Hospitalization for Lactic Acidosis Among Patients With Reduced Kidney Function Treated With Metformin or Sulfonylureas

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OBJECTIVE

To compare the risk of lactic acidosis hospitalization between patients treated with metformin versus sulfonylureas following development of reduced kidney function.

RESEARCH DESIGN AND METHODS

This retrospective cohort combined data from the National Veterans Health Administration, Medicare, Medicaid, and the National Death Index. New users of metformin or sulfonylureas were followed from development of reduced kidney function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 or serum creatinine ≥1.4 mg/dL [female] or 1.5 mg/dL [male]) through hospitalization for lactic acidosis, death, loss to follow-up, or study end. Lactic acidosis hospitalization was defined as a composite of primary discharge diagnosis or laboratory-confirmed lactic acidosis (lactic acid ≥2.5 mmol/L and either arterial blood pH <7.35 or serum bicarbonate ≤19 mmol/L within 24 h of admission). We report the cause-specific hazard of lactic acidosis hospitalization between metformin and sulfonylureas from a propensity score–matched weighted cohort and conduct an additional competing risks analysis to account for treatment change and death.

RESULTS

The weighted cohort included 24,542 metformin users and 24,662 sulfonylurea users who developed reduced kidney function (median age 70 years, median eGFR 55.8 mL/min/1.73 m^2). There were 4.18 (95% CI 3.63, 4.81) vs. 3.69 (3.19, 4.27) lactic acidosis hospitalizations per 1,000 person-years among metformin and sulfonylurea users, respectively (adjusted hazard ratio [aHR] 1.21 [95% CI 0.99, 1.50]). Results were consistent for both primary discharge diagnosis (aHR 1.11 [0.87, 1.44]) and laboratory-confirmed lactic acidosis (1.25 [0.92, 1.70]).

CONCLUSIONS

Among veterans with diabetes who developed reduced kidney function, occurrence of lactic acidosis hospitalization was uncommon and not statistically different between patients who continued metformin and those patients who continued sulfonylureas.

Metformin is considered first-line pharmacologic treatment for type 2 diabetes partly on the basis of the publication of the UK Prospective Diabetes Study (UKPDS) in 1998 (1,2). In addition to reducing glycated hemoglobin (HbA_{1c}) and microvascular complications, metformin users experience weight loss, enhanced insulin sensitivity,

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and reduced incidence of long-term macrovascular complications compared with sulfonylureas or insulin (2–6).

Metformin was approved in 1994 by the U.S. Food and Drug Administration (FDA) with a black box warning about lactic acidosis, and it was considered contraindicated for patients with serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females (7). The metformin label also listed heart failure and other hypoxic states under warnings and precautions because of an increased risk of lactic acidosis (7). These concerns surrounding metformin-associated lactic acidosis were based on the clinical experience with phenformin and buformin, other medications in the biguanide class (8,9). By the 1970s, there was evidence that phenformin and buformin use was associated with lactic acidosis, and they were withdrawn from the U.S. market in 1978 (9). On the basis of accumulating observational evidence on metformin safety, the FDA directed the metformin label to be revised in 2016 such that the contraindication was limited to severe kidney impairment defined as an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. While there have been prospective studies evaluating lactic acidosis in patients with normal kidney function taking metformin, the evidence supporting the safety of metformin use among patients with reduced kidney function is limited to studies with a small number of events or lack of laboratory confirmation of lactic acidosis (2,10). The aim of the current study was to compare the association of continued use of metformin or sulfonylureas with lactic acidosis hospitalization among patients with type 2 diabetes who developed mild to moderate kidney disease.

RESEARCH DESIGN AND METHODS

Study Design and Data Sources

We assembled a retrospective cohort of Veterans Health Administration (VHA) patients. Pharmacy data included dispensed prescriptions, medication name, date filled, days supplied, and dose. Demographic, diagnostic, and procedure information identified inpatient and outpatient encounters. We collected laboratory results and vital signs data from clinical sources. For Medicare or Medicaid enrollees, we obtained enrollment, claims files, and prescription (Part D) data. We obtained dates and causes of death from vital status and National Death Index files. The institutional review board of VHA Tennessee Valley Healthcare System approved this study.

Study Population

The population included veterans age ≥18 years who received regular VHA care, defined as having at least one medical encounter every 365 days for ≥2 years before cohort entry. We identified patients who were new users of metformin, glipizide, glyburide, or glimepiride. New users were patients who filled a first hypoglycemic prescription without any diabetes drug fill in the 180 days before that first fill. Patients were required to persist on this hypoglycemic medication with medication gaps no larger than 180 days until they reached the date of cohort entry. The date of cohort entry was the date of reaching a reduced kidney function threshold (Supplementary Fig. 1), defined as either an eGFR of <60 mL/min/1.73 m^2 or serum creatinine of ≥1.5 mg/dL for males or 1.4 mg/dL for females. Cohort entry was restricted to the period between 1 January 2002 and 30 December 2015 to allow sufficient collection of baseline data and follow-up. We excluded patients who added or switched medications, had a single episode of dialysis, had an organ transplant, or enrolled in hospice at or within the 2 years before reaching the reduced kidney function threshold.

Exposure

The study exposures were continued metformin or sulfonylurea use after reaching the reduced kidney function threshold. Sulfonylurea use included use of second-generation sulfonylureas glyburide, glipizide, or glimepiride. Follow-up began on the date when the reduced kidney function (eGFR <60 mL/min/1.73 m^2 or serum creatinine of ≥1.5 mg/dL for males or 1.4 mg/dL for females) was fulfilled. The follow-up period ended when the outcome of lactic acidosis hospitalization occurred (defined below). Follow-up also ended if there was a censoring event or a competing risk event. The censoring events, which are not influenced by the treatment, were the 181st day of no contact with any VHA facility (inpatient, outpatient, or pharmacy use) and end of study (31 December 2016). The competing risk events, which are potentially influenced by treatment, were death and therapy nonpersistence, defined as 90 days without the antidiabetic agent or filling an antidiabetic drug other than the current therapy.

The daily dose of metformin or sulfonylureas at the time of reaching kidney function decline was calculated using the World Health Organization criteria for defined daily dose criteria. Daily dose was determined by multiplying the number of pills dispensed by the dose per pill prescribed divided by the recorded days of supply. If drug dose was missing or was a liquid formulation (<2%), the dose was considered missing. If days of supply was missing, it was assumed to be 90 days because 70% of the population received 90-day prescriptions (11). One defined daily dose was 2,000 mg for metformin, 10 mg for glipizide, 10 mg for glyburide, and 2 mg for glimepiride (12).

Outcome: Hospitalization for Lactic Acidosis

The primary outcome was hospitalization for lactic acidosis, which was defined as a composite of two event types. The first event was a hospitalization with a primary discharge diagnosis code for lactic acidosis using ICD-9 or ICD-10 before or after 1 October 2015. Codes included ICD-9 276.2 or ICD-10 E87.2 (13,14). The second event was a hospitalization with laboratory evidence of lactic acidosis defined as a measured lactic acid ≥2.5 mmol/L in combination with either a pH <7.35 on arterial blood gas or a serum bicarbonate ≤19 mmol/L within 24 h before or after the hospital admission. The outcome date was the date of hospital admission. Composite event types were mutually exclusive, and if a patient had both a discharge diagnosis code and a laboratory-confirmed diagnosis of lactic acidosis, the laboratory-confirmed event was taken as the event type.

Covariates

Study covariates were included as the closest to cohort entry and were measured up to 720 days before the date of reaching the reduced kidney function threshold and included age, sex, race, fiscal year, number of months from initial antidiabetic medication start to reaching the reduced kidney function threshold, and Veterans Integrated Service Networks of care. Physiologic variables were evaluated as the most recent measure in the 720 days before reduced kidney

function threshold and included BMI, blood pressure, HbA_{1c}, LDL levels, hemoglobin, presence of proteinuria, and creatinine (both historical and level at cohort entry). Creatinine was used to calculate eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation (14,15). Health care utilization was measured in the year before the reduced kidney function threshold (hospitalization, nursing home, number of outpatient visits or medications, and additional insurance use, including Medicare or Medicaid). Selected medications filled within 180 days of cohort entry and identified through pharmacy claims, smoking, and other comorbidities defined in Supplementary Table 1 were covariates.

Statistical Analyses

The analysis used a propensity score–weighted model. The propensity score modeled the probability of metformin or sulfonylurea use at the time of the reduced kidney function threshold and included covariates, Veterans Integrated Service Networks, and an indicator of missing covariates. Missing covariates were handled with multiple imputations using 20 iterations of chained imputations and adjusting for canonical variates. We used matching weights derived from the propensity score to balance both exposure groups on observed covariates (16) (Supplementary Description of Propensity Score Model and Weighting, Supplementary Table 2, and Supplementary Figs. 2–4). Standardized mean differences (SMDs) were calculated as the difference between groups in number of SDs because this is the preferred measure of covariate balance when dealing with large sample sizes. Smaller SMD values indicate less difference between groups, with 0 indicating perfect balance in mean or proportion.

Cox proportional hazards models estimated the cause-specific hazard ratios (HRs) for metformin versus sulfonylureas (referent) in the weighted cohort and adjusted for the above covariates, including the mean metformin dose, to allow for possible dose effects on the hazard of lactic acidosis hospitalization. Statistical significance for the two-sided *P* value was set at 0.05. Fulfillment of the proportional hazards assumptions was verified through examination of Schoenfeld residuals over time (17). The Cox model estimates the relative increase in hazard of lactic acidosis associated with metformin exposure compared with sulfonylureas. In the presence of competing risks, it should not be used to estimate an absolute effect. Therefore, cumulative incidence plots used the Aalen-Johansen estimator. The outcome (lactic acidosis) and the competing risks (nonpersistence and death) were treated as terminal states to allow estimation of the cumulative incidence, while the underlying population at risk was changing over time because of nonpersistence and death. End of study and no VHA contact remained as censoring events. The cause-specific HR and cumulative incidence plot were compared for consistency regarding the overall clinical interpretation of the associations with metformin versus sulfonylureas.

Sensitivity and Subgroup Analyses

Sensitivity analysis varied the definition of the outcome or the population. First, the laboratory-confirmed lactic acidosis definition was made more specific. We maintained the requirement for arterial blood pH <7.35 or serum bicarbonate <19 mmol/L within 24 h of admission but required a lactate value ≥ 5 mmol/L (18). Second, we restricted the population to those with an eGFR <60 mL/min/1.73 m^2 and required a second eGFR <60 mL/min/1.73 m^2 within 30–180 days of the index reduced kidney function event and evaluated outcomes in this restricted cohort with chronic kidney disease. Follow-up started at 180 days after reaching the reduced kidney function threshold. Finally, the population excluded patients who were enrolled in Medicare Advantage during the baseline period and censored patients' follow-up upon enrollment in Medicare Advantage programs. In this sensitivity analysis, Medicare Advantage (Part C) individuals were excluded because their claims may be missing or incomplete during the time frame of the study. In addition, we conducted subgroup analyses and tested for effect modification by stratifying by the following covariates: age (≥ 65, <65 years) and race (black, nonblack). We also examined eGFR at the kidney function threshold date. We chose to examine eGFR subgroups stratified at ≥ 45 and <45 mL/min/1.73 m^2 to have sufficient numbers of patients and outcomes in each group. Because of the small number of outcome events in subgroup analyses, weighted unadjusted estimates are reported. Analyses were conducted using R (www.r-project.org).

Data and Resource Availability

The protocol, statistical code, and de-identified and anonymized data set are available from C.L.R. with a written request.

RESULTS

Study Cohort and Patient Characteristics

The study identified 67,381 new users of metformin and 28,801 new users of sulfonylureas who developed reduced kidney function (Fig. 1). This cohort of persistent new users represented 55.6% of 174,882 new users who had a baseline creatinine and reached the reduced kidney function threshold. There were 18,651 who reached the kidney threshold outside the prespecified time range, 49,755 whose regimens changed before or on the day that kidney function threshold was reached, 9,184 who had no active diabetes medications or had not accessed the health care system for at least 6 months before reaching the kidney function threshold, and 117 with data errors. There were an additional 993 who met exclusion criteria: 206 with organ transplant, 219 in hospice, 193 with a dialysis episode within the past 2 years, and 375 with a documented lactic acidosis hospitalization before reaching the reduced kidney function threshold. After propensity score calculation and weighting, the cohort included 24,542 metformin users and 24,662 sulfonylurea users (54% glipizide, 45% glyburide, and 1% glimepiride).

Cohort veterans were 96.5% male and 82.6% white. Metformin and sulfonylurea patients had similar baseline characteristics. However, metformin users were younger than sulfonylurea users (median age 67 vs. 71 years). After weighting, patient characteristics were similar between metformin and sulfonylureas, including age 70 years (interquartile range [IQR] 63, 78) vs. 70 years (63, 78), HbA_{1c} 6.5% (6.1, 7.1) vs. 6.6% (6.1, 7.2) (HbA_{1c} 48 mmol/mol [43, 54] vs. 49 mmol/mol [43, 55]), and eGFR 55.8 mg/min/1.73 m^2 (51.7, 58.2) vs. 55.8 mg/min/1.73 m^2 (51.5, 58.2) at the time of reduced kidney function threshold (Table 1). The median observed follow-up in the weighted cohort was 1.1 years (0.4, 2.6) for patients taking

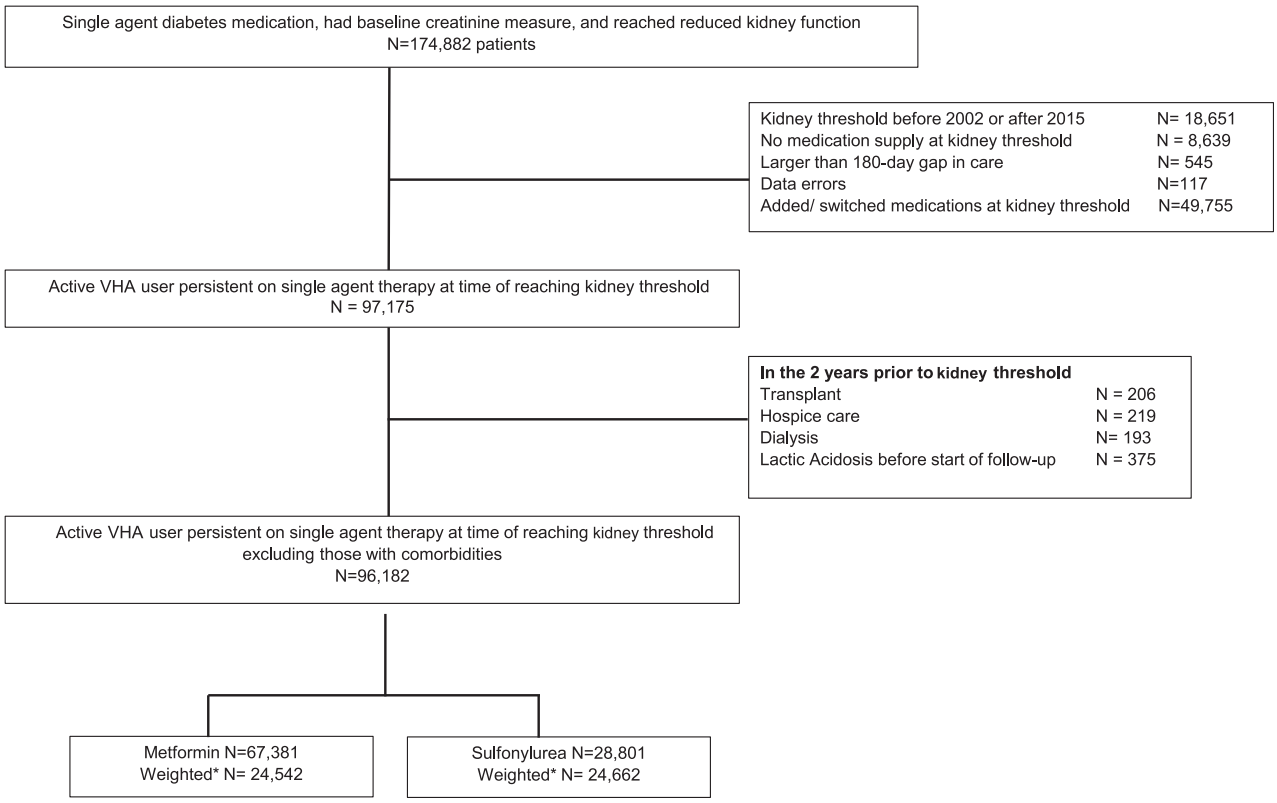

Figure 1—Flow of eligible patients in the VHA diabetes kidney disease cohort. *Weighted number uses matching weights derived from the propensity score to balance both exposure groups on observed covariates.

metformin and 1.2 years (0.5, 2.7) for sulfonylureas.

Primary Outcome: Hospitalization for Lactic Acidosis

In the weighted cohort, there were 193 composite lactic acidosis events in the metformin group and 180 in the sulfonylurea group, yielding 4.18 (95% CI 3.63, 4.81) vs. 3.69 (3.19, 4.27) composite lactic acidosis events per 1,000 person-years, respectively (Table 2). The cause-specific adjusted HR (aHR) was 1.21 (95% CI 0.99, 1.50) among patients using metformin compared with those using sulfonylureas. HRs were consistent for each component of the composite primary outcome, including lactic acidosis defined by primary discharge diagnosis code (aHR 1.11 [0.87, 1.44]) and laboratory-confirmed lactic acidosis hospitalizations (1.25 [0.92, 1.70]) (Table 2). Figure 2 depicts that the cumulative probability of lactic acidosis for patients persisting on metformin versus sulfonylureas at 5 years was 0.74% (95% CI 0.66, 0.83) vs. 0.71% (0.61, 0.82) and, at 10 years, was 0.85% (0.76, 0.95) vs. 0.79% (0.68, 0.90). These estimates accounted for the competing risks of nonpersistence (84.3% metformin vs. 82.7% sulfonylureas) and death (4.6% vs. 6.7%).

We conducted a post hoc evaluation of the primary diagnosis among patients who met the laboratory-confirmed lactic acidosis event criteria (84 metformin events and 75 sulfonylurea events). The sepsis code (ICD-9 038.x or ICD-10 A41) was the most common primary discharge diagnosis associated with laboratory-confirmed lactic acidosis (13.1% of metformin events vs. 19.6% of sulfonylurea events). The second most frequent diagnosis associated with laboratory-confirmed lactic acidosis was acute kidney injury (7.1% of metformin events vs. 2.7% of sulfonylurea events).

Impact of Dose

Patients were more likely to stop both metformin and sulfonylureas at reaching reduced kidney function than to have a dose change. The median (IQR) defined daily dose at the time of kidney function decline was 0.5 (0.5, 0.9) for metformin (1,000 mg) and 0.5 (0.3, 1.0) for sulfonylureas (5 mg for both glyburide and glipizide, which represented 99% of sulfonylureas). At 6 months after reaching the reduced kidney threshold, only 55% and 61% of metformin and sulfonylurea users, respectively, persisted on their regimens, and the median defined daily dose remained 0.5 (0.5, 0.9) for metformin and 0.5 (0.3, 1.0) for sulfonylureas. At 12 months after reaching the reduced kidney threshold, 43% vs. 48% persisted on therapy, and the median doses remained the same. We further evaluated metformin dose among patients who had an event stratified by eGFR. At the time of the lactic acidosis hospitalization, there were 46 patients with an eGFR $<$45 mL/min/1.73 m^2, and the median metformin dose at the event was 1,000 mg (1,000, 2,000). There were 146 patients with an eGFR $\geq$45 mL/min/1.73 m^2, and the median metformin dose at the event was 1,000 mg (1,000, 2,000). After accounting for the main effect of metformin use, the independent effect of metformin dose associated with lactic acidosis hospitalization was negligible.

Sensitivity and Subgroup Analysis

Results were similar in all sensitivity analyses. Sensitivity analyses that required a lactate value $\geq$5 mmol/L resulted in 146 events among metformin users

Table 1—Patient characteristics

	Full unweighted cohort		Weighted cohort		
	Metformin	Sulfonylureas	Metformin	Sulfonylureas	SMD†
Patients, *n*	67,381	28,801	24,542	24,662	
Age (years)*	67 (62, 74)	71 (63, 79)	70 (63, 78)	70 (63, 78)	0.001
Male, *n* (%)	64,571 (95.8)	28,288 (98.2)	24,056 (98.0)	24,172 (98.0)	<0.001
Race, *n* (%)					
White	56,104 (83.3)	23,394 (81.2)	20,082 (81.8)	20,184.6 (81.9)	0.001
Black	9,807 (14.6)	4,883 (17.0)	4,004 (16.3)	4,014.1 (16.3)	
Other	1,470 (2.2)	524 (1.8)	456 (1.9)	460 (1.9)	
Medication start to kidney threshold (months)*	16.2 (6.5, 35.0)	13.6 (5.9, 29.0)	14 (5.8, 30.2)	14.0 (6.0, 30.3)	0.013
Year of reaching kidney threshold, *n* (%)					0.027
2002–2003	3,158 (4.7)	4,880 (16.9)	2,913 (11.8)	2,907 (11.8)	
2004–2005	5,770 (8.6)	5,706 (19.8)	4,463 (18.2)	4,423 (17.9)	
2006–2007	9,041 (13.4)	6,068 (21.1)	5,184 (21.2)	5,413 (22.0)	
2008–2009	9,905 (14.7)	4,026 (14.0)	3,856 (15.7)	3,870 (15.7)	
2010–2011	12,146 (18.0)	3,318 (11.5)	3,340 (13.6)	3,267 (13.2)	
2012–2013	12,773 (19.0)	2,600 (9.0)	2,629 (10.7)	2,580 (10.4)	
2014–2015	14,588 (21.6)	2,203 (7.7)	2,157 (8.8)	2,198 (8.9)	
Laboratory variables					
HbA_{1c} (%)*	6.5 (6.1, 7.0)	6.6 (6.1, 7.3)	6.5 (6.1, 7.1)	6.6 (6.1, 7.2)	0.005
HbA_{1c} (mmol/mol)*	48 (43, 53)	49 (43, 56)	48 (43, 54)	49 (43, 55)	
Missing HbA_{1c} measure	2,758 (4.1)	1,127 (3.9)	1,003.3 (4.1)	987.5 (4.0)	0.004
eGFR before threshold (mL/min/1.73 m^2)*	70.4 (65.1, 78.6)	69.2 (64.5, 76.4)	69.6 (64.7, 77.0)	69.6 (64.7, 77.0)	0.001
eGFR at kidney threshold (mL/min/1.73 m^2)*	55.9 (51.7, 58.2)	55.8 (51.5, 58.2)	55.8 (51.7, 58.2)	55.8 (51.6, 58.2)	0.002
Hemoglobin (g/dL)*	14.0 (12.9, 15.0)	14.1 (13.0, 15.2)	14.1 (13.0, 15.1)	14.1 (13.0, 15.2)	0.003
Missing hemoglobin measure, *n* (%)	3,625 (5.4)	1,709 (5.9)	1,510.8 (6.2)	1,505.3 (6.1)	0.002
LDL (mg/dL)*	85 (67, 106)	89 (72, 111)	88.0 (70, 110)	88 (71, 110)	0.001
Missing LDL measure, *n* (%)	1,312 (1.9)	1,133 (3.9)	790.6 (3.2)	792.4 (3.2)	<0.001
MACR stage, *n* (%)					
A1 (<30 mg/g, normal to mild increased albuminuria)	29,514 (43.8)	10,577 (36.7)	9,426.4 (38.4)	9,485.9 (38.5)	0.003
A2 (30–300 mg/g, moderate increased albuminuria)	7,345 (10.9)	3,055 (10.6)	2,659.5 (10.8)	2,659.3 (10.8)	
A3 and positive unable to quantify (>300 mg/g, severely increased albuminuria)	1,801 (2.7)	925 (3.2)	764.0 (3.1)	757.7 (3.1)	
Missing MACR measure, *n* (%)	28,721 (42.6)	14,244 (49.5)	11,691.8 (47.6)	11,756.2 (47.7)	
Proteinuria by urinalysis, negative, *n* (%)	32,812 (48.7)	13,441 (46.7)	11,589 (47.2)	11,644 (47.2)	0.002
Urine protein trace or 1+	9,971 (14.8)	4,137 (14.4)	3,536 (14.4)	3,565 (14.5)	
Proteinuria present at 2+	2,150 (3.2)	976 (3.4)	794 (3.2)	800 (3.2)	
Proteinuria present at 3+ or 4+	622 (0.9)	479 (1.7)	343 (1.4)	344 (1.4)	
Missing urine protein measure, *n* (%)	21,826 (32.4)	9,768 (33.9)	8,280 (33.7)	8,306 (33.7)	
Clinical variables					
Systolic blood pressure (mmHg)*	129 (118, 140)	131 (120, 143)	131 (119, 142)	131 (119, 142)	0.002
Diastolic blood pressure (mmHg)*	73 (65, 80)	71 (64, 80)	72 (64, 80)	72 (64, 80)	<0.001
BMI (kg/m^2)*	31.1 (27.7, 35.2)	30.1 (26.9, 34.1)	30.4 (27.1, 34.4)	30.3 (27.1, 34.4)	0.004
Missing BMI measure, *n* (%)	11,471 (17.0)	5,707 (19.8)	4,591 (18.7)	4,617 (18.7)	<0.001
Baseline comorbidities, *n* (%)‡					
Malignancy	7,118 (10.6)	3,486 (12.1)	2,867 (11.7)	2,884 (11.7)	<0.001
Liver disease	1,087 (1.6)	786 (2.7)	571 (2.3)	568 (2.3)	0.001
HIV	231 (0.3)	112 (0.4)	92 (0.4)	94 (0.4)	0.001
Congestive heart failure	5,419 (8.0)	4,154 (14.4)	2,939 (12.0)	2,960 (12.0)	0.001
Cardiovascular disease	17,525 (26.0)	9,726 (33.8)	7,729 (31.5)	7,798 (31.6)	0.003
Stroke	1,877 (2.8)	1,017 (3.5)	822 (3.4)	819 (3.3)	0.002
Transient ischemic attack	704 (1.0)	406 (1.4)	318 (1.3)	328 (1.3)	0.003
Serious mental illness	16,446 (24.4)	5,755 (20.0)	4,988 (20.3)	5,063 (20.5)	0.005
Smoking	8,654 (12.8)	3,515 (12.2)	3,032 (12.4)	3,054 (12.4)	0.001
Chronic obstructive pulmonary disease	10,161 (15.1)	5,203 (18.1)	4,146.7 (16.9)	4,181.6 (17.0)	0.002
History of respiratory failure	1,884 (2.8)	927 (3.2)	763.6 (3.1)	762.0 (3.1)	0.001
History of sepsis	893 (1.3)	482 (1.7)	370 (1.5)	378 (1.5)	0.002
History of pneumonia	2,111 (3.1)	1,389 (4.8)	1,027 (4.2)	1,045 (4.2)	0.003
Arrhythmia	9,383 (13.9)	5,408 (18.8)	4,244 (17.3)	4,272 (17.3)	0.001
Cardiac valve disease	1,869 (2.8)	1,181 (4.1)	888 (3.6)	895 (3.6)	0.001
Parkinson disease	495 (0.7)	309 (1.1)	227 (0.9)	230 (0.9)	0.001
Urinary tract infection	2,197 (3.3)	1,346 (4.7)	1,011 (4.1)	1,021 (4.1)	0.001
Osteomyelitis	299 (0.4)	192 (0.7)	151 (0.6)	149 (0.6)	0.002

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Table 1—Continued

	Full unweighted cohort		Weighted cohort		
	Metformin	Sulfonylureas	Metformin	Sulfonylureas	SMD†
Osteoporosis	468 (0.7)	238 (0.8)	195 (0.8)	200 (0.8)	0.002
Falls	143 (0.2)	73 (0.3)	55 (0.2)	56 (0.2)	0.001
Fractures	1,236 (1.8)	668 (2.3)	538 (2.2)	538 (2.2)	0.001
Amputation	224 (0.3)	168 (0.6)	115 (0.5)	118 (0.5)	0.002
Retinopathy	502 (0.7)	394 (1.4)	286 (1.2)	287 (1.2)	<0.001
Use of medications, *n* (%)					
ACE inhibitors	42,993 (63.8)	18,703 (64.9)	15,881 (64.7)	16,002 (64.9)	0.004
Angiotensin II receptor blockers	8,643 (12.8)	3,095 (10.7)	2,800 (11.4)	2,792 (11.3)	0.003
β-Blockers	33,084 (49.1)	14,674 (50.9)	12,414 (50.6)	12,485 (50.6)	0.001
Calcium channel blockers	19,585 (29.1)	8,611 (29.9)	7,333 (29.9)	7,367 (29.9)	<0.001
Thiazide and potassium-sparing diuretics	29,836 (44.3)	11,508 (40.0)	10,051 (41.0)	10,143 (41.1)	0.004
Loop diuretics	10,190 (15.1)	6,544 (22.7)	4,900 (20.0)	4,925 (20.0)	<0.001
Other antihypertensive medications	18,349 (27.2)	7,783 (27.0)	6,676 (27.2)	6,685 (27.1)	0.002
Statin lipid-lowering drugs	49,632 (73.7)	18,566 (64.5)	16,456 (67.1)	16,605 (67.3)	0.006
Nonstatin lipid-lowering agents	13,087 (19.4)	4,639 (16.1)	4,222 (17.2)	4,250 (17.2)	0.001
Antiarrhythmics digoxin and inotropes	4,346 (6.4)	3,114 (10.8)	2,239 (9.1)	2,249 (9.1)	<0.001
Anticoagulants, platelet inhibitors	5,961 (8.8)	3,068 (10.7)	2,465 (10.0)	2,471 (10.0)	0.001
Nitrates	7,752 (11.5)	4,671 (16.2)	3,595 (14.6)	3,631 (14.7)	0.002
Aspirin	14,232 (21.1)	6,476 (22.5)	5,305 (21.6)	5,351 (21.7)	0.002
Platelet inhibitors not aspirin	6,201 (9.2)	3,067 (10.6)	2,551 (10.4)	2,569 (10.4)	0.001
Antipsychotics	5,344 (7.9)	1,960 (6.8)	1,714 (7.0)	1,735 (7.0)	0.002
Oral glucocorticoids	4,988 (7.4)	2,106 (7.3)	1,771 (7.2)	1,787 (7.2)	0.001
Indicators of health care utilization, *n* (%)					
Hospitalized within year (VHA)	8,809 (13.1)	4,394 (15.3)	3,475 (14.2)	3,528 (14.3)	0.004
Hospitalized within year (Medicare/Medicaid)	5,563 (8.3)	3,560 (12.4)	2,745 (11.2)	2,762 (11.2)	<0.001
Hospitalized in 30 days (VHA)	2,385 (3.5)	1,144 (4.0)	900 (3.7)	919 (3.7)	0.003
Hospitalized in 30 days (Medicare/Medicaid)	965 (1.4)	569 (2.0)	433 (1.8)	443 (1.8)	0.003
Nursing home encounter in last year	187 (0.3)	131 (0.5)	89 (0.4)	95 (0.4)	0.003
Number medications*	7 (5, 11)	7 (4, 10)	7 (4, 10)	7 (4, 10)	0.003
Outpatient visits in past year*	6 (3, 11)	7 (4, 12)	6 (4, 11)	6 (4, 11)	0.001
Medicare insurance use in last year	21,311 (31.6)	10,486 (36.4)	8,768 (35.7)	8,772 (35.6)	0.003
Medicaid insurance use in last year	659 (1.0)	428 (1.5)	319 (1.3)	327 (1.3)	0.002
Medicare Advantage use	10,208 (15.1)	4,319 (15.0)	3,755 (15.3)	3,768 (15.3)	0.001

MACR, microalbumin-to-creatinine ratio. *Median (IQR). †SMDs are the absolute difference in means or percent divided by an evenly weighted pooled SD or the difference between groups in number of SDs. In the weighted cohort, all standardized differences were not statistically significant (see Supplementary Fig. 3 for the plot of the mean standardized differences of the prematched and matched cohorts). ‡Definitions of comorbidities in Supplementary Table 1.

(116 ICD and 30 laboratory-confirmed lactic acidosis diagnoses) and 140 events among sulfonylurea users (111 ICD and 29 laboratory-confirmed lactic acidosis diagnoses). For the analysis that required a second reduced eGFR within 30–180 days of the index date results, the median number of days to the second confirmatory eGFR was 112 (IQR 72, 147), and the median eGFR at that time was 54 mL/min/1.73 m^2 (48,57). Results were consistent with the main results (Table 2). Excluding patients with Medicare Advantage and censoring upon enrollment in Advantage plans were also similar. Subgroups stratified by age, race, and eGFR at time of kidney function decline were consistent with the main analysis, with no evidence of effect modification (Supplementary Table 3). The 95% CIs were wide for some groups, including for those with eGFR in the lowest categorization. Among patients with eGFR <45 mL/min/1.73 m^2, point estimates of lactic acidosis rates were numerically greater among metformin users versus sulfonylurea users, with lactic acidosis rates of 12.89 (95% CI 9.14, 18.17) vs. 8.62 (6.04, 12.29) per 1,000 person-years (weighted HR 1.31 [0.85, 2.01]).

CONCLUSIONS

In this national evaluation of patients with diabetes, there was no statistically significant association between hospitalizations for lactic acidosis among patients who continued to use metformin versus sulfonylureas after they reached a reduced kidney threshold. Lactic acidosis hospitalization was uncommon and comparable between those using metformin and sulfonylureas, and the cumulative probability of lactic acidosis for patients persisting on metformin and sulfonylureas at 5 years was 0.74% vs. 0.71%. On the basis of our estimates, this risk difference of 0.03% over 5 years translates into one additional lactic acidosis hospitalization per 3,300 patients treated with metformin for 5 years. Our prior work estimated that a single year of metformin versus sulfonylurea treatment in this same cohort of patients with diabetes and reduced kidney function was associated with prevention of 167 major adverse cardiovascular events (19). Taken together, in patients with type 2 diabetes and kidney disease, the association of lactic acidosis hospitalization with metformin is small and

Table 2—Rates and aHRs (95% CIs) for lactic acidosis hospitalizations among patients with reduced GFR who used metformin vs. sulfonylureas in weighted cohort

	Metformin	Sulfonylureas
Number at risk matched weighted	24,542	24,662
Primary outcome: lactic acidosis hospitalization	193	180
Person-years	46,197	48,748
Unadjusted rate/1,000 person-years (95% CI)	4.18 (3.63, 4.81)	3.69 (3.19, 4.27)
aHR[b] (95% CI)	1.21 (0.99, 1.48)	Reference
Laboratory-confirmed lactic acid hospitalization	84	75
Person-years	46,283	48,860
Unadjusted rate/1,000 person-years (95% CI)	1.81 (1.46, 2.24)	1.54 (1.23, 1.93)
aHR[b] (95% CI)	1.25 (0.92, 1.70)	Reference
Primary discharge diagnosis of lactic acidosis hospitalization	122	121
Person-years	46,250	48,785
Unadjusted rate/1,000 person-years (95% CI)	2.63 (2.20, 3.14)	2.49 (2.08, 2.97)
aHR[b] (95% CI)	1.11 (0.87, 1.44)	Reference
Sensitivity analysis: requiring lactate ≥5 mmol/L		
Number at risk matched weighted	24,542	24,662
Composite lactic acidosis hospitalizations	146	140
Person-years	46,238	48,769
Unadjusted rate/1,000 person-years (95% CI)	3.16 (2.69, 3.72)	2.89 (2.45, 3.41)
aHR[b] (95% CI)	1.15 (0.91, 1.46)	Reference
Sensitivity analysis: population with second reduced eGFR		
Number at risk matched weighted	3,851	3,872
Composite lactic acidosis hospitalizations	22	27
Person-years	7,160	8,487
Unadjusted rate/1,000 person-years (95% CI)	3.07 (2.02, 4.64)	3.17 (2.18, 4.60)
aHR[b] (95% CI)	1.09 (0.64, 1.84)	Reference
Sensitivity analysis: excluding Medicare Advantage		
Number at risk matched weighted[a]	20,787	20,893
Composite lactic acidosis hospitalizations	163	154
Person-years	37,216	39,507
Unadjusted rate/1,000 person-years (95% CI)	3.89 (3.33, 4.56)	4.37 (3.75, 5.10)
aHR (95% CI)[b]	1.18 (0.94, 1.47)	Reference

[a]Primary analysis considers patients persistent on regimen until they do not have oral antidiabetic medications for 90 days. [b]Cox proportional hazards model for time to event. Adjusted for mean-centered metformin dose, demographics, clinical information derived from the electronic health record, comorbidities, use of medications, and health care utilization (see Supplementary Table 1). All continuous variables were modeled as restricted cubic splines.

unequivocally outweighed by the prevention of major adverse cardiovascular events.

Some studies estimated that as many as 1 million U.S. patients with diabetes and eGFR between 31 and 89 mL/min/1.73 m^2 who could take metformin are not taking this medication (20). A major reason metformin is discontinued in patients is the development of kidney disease and the concern for increased risk of lactic acidosis, despite guidance recommending the continuation of metformin at reduced eGFR (21,22). While there is laboratory evidence that metformin does increase lactic acid levels, the clinical significance of these laboratory abnormalities remains unclear (23,24). Multiple studies have demonstrated that the association of metformin with lactic acidosis is low and comparable to that associated with sulfonylurea use. Often, instances of lactic acidosis occurred in the context of another critical illness that was the more likely cause of lactic acidosis (24,25). Furthermore, a recent publication noted no statistically significant increase in the FDA's Adverse Event Reporting System reports for metformin and lactic acidosis compared with any other diabetes medications after the 2016 change in FDA prescribing guidance (26).

This study adds to the growing body of evidence of a low risk for lactic acidosis hospitalizations in patients with type 2 diabetes and mild to moderate reduction in kidney function. While metformin may increase lactic acid levels, it was not associated with a significantly increased risk of lactic acidosis hospitalizations compared with sulfonylureas in our cohort. Inzucchi et al. (25) conducted a systematic review of published clinical trials and observational studies, with most appearing to confirm the drug's overall safety profile, finding lactic acidosis rates not significantly different in patients with type 2 diabetes and reduced kidney function compared with the general population on metformin. The range of incident metformin-associated lactic acidosis was estimated at ~3–10 per 100,000 person-years and not significantly different from those in the general population of patients treated with alternate agents. Lazarus et al. (27) performed a retrospective cohort study of 75,413 patients that used billing and discharge diagnosis data from the Geisinger Health System. They found no significant difference in rates of incident lactic acidosis between metformin users and sulfonylurea users who had an eGFR between 30 and 60 mL/min/1.73 m^2. The association of lactic acidosis diagnosis

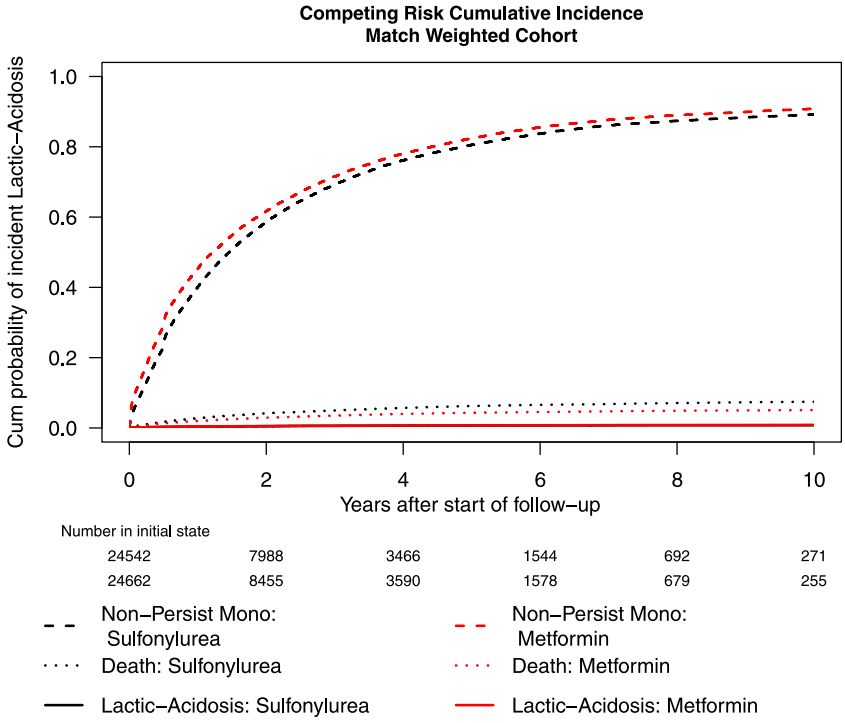

Figure 2—Aalen-Johansen cumulative (Cum) incidence demonstrating lactic acidosis events with the competing risks of nonpersistence and death in the weighted cohort. Non-Persist Mono, nonpersistent monotherapy.

codes in metformin users ranged between 4 and 10 per 1,000 person-years for patients with eGFR between 30 and 89 mL/min/1.73 m^2, which is similar to the rate of 4.18 (95% CI 3.63, 4.81) events per 1,000 person-years reported in this study. Notably, Lazarus et al. did find an increased hazard of lactic acidosis associated with metformin compared with sulfonylurea users in the subgroup of patients with eGFR <30 mL/min/1.73 m^2 (20 per 1,000 person-years, aHR 2.07 [95% CI 1.33, 3.22]). The current study adds to the work of Lazarus et al. by incorporating laboratory data and reporting both highly sensitive and specific definitions of laboratory-confirmed lactic acidosis hospitalizations.

A major strength of our study was the large sample size. With 180,000 person-years of follow-up and an average event rate of 4 per 1,000 person-years, if the true risk of metformin was double that of sulfonylureas, a study of this size would have detected it with near certainty. Our study yielded precise estimates of the HR for lactic acidosis with 95% CI widths of ~0.4. Nevertheless, although our study cannot completely rule out smaller increases in risk associated with metformin use, the study's results can be used to rule out HRs >1.5 when comparing metformin with sulfonylureas in this cohort. Therefore, our study findings support the recent change in the FDA label for metformin to include patients with mild to moderate kidney dysfunction. This is especially important in light of recent studies demonstrating that metformin is associated with a reduced risk of major cardiovascular events in patients with reduced kidney function (19).

This study has several limitations. First, persistence on incident therapy through the time of reaching the kidney function threshold was required, excluding many patients who discontinued, added, or switched initial medications at or before reaching the kidney threshold. While reducing sample size, this design choice allowed evaluation of patients with deteriorating kidney function. Furthermore, a competing risk model was used to address concerns that glucose-lowering medication nonpersistence or death would bias the assessment of lactic acidosis events. Second, veterans may not receive all their care at VHA facilities, and some lactic acidosis hospitalizations may have been missed despite the linkage to Medicare and Medicaid data. Furthermore, events captured in Medicare or Medicaid were not eligible for laboratory confirmation since laboratory data from these hospitalizations are not systematically available. Still, we have no reason to believe that this potential underreporting would be differentially distributed among our exposures. Third, cohort entry and the start of follow-up was either an elevated serum creatinine or a reduced eGFR <60 mL/min/1.73 m^2. It is possible that for some patients, this kidney threshold may represent an acute kidney injury event rather than progression of chronic kidney disease. We believe, however, that providers made clinical decisions on the basis of the patient reaching this reduced kidney function threshold. At the time of the reduced kidney threshold, the cohort patients had continued their antidiabetic medication for a median of 14 months, and within 6 months of reaching the threshold, ~50% of this cohort switched their antidiabetic medication or became nonpersistent (>90 days without a medication fill). This pattern of drug nonpersistence may be more consistent with a trajectory of chronic reduction in kidney function rather than a transient acute kidney injury. Fourth, although propensity score weighting and direct covariate adjustment were used to reduce concerns about confounding, residual confounding may exist. Fifth, we do not have serum metformin levels at the time of lactic acidosis hospitalizations, thereby complicating the assessment of a causal relationship. Furthermore, the hospitalization for lactic acidosis may be related to another underlying condition. Given the concern about metformin causing lactic acidosis, there may also be surveillance bias, such that lactic acid levels may be obtained more often in metformin patients. This type of bias would, however, tend to exaggerate risk. Finally, the study population was mostly elderly white men and may not be representative of the larger population of patients with diabetes and reduced kidney function. This should be considered when generalizing the study results to other populations.

The current study, like previous smaller cohort studies, finds that in patients with type 2 diabetes and reduced kidney function metformin is not associated with a statistically significant increased rate of lactic acidosis compared with sulfonylureas. Our findings support the 2016 FDA metformin label change, which indicates that metformin can be used in patients with mild to moderate reduced kidney function with

appropriate dosage reductions and continued monitoring and assessments of kidney function.

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