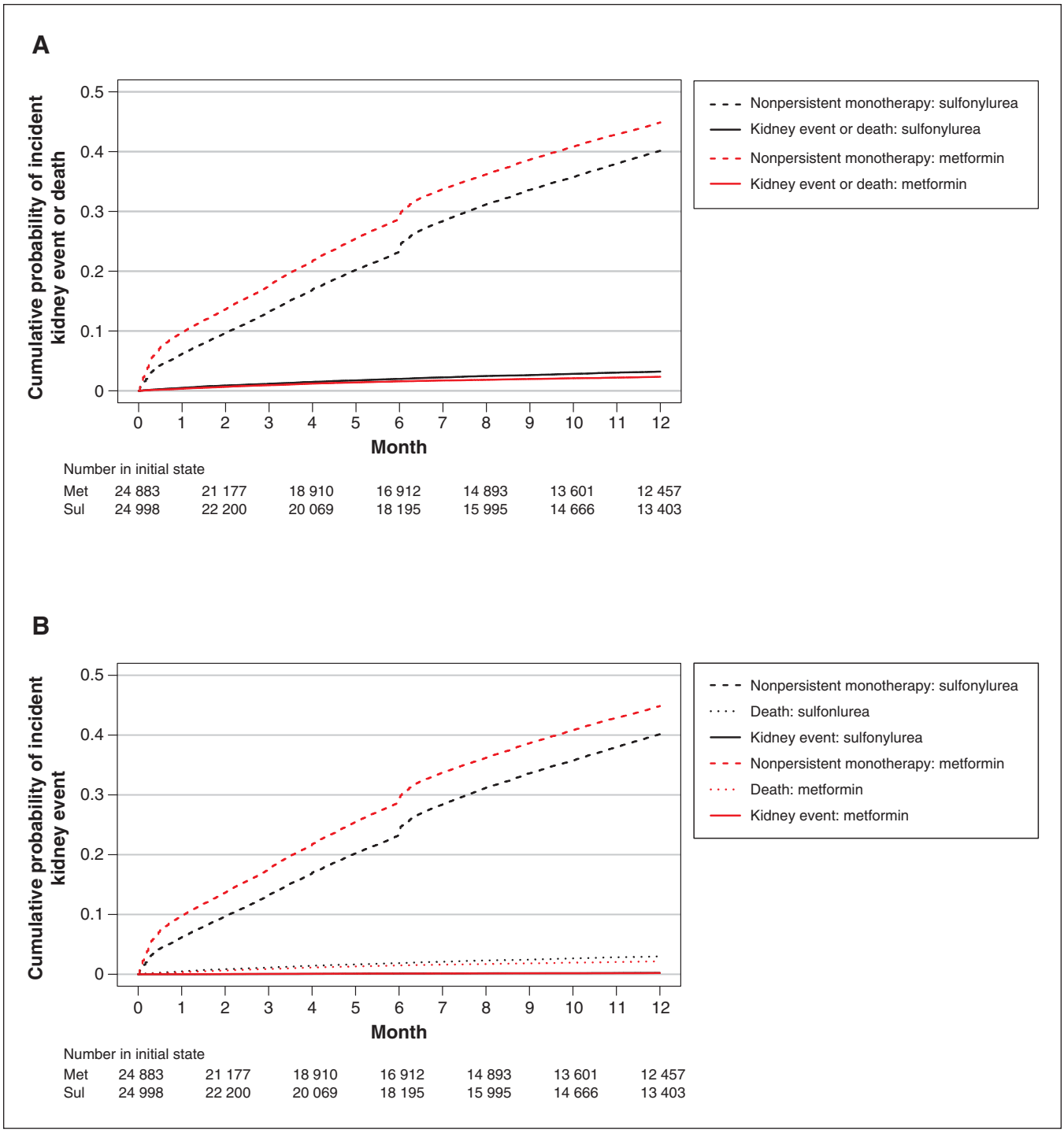

Figure 2: Full Aalen–Johansen cumulative probability plot of a kidney event (i.e., 40% decline in estimated glomerular filtration rate or end-stage renal disease) or death (panel A) or of a kidney event (panel B) in the weighted cohort for the first 360 days after reaching an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 by treatment group. Note: Met = metformin, Sul = sulfonylurea.

compared with sulfonylureas among patients with preserved kidney function.[6,22] Metformin has properties that may affect the kidney, including antioxidant, anti-inflammatory, antifibrotic and insulin-sensitizing properties.[23–26] Many of these properties can potentially improve endothelial function in patients with kidney disease.[27] Few studies have evaluated the association of metformin on kidney function decline among patients with moderately reduced kidney function, in whom metformin is now indicated as the first-line therapy for diabetes management.[28] Patients with diabetes and reduced eGFR have higher mortality (all cause and cardiovascular) when compared with patients with diabetes and

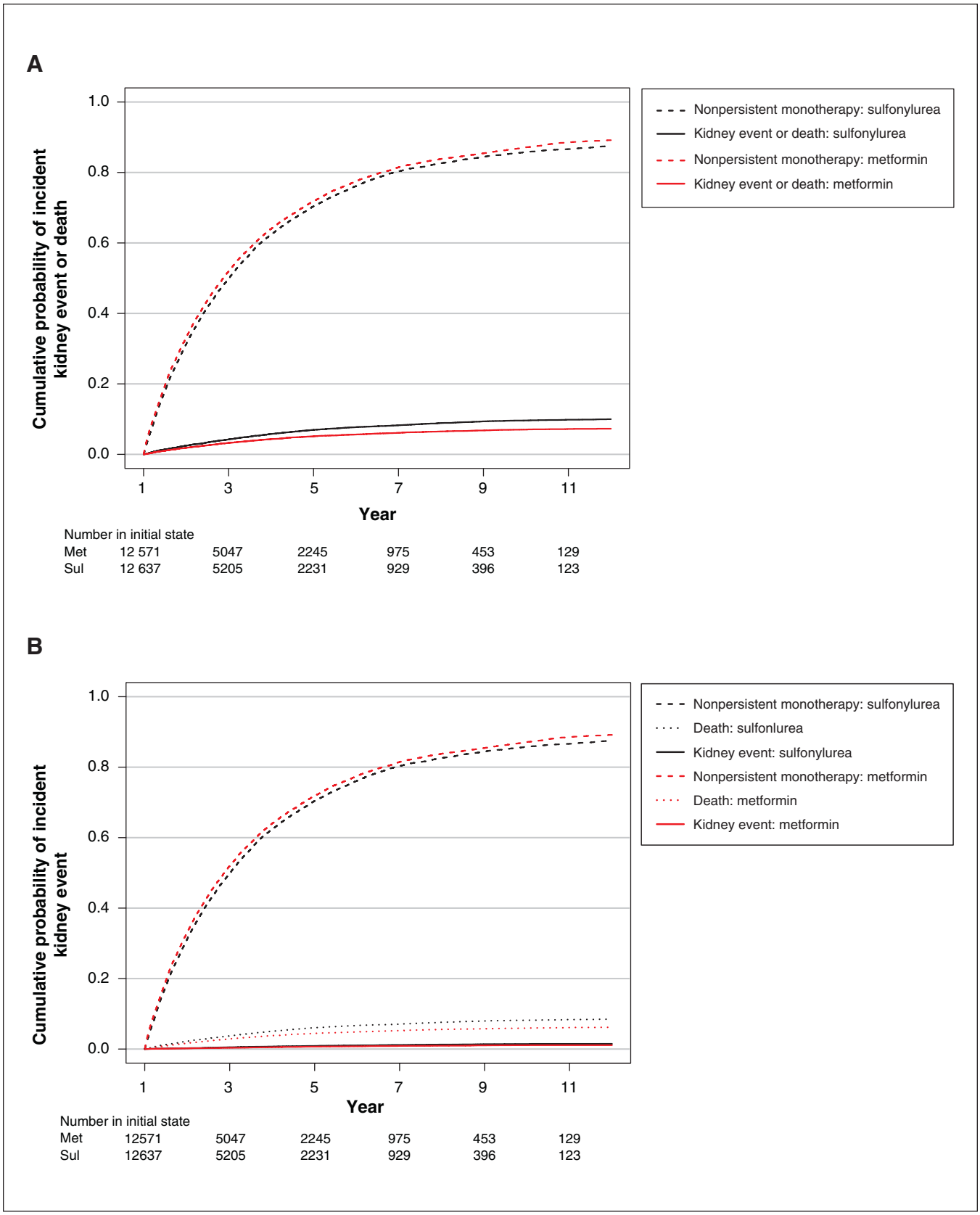

Figure 3: Full Aalen–Johansen cumulative probability of a kidney event (i.e., 40% decline in estimated glomerular filtration rate or end-stage renal disease) or death (panel A) or of a kidney event (panel B) in the weighted cohort for those who persisted on their treatment for at least 361 days after reaching an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 by treatment group. Note: Met = metformin, Sul = sulfonylurea.

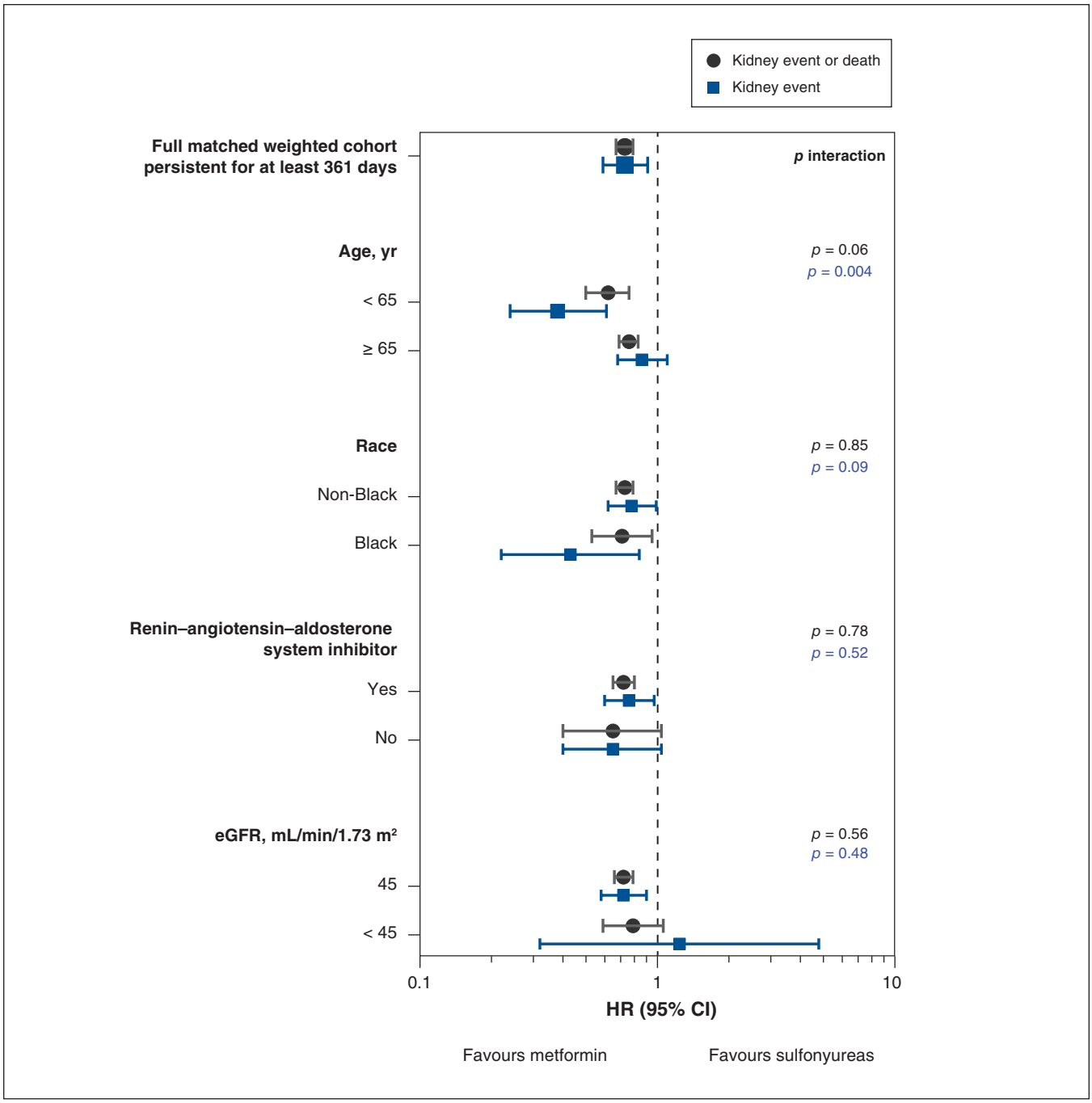

Figure 4: Propensity score–weighted hazard ratios (HRs) for the primary and secondary outcomes by subgroup for patients persistent on therapy at 361 days after reaching an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2. Note: CI = confidence interval.

preserved kidney function.[28,29] Our current study findings, taken in the context of previous reports, suggest that metformin should remain the first-line agent among those who develop kidney decline.[6,22,30–33]

Limitations

We required persistence on diabetes incident medication at the index date (kidney threshold) and at 361 days beyond the index date for analyses. These criteria excluded patients who stopped, added or switched medications at or before reaching the kidney threshold and limited follow-up for patients who changed their medications or died so that our outcomes could be attributed to the drug exposure. Furthermore, many factors influenced the choice of diabetes medication (sulfonylurea v. metformin monotherapy) at onset of disease during the study period, which could potentially be confounding. The study years were before 2016 when guidance suggested stopping metformin if patients reached a creatinine level of 1.4–1.5 mg/dL.[34] During

the same time period, guidance suggested stopping glyburide at a serum creatinine level over 2.0 mg/dL. These time trends were accounted for, but we noted that medication nonpersistence and early changes to medications were common and limited the sample size available for analysis. Veterans may not receive all their care at VHA facilities, and some events were likely missed. The kidney event relies solely on VHA-collected laboratory data. It is possible those patients older than 65 years were less likely to receive their care or bloodwork within VHA as they are eligible for care through Medicare coverage across many health care systems, leading to a systematic exclusion of some events. The kidney threshold may represent an acute kidney injury event rather than progression of chronic kidney disease. Although we used propensity score weighting to reduce concerns about confounding, this was an observational study and residual confounding may exist. Finally, the study population was mostly older white men, and may not be representative of the larger population of patients with diabetes and reduced kidney function. This should be considered when extrapolating the study results to other populations including women.

Conclusion

Treatment with metformin in the first 360 days of reduced kidney function was associated with a lower incidence of kidney event or death in patients with diabetes, compared with sulfonylureas. Persistent treatment with metformin beyond 361 days was associated with fewer kidney events (including eGFR decline and end-stage renal disease) or deaths, compared with sulfonylureas. Furthermore, our study provides reassurance that continued use of metformin in patients with reduced kidney function supports the use of metformin as the first-line therapy for patients with mild-to-moderate kidney disease.

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Affiliations: Department of Medicine, Division of Nephrology and Hypertension (Hung), Vanderbilt University Medical Center; Precision Nephrology Program (Hung), Vanderbilt University Medical Center; Geriatric Research Education Clinical Center (Hung, Hackstadt, Grijalva, Greevy Jr., Roumie), Veteran Administration Tennessee Valley Healthcare System; Department of Medicine (Roumie), Vanderbilt University Medical Center; Department of Biostatistics (Hackstadt, Greevy Jr.), Vanderbilt University School of Medicine; Department of Health Policy (Griffin, Grijalva, Roumie), Vanderbilt University Medical Center, Nashville, Tenn.

Contributors: Adriana Hung, Amber Hackstadt, Carlos Grijalva, Robert Greevy Jr. and Christianne Roumie contributed to study conception and design, as well as data collection. Adriana Hackstadt, Robert Greevy Jr. contributed to data analysis. Adriana Hung and Christianne Roumie drafted the manuscript. All of the authors revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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