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Association of Metformin Use With Risk of Lactic Acidosis Across the Range of Kidney Function
A Community-Based Cohort Study

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IMPORTANCE Approximately 1 million patients in the United States with type 2 diabetes mellitus and mild-to-moderate kidney disease do not receive guideline-directed therapy with metformin. This may reflect uncertainty regarding the risk of acidosis in patients with chronic kidney disease.

OBJECTIVE To quantify the association between metformin use and hospitalization with acidosis across the range of estimated glomerular filtration rate (eGFR), accounting for change in eGFR stage over time.

DESIGN, SETTING, AND PARTICIPANTS Community-based cohort of 75 413 patients with diabetes in Geisinger Health System, with time-dependent assessment of eGFR stage from January 2004 until January 2017. Results were replicated in 67 578 new metformin users and 14 439 new sulfonylurea users from 2010 to 2015, sourced from 350 private US health systems.

EXPOSURES Metformin use.

MAIN OUTCOMES AND MEASURES Hospitalization with acidosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* code of 276.2).

RESULTS In the primary cohort (n = 75 413), mean (SD) patient age was 60.4 (15.5) years, and 51% (n = 38 480) of the participants were female. There were 2335 hospitalizations with acidosis over a median follow-up of 5.7 years (interquartile range, 2.5-9.9 years). Compared with alternative diabetes management, time-dependent metformin use was not associated with incident acidosis overall (adjusted hazard ratio [HR], 0.98; 95% CI, 0.89-1.08) or in patients with eGFR 45 to 59 mL/min/1.73 m^2 (adjusted HR, 1.16; 95% CI, 0.95-1.41) and eGFR 30 to 44 mL/min/1.73 m^2 (adjusted HR, 1.09; 95% CI, 0.83-1.44). On the other hand, metformin use was associated with an increased risk of acidosis at eGFR less than 30 mL/min/1.73 m^2 (adjusted HR, 2.07; 95% CI, 1.33-3.22). Results were consistent when new metformin users were compared with new sulfonylurea users (adjusted HR for eGFR 30-44 mL/min/1.73 m^2, 0.77; 95% CI, 0.29-2.05), in a propensity-matched cohort (adjusted HR for eGFR 30-44 mL/min/1.73 m^2, 0.71; 95% CI, 0.45-1.12), when baseline insulin users were excluded (adjusted HR for eGFR 30-44 mL/min/1.73 m^2, 1.16; 95% CI, 0.87-1.57), and in the replication cohort (adjusted HR for eGFR 30-44 mL/min/1.73 m^2, 0.86; 95% CI, 0.37-2.01).

CONCLUSIONS AND RELEVANCE In 2 real-world clinical settings, metformin use was associated with acidosis only at eGFR less than 30 mL/min/1.73 m^2. Our results support cautious use of metformin in patients with type 2 diabetes and eGFR of at least 30 mL/min/1.73 m^2.

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Supplemental content

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More than 380 million people worldwide are affected by type 2 diabetes mellitus (DM) and approximately 20% have an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2.[1] Metformin hydrochloride is recommended as the first-line medication for type 2 DM because of its low cost, favorable adverse effect profile, and a possible beneficial effect on cardiovascular risk.[2-5] However, it is frequently avoided in patients with chronic kidney disease (CKD) because of the concern of drug accumulation and lactic acidosis,[6] which arose following the withdrawal of phenformin from the US market in 1978,[7,8] and case reports of metformin-associated lactic acidosis in patients with CKD.[9-15]

Regulatory and professional society guidelines suggest that metformin may be an option in patients with mild to moderate CKD.[16] The US Food and Drug Administration (FDA) recently changed the metformin label from contraindicated at serum creatinine level greater than 1.5 mg/dL in men and greater than 1.4 mg/dL in women (to convert to micromoles per liter, multiply by 88.4) to contraindicated at eGFR less than 30 mL/min/1.73 m^2, and not recommended to initiate metformin at eGFR less than 45 mL/min/1.73 m^2.[17] Other guidelines cautiously support the use of metformin at eGFR 30 to 60 mL/min/1.73 m^2, recommending that metformin be reviewed[18,19] at eGFR 30 to 45 mL/min/1.73 m^2 and that dose adjustment be considered.[20,21]

Despite recent changes to metformin labeling, data addressing the safety of metformin in patients with eGFR less than 60 mL/min/1.73 m^2 are inconclusive.[22,23] Large retrospective studies have reported conflicting results regarding the association between metformin therapy and acidosis at eGFR less than 60 mL/min/1.73 m^2, and have not addressed individual variation in eGFR over time, or possible confounding by concomitant insulin use.[24-31] Although a systematic review of 347 trials and cohort studies found no evidence that metformin therapy increased the risk of acidosis compared with alternative antihyperglycemic therapies, 191 of the studies specifically excluded patients with CKD, and few of the remaining reported subgroup analyses for the participants with lower eGFR.[24,30]

We aimed to investigate the relationship between metformin therapy and acidosis across the full spectrum of eGFR in a large, integrated electronic medical record cohort, accounting for time-dependent eGFR stage, and for potential confounding from multiple variables, including concomitant insulin use. We sought to replicate findings in a separate nationwide cohort derived from 350 private health systems. In both cohorts, we compared acidosis risk during metformin use with the risk during alternative management of DM, hypothesizing that acidosis would be no more common among metformin users within categories of eGFR.

Key Points

Question Does metformin use increase the risk of acidosis in patients with chronic kidney disease?

Findings In 2 large retrospective cohorts of patients with diabetes mellitus (Geisinger Health System, n = 75 413 and MarketScan, n = 82 017), metformin use was not significantly associated with incident acidosis at estimated glomerular filtration rate (eGFR) greater than 30 mL/min/1.73 m^2.

Meaning Metformin therapy may be safe in patients with type 2 diabetes and eGFR 30 to 60 mL/min/1.73 m^2.

Methods

Study Population and Design

We studied a community-based cohort of patients with a diagnosis of DM and a postdiagnosis serum creatinine measurement between January 1, 2004, and January 20, 2017, receiving primary care in Geisinger Health System. Deidentified individual patient data from inpatient and outpatient encounters, including problem lists, prescriptions, diagnostic codes, and laboratory measurements, were used. We classified DM using the Health Plan Employer Data and Information Set (HEDIS) criteria, defined as 1 inpatient or 2 outpatient diagnostic codes (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*]) of 250.x, 357.2, 362.0, and 366.41, or a prescription for a medication to treat DM other than metformin monotherapy.[32] The baseline date for the primary analysis was the first serum creatinine measurement on or after DM diagnosis and January 1, 2004. We excluded patients with missing serum creatinine level (n = 2232), end-stage renal disease status at baseline (n = 399), or initial eGFR less than 15 mL/min/1.73 m^2 (n = 711), for a total study population of 75 413. We censored patient time at death or at the end of study follow-up (February 2, 2017).

Outcome, Exposure, and Covariate Definitions

The primary outcome was a hospitalized acidosis event, defined as an inpatient *ICD-9-CM* code of 276.2.[29,31] This diagnostic code broadly encapsulates acidosis but specifically excludes diabetic ketoacidosis. We also evaluated the occurrence of *ICD-9-CM* 276.2 as a primary code.

Metformin use and daily dose were ascertained from electronic prescription records. Start time was defined as the date of electronic prescription, and stop time was the end date of the prescription, or the date that a clinician discontinued the medication, whichever came earlier. A gap between prescriptions of less than 60 days was not considered a medication discontinuation to allow for the possibility of stockpiling of medications.

The eGFR was estimated from serum creatinine level using the CKD-Epidemiology equation and staged according to the Kidney Disease Improving Global Outcomes guidelines (<30, 30-44, 45-59, 60-89, and ≥90 mL/min/1.73 m^2).[33] In analyses using time-dependent eGFR stage, all outpatient serum creatinine levels were assessed. Each time a participant changed eGFR stage, the variable was updated and subsequent follow-up time was categorized accordingly.

Other covariates included age, sex, race, smoking status, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), serum bicarbonate, hemoglobin A_{1c} (HbA_{1c}), comorbid cardiovascular disease, heart

failure, hypertension, and medication use. We categorized patients as ever or never cigarette smokers, and determined comorbid cardiovascular disease (coronary artery disease, stroke, or peripheral arterial disease), heart failure, and hypertension by the presence of relevant diagnostic codes at any time prior to cohort inclusion (eTable 1 in the Supplement). We abstracted serum bicarbonate and HbA_{1c} from outpatient laboratory data within 1 year prior to index date. We recorded baseline and time-dependent use of statins, renin-angiotensin system inhibitors, diuretics, nonsteroidal anti-inflammatory drugs, insulin, sulfonylureas (eg, glimepiride, glyburide, glipizide), and other hypoglycemic medications in a manner similar to metformin use. We determined deaths by linkage to the National Death Index.

Statistical Analysis

We compared baseline characteristics of patients according to baseline eGFR stage. Differences across categories were determined using linear regression for continuous variables and logistic regression for binary variables on the median eGFR value within each eGFR category.

We analyzed risk of acidosis in metformin use, compared with no metformin use, using Cox proportional hazards regression. We used a model in which metformin use and eGFR category were captured as time-dependent variables. In other words, values were allowed to change over time, with metformin use initiated or discontinued with prescription start and stop time, and eGFR category updated when outpatient eGFR changed. Models were run unadjusted, demographic-adjusted, and fully adjusted for baseline covariates (demographic characteristics, eGFR, serum bicarbonate level, smoking status, BMI, cardiovascular disease, heart failure, hypertension, and medication use). A linear spline was used for bicarbonate level, with a knot at the mean (27.5 mEq/L [1:1 conversion to millimoles per liter]), to address the nonlinear association between bicarbonate and acidosis. We tested for modification of the association between metformin and acidosis by eGFR stage by including a product term with eGFR stage modeled as an ordinal variable. In secondary analysis, we also captured the use of other medications as time-dependent variables.

Sensitivity Analyses

First, we performed an active comparator study, in which new (first-time) metformin users were compared with new sulfonylurea users without accounting for time-dependent eGFR. Second, we constructed propensity-matched cohorts for prevalent metformin users within each category of eGFR, censoring at metformin discontinuation for cases, metformin initiation for controls, or eGFR category change. The propensity score was created using logistic regression of metformin status on the aforementioned covariates. Cases (metformin users) and controls (non–metformin users) were matched using nearest-neighbor matching on a 1:1 basis within each category of eGFR using a caliper of one-fifth the standard error (0.044). Third, we tested associations after excluding the 12 971 baseline insulin users. Fourth, we included baseline HbA_{1c} in the fully adjusted model. Fifth, we replicated the analysis in persons with a new diagnosis of DM after January 1, 2004. Finally, to address the possibility of incomplete capture of metformin discontinuation and thus overestimation of metformin exposure during which no events occurred, we censored all metformin users without acidosis events 90 days earlier.

Replication in Commercial Claims Database

We replicated active comparator results in the MarketScan database, an individual-level inpatient and outpatient claims data source from 350 private health systems, linked to outpatient laboratory test results for some patients. We included adults with DM defined by the HEDIS criteria and at least 1 creatinine level assessed on or after diagnosis. Medication use was sourced from pharmacy dispensing claims. Covariates, laboratory values, and acidosis outcomes were determined from diagnostic codes in a parallel manner to Geisinger Health System. Time at risk began at prescription for either metformin or sulfonylurea after January 1, 2010, and ended at hospitalization with acidosis, use of the opposite medication class, cessation of medication use, death, or end of study follow-up on December 31, 2014, whichever came first. Cessation of medication use was recorded as the date of last prescription, plus days of supply. Baseline eGFR was defined as the closest serum eGFR measurement within 1 year prior to first medication use. We compared risk of acidosis in metformin users with sulfonylurea users using Cox proportional hazards regression, adjusted for baseline age, sex, eGFR, cardiovascular disease, heart failure, hypertension, and use of insulin, renin-angiotensin system inhibitors, diuretics, and nonsteroidal anti-inflammatory drugs. All calculations were performed using statistical software (Stata, version 13.1/14.2; StataCorp LP).

Patient Involvement

Patients were not involved in the design or implementation of the study. The study was reviewed and deemed exempt by the Geisinger Health System and Johns Hopkins University Institutional Review Boards.

Results

Study Population

There were 75 413 individuals included in the Geisinger study population. Mean (SD) age at baseline was 60.4 (15.5) years, 51% were female, and mean (SD) BMI was 34.1 (8.1) (**Table 1**). At cohort enrollment, 14 662 patients had an eGFR less than 60 mL/min/1.73 m^2 and 1765 had an eGFR less than 30 mL/min/1.73 m^2. Median follow-up duration was 5.7 years (interquartile range [IQR], 2.5-9.9 years). The median number of creatinine measurements per year was 2.1 (IQR, 1.1-3.4), which increased with lower eGFR (**Table 2**).

Time-Dependent Metformin Use and Acidosis Events

Forty-five percent of patients were taking metformin at enrollment in the study (n = 34 095), and 13 781 of the remaining patients were subsequently prescribed metformin during follow-up (Table 2). The median duration of metformin use was 2.8 years (IQR, 0.9-6.2 years).

Table 1. Baseline Characteristics of 75 413 Patients With Diabetes Mellitus Stratified by Baseline Estimated Glomerular Filtration Rate (eGFR) Category in Geisinger Health System[a]

Baseline Characteristics	Baseline eGFR, mL/min/1.73 m^2						*P* Value for Trend
	Overall	≥90	60-89	45-59	30-44	<30	
Participants, No.	75 413	32 548	28 203	8144	4753	1765	<.001
Age, mean (SD), y	60.4 (15.5)	50.1 (13.1)	65.7 (12.1)	72.2 (10.7)	74.6 (11.3)	74.2 (12.2)	<.001
Female sex	38 480 (51.0)	16 149 (49.6)	14 019 (49.7)	4511 (55.4)	2766 (58.2)	1035 (58.6)	<.001
Black race	2026 (2.7)	1350 (4.1)	502 (1.8)	96 (1.2)	48 (1.0)	30 (1.7)	<.001
eGFR, mean (SD), mL/min/1.73 m^2	82.8 (25.3)	105.5 (12.6)	76.3 (8.6)	53.0 (4.3)	38.4 (4.2)	24.1 (4.1)	
Ever smoking	36 127 (47.9)	16 500 (50.7)	13 280 (47.1)	3611 (44.3)	2029 (42.7)	707 (40.1)	<.001
BMI, mean (SD)	34.1 (8.1)	35.4 (8.6)	33.3 (7.4)	32.7 (7.4)	32.6 (7.6)	32.6 (7.7)	<.001
Hypertension	51 937 (68.9)	18 522 (56.9)	21 047 (74.6)	6783 (83.3)	4074 (85.7)	1511 (85.6)	<.001
Cardiovascular disease	9070 (12.0)	1987 (6.1)	3895 (13.8)	1650 (20.3)	1115 (23.5)	423 (24.0)	<.001
Heart failure	7809 (10.4)	1296 (4.0)	2808 (10.0)	1626 (20.0)	1404 (29.5)	675 (38.2)	<.001
Serum bicarbonate, mean (SD), mEq/L	27.3 (3.1)	27.0 (2.9)	27.7 (2.9)	27.5 (3.2)	27.0 (3.6)	25.8 (4.3)	<.001
Hemoglobin A_{1c} %, mean (SD)	7.4 (1.7)	7.8 (2.0)	7.1 (1.4)	7.1 (1.4)	7.2 (1.5)	7.2 (1.4)	<.001
Drug use							
Insulin	12 971 (17.2)	6228 (19.1)	3674 (13.0)	1465 (18.0)	1080 (22.7)	524 (29.7)	.003
Statin	32 336 (42.9)	11 755 (36.1)	13 549 (48.0)	3997 (49.1)	2273 (47.8)	762 (43.2)	<.001
Renin-angiotensin system inhibitor	35 550 (47.1)	13 521 (41.5)	14 188 (50.3)	4568 (56.1)	2536 (53.4)	737 (41.8)	<.001
Diuretics	25 303 (33.6)	7615 (23.4)	10 274 (36.4)	3973 (48.8)	2535 (53.3)	906 (51.3)	<.001
Nonsteroidal anti-inflammatory drugs	15 482 (20.5)	7081 (21.8)	5934 (21.0)	1525 (18.7)	752 (15.8)	190 (10.8)	<.001

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

SI conversion factor: bicarbonate, 1:1 conversion to millimoles per liter.

[a] Unless otherwise indicated, data are reported as number (percentage) of patients.

Table 2. Number of Prevalent and Incident Metformin Users in Geisinger Health System, Frequency of Estimated Glomerular Filtration Rate (eGFR) Measurements, and Mean Daily Metformin Dose by Baseline eGFR Category

Baseline Use of Metformin	Baseline eGFR Category, mL/min/1.73 m^2				
	≥90	60-89	45-59	30-44	<30
Not using at baseline, No.	15 080	15 566	5385	3708	1579
Frequency of eGFR measurements per year, median (IQR)	1.58 (0.77-2.71)	2.19 (1.25-3.46)	2.73 (1.54-4.57)	3.35 (1.81-5.83)	4.72 (2.17-9.70)
Initiated metformin use after baseline, No.	6295	5823	1196	400	67
Using at baseline, No.	17 468	12 637	2759	1045	186
Frequency of eGFR measurements per year, median (IQR)	1.77 (1.02-2.72)	2.24 (1.40-3.33)	2.78 (1.75-4.09)	3.10 (1.69-4.76)	4.29 (2.70-7.16)
Daily dose at baseline, mean (SD), g	1.37 (0.58)	1.34 (0.59)	1.34 (0.60)	1.35 (0.59)	1.38 (0.59)

Abbreviation: IQR, interquartile range.

Overall, there were 2335 hospitalizations with acidosis over 470 114 person-years of follow-up: 737 events occurred over 188 578 person-years of metformin use and 1598 events occurred over 281 536 person-years of no metformin use. Of these events, only 29 had an acidosis diagnostic code in the primary position.

Metformin Use and Risk of Acidosis by Time-Dependent eGFR Category

The adjusted hazard ratio (HR) of acidosis during metformin use compared with nonuse was 0.98 (95% CI, 0.89-1.08) (**Table 3**). There was a higher acidosis risk associated with metformin at lower GFR (*P* = .01 for interaction). However, the risk associated with metformin use was not statistically significant at eGFR greater than 90 mL/min/1.73 m^2 (adjusted HR, 0.88; 95% CI, 0.73-1.05), eGFR 60 to 89 mL/min/1.73 m^2 (adjusted HR, 0.87; 95% CI, 0.75-1.02), eGFR 45 to 59 mL/min/1.73 m^2 (adjusted HR, 1.16; 95% CI, 0.95-1.41), and eGFR 30 to 44 mL/min/1.73 m^2 (adjusted HR, 1.09; 95% CI, 0.83-1.44). There was an increased risk of acidosis associated with metformin use at eGFR less than 30 mL/min/1.73 m^2 (adjusted HR, 2.07; 95% CI, 1.33-3.22). Results were consistent when ad-

Table 3. Association of Time-Dependent Metformin Use With Acidosis Hospitalization by Time-Dependent Estimated Glomerular Filtration Rate (eGFR) Category in Geisinger Health System

	HR[a] (95% CI) for Acidosis Associated With Metformin Use by Time-Dependent eGFR Category, mL/min/1.73 m^2					
Parameter	Overall[b]	≥90	60-89	45-59	30-44	<30
Person-time (on metformin/off metformin)	188 578/281 536	80 653/98 905	79 788/102 110	21 232/40 861	6358/29 834	548/9827
Acidosis events (on metformin/off metformin)	737/1598	206/323	288/446	157/286	64/314	22/229
Unadjusted (n = 75 413)	0.89 (0.81-0.97)	0.77 (0.65-0.92)	0.82 (0.71-0.95)	1.05 (0.87-1.28)	0.95 (0.73-1.25)	1.71 (1.10-2.64)
Demographic adjusted[c] (n = 75 413)	0.89 (0.81-0.97)	0.75 (0.63-0.90)	0.82 (0.71-0.96)	1.07 (0.88-1.30)	0.98 (0.75-1.28)	1.76 (1.14-2.73)
Fully adjusted[d] (n = 72 232)	0.98 (0.89-1.08)	0.88 (0.73-1.05)	0.87 (0.75-1.02)	1.16 (0.95-1.41)	1.09 (0.83-1.44)	2.07 (1.33-3.22)
Fully adjusted with time-dependent medication use[e] (n = 72 232)	0.94 (0.83-1.05)	0.80 (0.66-0.97)	0.81 (0.68-0.95)	1.14 (0.93-1.40)	1.13 (0.85-1.49)	2.21 (1.42-3.44)
Sensitivity analyses						
Fully adjusted[d] excluding baseline insulin users (n = 60 112)	1.02 (0.91-1.13)	0.88 (0.71-1.09)	0.89 (0.75-1.06)	1.21 (0.97-1.50)	1.16 (0.87-1.57)	2.22 (1.41-3.51)
Fully adjusted[d] including adjustment for baseline hemoglobin A_{1c} (n = 58 093)	1.01 (0.90-1.14)	0.84 (0.67-1.04)	0.93 (0.78-1.12)	1.23 (0.98-1.55)	1.07 (0.78-1.46)	2.22 (1.37-3.59)
Fully adjusted[d] in incident diabetes mellitus cohort (n = 49 839)	0.91 (0.79-1.04)	0.85 (0.68-1.06)	0.82 (0.66-1.01)	1.15 (0.86-1.53)	0.88 (0.55-1.39)	2.37 (1.20-4.71)
Fully adjusted[d] with early censoring of metformin (n = 72 232)	1.04 (0.95-1.15)	0.93 (0.78-1.12)	0.93 (0.80-1.09)	1.23 (1.01-1.50)	1.17 (0.89-1.54)	2.26 (1.45-3.51)

Abbreviation: HR, hazard ratio.

[a] Reference for HR: no metformin use.

[b] Overall, adjusted for eGFR category.

[c] Adjusted for age, sex, and race.

[d] Adjusted for baseline age, sex, race, serum bicarbonate level, smoking status, comorbid cardiovascular disease, heart failure, peripheral vascular disease, hypertension, eGFR, use of statin medications, renin-angiotensin system inhibitors, diuretics, nonsteroidal anti-inflammatory drugs, insulin, and other antidiabetic medications. eGFR category and metformin use were the only time-dependent variables. Patients with missing data were excluded from the fully adjusted analysis.

[e] Adjusted for all variables in fully adjusted model; however, all medications were treated as time dependent along with eGFR category and metformin use. Patients with missing data were excluded from the fully adjusted analysis.

justed for other time-dependent medication use, including diuretics, renin-angiotensin system inhibitors, statins, nonsteroidal anti-inflammatory drugs, insulin, and other antidiabetic medications: eGFR 30 to 44 mL/min/1.73 m^2 had an adjusted HR of 1.13 (95% CI, 0.85-1.49), and eGFR less than 30 mL/min/1.73 m^2 had an adjusted HR of 2.21 (95% CI, 1.42-3.44).

In both metformin users and nonusers, lower eGFR itself was associated with a higher incidence of acidosis. Incidence increased from 4 events per 1000 person-years at eGFR 60 to 89 mL/min/1.73 m^2, to 7 events per 1000 person-years at eGFR 45 to 59 mL/min/1.73 m^2, to 10 events per 1000 person-years at eGFR 30 to 44 mL/min/1.73 m^2, to 24 events per 1000 person-years at eGFR less than 30 mL/min/1.73 m^2.

Active Comparator and Propensity-Score Matched Analyses

In the active comparator cohort analysis in Geisinger Health System (n = 12 690), the crude incidence of acidosis among metformin users was 4.1 events per 1000 person-years and for sulfonylurea users was 6.9 events per 1000 person-years. Sulfonylurea use was more common at lower eGFR. Compared with sulfonylurea use, metformin use had similar associations with acidosis overall (adjusted HR, 0.91; 95% CI, 0.70-1.18), and in eGFR 45 to 59 mL/min/1.73 m^2 (adjusted HR, 1.03; 95% CI, 0.60-1.77) and eGFR 30 to 44 mL/min/1.73 m^2 (adjusted HR, 0.77; 95% CI, 0.29-2.05) (**Table 4**). For eGFR less than 30 mL/min/1.73 m^2, there was higher risk for acidosis associated with metformin use, although there were only 3 events among metformin users, limiting power.

In propensity score–matched cohorts within strata of eGFR, metformin use was associated with similar risk of acidosis compared with use of alternative hypoglycemic medications at eGFR 45 to 59 mL/min/1.73 m^2 (adjusted HR, 0.82; 95% CI, 0.55-1.23) and eGFR 30 to 44 mL/min/1.73 m^2 (adjusted HR, 0.71; 95% CI, 0.45-1.12), and there was an increased risk of acidosis at eGFR less than 30 mL/min/1.73 m^2 that was not statistically significant (adjusted HR, 1.46; 95% CI, 0.86-2.48).

Additional Sensitivity Analyses

Excluding baseline insulin users resulted in a slightly lower prevalence of low eGFR (eTable 2 in the Supplement), but no increase in risk for metformin use at eGFR of at least 30 mL/min/1.73 m^2 (Table 3). Adjusting for baseline HbA_{1c} yielded similar results, as did analyses in 49 839 patients with incident DM. Early censoring of metformin use showed some increased risk in patients with eGFR 45 to 60 mL/min/1.73 m^2 but not eGFR 30 to 44 mL/min/1.73 m^2. However, higher acidosis risk in patients with eGFR less than 30 mL/min/1.73 m^2 was seen in each of these analyses.

Table 4. Results of Active Comparator and Propensity-Matched Analyses in Geisinger Health System

Cohort	HR (95% CI) for Acidosis Associated With Metformin Use by Baseline eGFR Category, mL/min/1.73 m^2				
	≥90	60-89	45-59	30-44	<30
Active comparator cohort[a]					
Person-time (metformin/sulfonylurea)	14 785/10 970	16 965/13 452	4351/5906	1228/4448	86/1316
Acidosis events (metformin/sulfonylurea)	45/44	66/73	28/54	13/56	3/23
Unadjusted (n = 12 690)	0.78 (0.51-1.19)	0.87 (0.61-1.25)	0.83 (0.52-1.32)	0.77 (0.33-1.82)	9.51 (0.99-91.42)
Demographic adjusted[b] (n = 12 690)	0.80 (0.53-1.22)	0.94 (0.65-1.35)	0.89 (0.56-1.41)	0.81 (0.34-1.92)	10.54 (1.10-101.42)
Fully adjusted[c] (n = 10 751)	0.91 (0.55-1.50)	0.81 (0.55-1.18)	1.03 (0.60-1.77)	0.77 (0.29-2.05)	10.03 (1.04-96.93)
Propensity-matched cohort[d]					
Person-time (on metformin/off metformin)	18 677/13 626	18 544/12 134	6132/5489	2846/3973	401/2067
Acidosis events (on metformin/off metformin)	61/92	78/82	45/50	28/55	22/64
Propensity-matched cohort[e]	0.51 (0.37-0.71)	0.65 (0.48-0.88)	0.82 (0.55-1.23)	0.71 (0.45-1.12)	1.46 (0.86-2.48)

Abbreviations: eGFR, estimated glomerular filtration rate; HR, hazard ratio; RASI, renin-angiotensin system inhibitor; NSAID, nonsteroidal anti-inflammatory drug.

[a] Reference for HR: sulfonylurea use.

[b] Adjusted for age, sex, and race.

[c] Adjusted for baseline age, sex, race, serum bicarbonate level, smoking status, body mass index, cardiovascular disease, hypertension, and concomitant statin, RASI, diuretics, and NSAID medication use.

[d] Reference for HR: no metformin use.

[e] 1:1 Matching was performed on propensity score for metformin use based on age, sex, race, serum bicarbonate level, smoking status, body mass index, cardiovascular disease, hypertension, and concomitant statin, RASI, diuretics, NSAID, insulin, and other hypoglycemic medication use within each time-dependent eGFR stage separately. Analyses were adjusted for propensity score.

Table 5. Results of Active Comparator Analyses in the Replication Cohort (MarketScan)

Parameter	HR[a] (95% CI) for Acidosis Associated With Metformin Use by Baseline eGFR Category, mL/min/1.73 m^2				
	≥90	60-89	45-59	30-44	<30
Person-time (on metformin/off metformin)	47 564/8933	36 563/7153	3947/1467	654/754	64/328
Acidosis events (on metformin/off metformin)	100/24	100/34	25/13	9/13	4/10
Unadjusted (n = 82 017)	0.78 (0.50-1.22)	0.58 (0.39-0.85)	0.71 (0.36-1.39)	0.79 (0.34-1.85)	2.04 (0.64-6.50)
Demographic adjusted[b] (n = 82 017)	0.79 (0.51-1.24)	0.58 (0.39-0.86)	0.73 (0.38-1.44)	0.85 (0.36-1.99)	2.17 (0.68-6.93)
Fully adjusted[c] (n = 82 017)	0.81 (0.52-1.26)	0.60 (0.41-0.89)	0.83 (0.42-1.62)	0.86 (0.37-2.01)	1.83 (0.57-5.88)

Abbreviations: eGFR, estimated glomerular filtration rate; HR, hazard ratio.

[a] Reference for HR: sulfonylurea use.

[b] Adjusted for age and sex.

[c] Adjusted for age, sex, eGFR, cardiovascular disease, heart failure, hypertension, insulin, renin-angiotensin inhibitor, diuretics, and nonsteroidal anti-inflammatory drug use.

Replication Analysis

There were 67 578 new metformin users and 14 439 new sulfonylurea users in MarketScan. Metformin users were slightly younger and more often female compared with sulfonylurea users (eTable 3 in the Supplement). Median follow-up of metformin users was 12.0 months (IQR, 5.5-22.6 months) and of sulfonylurea users was 11.5 months (IQR, 4.6-22.4 months).

There were 238 acidosis events among metformin users, and 94 among sulfonylurea users. The incidence of acidosis was 2.7 events per 1000 person-years in metformin users, and 5.0 events per 1000 person-years in sulfonylurea users (**Table 5**). Lower eGFR was a risk factor for acidosis in both metformin and sulfonylurea users. The risk of acidosis associated with metformin use was slightly lower overall (adjusted HR, 0.75; 95% CI, 0.58-0.97), and not increased in patients with eGFR 45 to 59 mL/min/1.73 m^2 (adjusted HR, 0.83; 95% CI, 0.42-1.62) and eGFR 30 to 44 mL/min/1.73 m^2 (adjusted HR, 0.86; 95% CI, 0.37-2.01). There was a higher risk in patients with eGFR less than 30 mL/min/1.73 m^2, but this was not statistically significant (adjusted HR, 1.83; 95% CI, 0.57-5.88; P = .49 for interaction).

Discussion

In 2 large retrospective cohorts of patients with DM, metformin use in those with eGFR of at least 30 mL/min/1.73 m^2 was not associated with incident hospitalization with acidosis, even after accounting for change in eGFR stage over time and for potential confounding variables, including demographic characteristics, cardiovascular risk factors, HbA_{1c}, and concomitant medications, including insulin. This was true in adjusted, active comparator, and propensity score–matched analyses, and in a replication cohort of 82 017 patients from a nationwide database of health care claims. These findings support the recent expansion of the eGFR thresholds for metfor-

min use by the FDA, and recommendations from other regulatory bodies, which suggest that metformin can be used when eGFR is 45 to 59 mL/min/1.73 m^2 and cautiously when eGFR is 30 to 44 mL/min/1.73 m^2.[18-20]

Our finding of no association between metformin use and acidosis at eGFR of 30 mL/min/1.73 m^2 or greater adds to existing literature by rigorously accounting for changes in eGFR over time and addressing confounding through propensity score matching and multiple sensitivity analyses. Our findings support results from smaller cohorts that assessed lactic acidosis through medical record review,[16,24] and using a wide range of diagnostic codes.[26,34,35] Although randomized clinical trials are the benchmark in assessing causality, they are generally underpowered to evaluate rare events. The 1 trial that randomized 393 participants with moderate CKD (serum creatinine level, 1.47-2.49 mg/dL) to cease or continue metformin therapy observed no events of lactic acidosis.[36] On the other hand, our observation of increased risk among patients with eGFR less than 30 mL/min/1.73 m^2 strengthens the evidence against metformin use in this group, which previously consisted of case reports and limited evidence from cohort studies.

Our results partially contradict a large cohort study investigating the association between metformin use and acidosis at low eGFR.[27] The UK General Practice Database, with 258 539 patients, found that current metformin users with eGFR less than 60 mL/min/1.73 m^2 had a higher risk of lactic acidosis, defined by diagnostic code or plasma lactate concentration greater than 5 mmol/L (45 mg/dL), compared with never metformin users (adjusted HR, 6.37; 95% CI, 1.48-27.5). However, this study was limited by sparse eGFR data and did not account for changes in eGFR over time, leaving the possibility of confounding by GFR, which we show is itself a strong risk factor for acidosis. In the UK study, more than 70% of the never metformin users had either eGFR greater than 60 mL/min/1.73 m^2 or an unknown eGFR status.

From a public health perspective, the potential benefits of using metformin for patients with DM and CKD are vast, given the increasing number of people affected with both diseases worldwide.[1,6] Metformin is the first-line therapy for type 2 DM owing to its cost-effectiveness and favorable adverse effect profile. Metformin may also have pleiotropic health benefits beyond its effect on glycemic control.[16] In an observational study, patients with type 2 DM and eGFR 30 to 44 mL/min/1.73 m^2 had less mortality with the use of metformin than sulfonylureas.[37] Patients using metformin may have less weight gain, lower risk of myocardial infarction, and even lower long-term mortality than those receiving other hypoglycemic therapies.[36,38,39]

Limitations

The present study, while benefiting from a large sample size, has certain limitations. First, as with all observational studies, residual confounding is possible. Patients receiving metformin could have different acidosis risk than those who did not receive metformin, for reasons other than their metformin use. The previous contraindication to metformin use in patients with elevated serum creatinine (>1.5 mg/dL in men and >1.4 mg/dL in women) may have introduced a channeling bias, where patients with reduced eGFR might have been more likely to receive metformin therapy if they were healthier. However, we observed consistent results in propensity-matched analyses, with multivariable adjustment, and when excluding insulin users and directly comparing with alternative therapies. Second, the diagnostic code that we used to measure acidosis (*ICD-9-CM* 276.2) is not specific for lactic acidosis and may dilute the power of the study. On the other hand, the diagnostic code maintains consistency with earlier epidemiological studies,[26,29] and allows for the possibility that metformin may contribute to acidosis from other metabolic factors such as malnutrition, liver disease, sepsis, and drug toxicity, which are all clinically relevant for patients. Furthermore, we showed increased risk associated with metformin use in patients with eGFR less than 30 mL/min/1.73 m^2, which is consistent with current FDA recommendations. Third, if the effect of metformin use on lactic acidosis were mediated by decline in eGFR, the use of time-dependent eGFR in our analyses could bias results to the null. However, we found similar results when only adjusting for baseline eGFR in active comparator analyses. Fourth, we could not differentiate whether a change in eGFR stage occurred due to CKD progression or an acute kidney injury. In theory, metformin accumulation may be enhanced in prerenal acute kidney injury compared with CKD, where tubular function and active secretion may be disproportionately impaired due to concurrent volume depletion.[23] Fifth, we could not discern the specialty of the prescribing clinician, and medication use was derived from electronic medical records or claims and not verified by patient report. Finally, although we have no reason to suspect that results would be different by race, most of the Geisinger Health System population was white, which may limit generalizability.

Conclusions

Metformin use was not associated with incident acidosis in patients with eGFR 30 to 60 mL/min/1.73 m^2 in 2 large and diverse cohorts, but there was increased risk at eGFR less than 30 mL/min/1.73 m^2. Our results support cautious use of metformin in patients with type 2 DM and eGFR of at least 30 mL/min/1.73 m^2.

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Conflict of Interest Disclosures: Dr Alexander is Chair of the FDA's Peripheral and Central Nervous System Advisory Committee; serves on the Advisory Board of MesaRx Innovations; holds equity in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and serves as a member of OptumRx's P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. No other disclosures are reported.

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