Risk of Lactic Acidosis or Elevated Lactate Concentrations in Metformin Users With Renal Impairment: A Population-Based Cohort Study

Willemijn L. Eppenga,[1,2] Arief Lalmohamed,[3,4] Arjen F. Geerts,[3] Hieronymus J. Derijks,[2,3] Michel Wensing,[1] Antoine Egberts,[3,4] Peter A.G.M. De Smet,[1,5] and Frank de Vries[3,6,7]

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OBJECTIVE

The objective of this study was to determine whether treatment with metformin in patients with renal impairment is associated with a higher risk of lactic acidosis or elevated lactate concentrations compared with users of a noninsulin antidiabetic drug (NIAD) who had never used metformin.

RESEARCH DESIGN AND METHODS

A cohort of 223,968 metformin users and 34,571 diabetic patients who had never used metformin were identified from the Clinical Practice Research Datalink (CPRD). The primary outcome was defined as either a CPRD READ code *lactic acidosis* or a record of a plasma lactate concentration >5 mmol/L. The associations between renal impairment, dose of metformin, and the risk of lactic acidosis or elevated lactate concentrations were determined with time-dependent Cox models and expressed as hazard ratios (HRs).

RESULTS

The crude incidence of lactic acidosis or elevated lactate concentrations in current metformin users was 7.4 per 100,000 person-years (vs. 2.2 per 100,000 person-years in nonusers). Compared with nonusers, risk of lactic acidosis or elevated lactate concentrations in current metformin users was significantly associated with a renal function <60 mL/min/1.73 m^2 (adjusted HR 6.37 [95% CI 1.48–27.5]). The increased risk among patients with impaired renal function was further increased in users of ≥730 g of metformin in the preceding year (adjusted HR 11.8 [95% CI 2.27–61.5]) and in users of a recent high daily dose (>2 g) of metformin (adjusted HR 13.0 [95% CI 2.36–72.0]).

CONCLUSIONS

Our study is consistent with current recommendations that the renal function of metformin users should be adequately monitored and that the dose of metformin should be adjusted, if necessary, if renal function falls below 60 mL/min/1.73 m^2.

There is good evidence that metformin reduces the long-term incidence of macrovascular complications in type 2 diabetes mellitus, especially among overweight patients (1–3). In contrast to alternative oral noninsulin antidiabetic drugs (NIADs) and insulin, metformin is not associated with a risk of hypoglycemia (3–5). The most serious adverse event that has been observed during metformin use is lactic acidosis, which is

[1]Scientific Institute for Quality of Healthcare, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands
[2]Hospital Pharmacy 'ZANOB', 's-Hertogenbosch, the Netherlands
[3]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht, the Netherlands
[4]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, the Netherlands
[5]Department of Clinical Pharmacy, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands
[6]Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre, Maastricht, the Netherlands
[7]Care and Public Health Research Institute (CAPHRI), Maastricht, the Netherlands

Corresponding author: Frank de Vries, f.devries@uu.nl.

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characterized by an elevated blood lactate concentration (>5 mmol/L), decreased blood pH (<7.35) and electrolyte disturbances with an increased anion gap (1,6–9). Estimated rates of lactic acidosis incidence during metformin use range from 1 to 47 cases per 100,000 patient-years (10,11). Reported predisposing factors include acute kidney injury; history of lactic acidosis; hypovolemia; decreased tissue perfusion or hemodynamic instability due to infection or other causes; seizure; concurrent liver disease; alcohol abuse; acute heart failure; myocardial infarction; and shock (12–14). Although lactic acidosis during metformin use has a better prognosis than other types of severe lactic acidosis (15), reported mortality rates may be as high as 25–50% (1,4,8). Yet metformin itself has not been linked to mortality in users developing lactic acidosis during metformin use, which perhaps reflects a primary effect of other underlying causes of the acidosis (16).

According to current guidelines, the dose of metformin should be reviewed if the estimated glomerular filtration rate (eGFR) falls to <45 mL/min/1.73 m^2, and the drug should be stopped in patients with an eGFR <30 mL/min/1.73 m^2 (3,17,18). A decreased glomerular filtration rate may theoretically increase the risk of lactic acidosis during metformin use because metformin is eliminated unchanged by the kidneys and may therefore accumulate when kidney function becomes impaired (3,19). However, the role of chronic renal insufficiency as a risk factor for lactic acidosis during metformin use remains controversial.

On the one hand, some authors argue that an association between high concentrations of metformin and lactic acidosis should be assumed because, for example, supratherapeutic plasma concentrations of metformin have frequently been found in patients with lactic acidosis during metformin use and because high metformin concentrations have been shown to increase plasma lactate in rats (4,9,20). On the other hand, a contributory role of chronic renal insufficiency to lactic acidosis during metformin use was not confirmed in large epidemiological studies (12,21), and a recent study of 56 cases of severe lactic acidosis during metformin use did not find a prognostic value for blood lactate (22).

Duong et al. (9) argue that there may be three different forms of lactic acidosis during metformin use and that one of these is characterized by the accumulation of metformin together with acute impairment of renal function and organ decompensation, such as acute or chronic heart failure, induced by sepsis and/or dehydration. They hypothesize that this type of lactic acidosis during metformin use involves a positive feedback system comprising one or more of the following factors: vomiting and diarrhea, acute kidney injury, high doses or excessive accumulation of metformin, and acute disease states leading to tissue hypoxia. They suggest that lactic acidosis may commence with relatively small changes in hydration, kidney function, plasma concentrations of metformin, or tissue oxygenation, which then lead to positive feedback and severe lactic acidosis. The aim of this study, therefore, was to evaluate retrospectively, in a large cohort of patients using a NIAD, whether treatment with metformin is associated with a higher risk of lactic acidosis or elevated lactate concentrations in patients with renal impairment compared with patients who had never used metformin. In addition, the risk of lactic acidosis or elevated lactate concentrations in patients with different metformin doses was evaluated.

RESEARCH DESIGN AND METHODS

Data Sources

We conducted a retrospective cohort study using the Clinical Practice Research Datalink (CPRD), previously known as the General Practice Research Database. The CPRD collates the computerized medical records of general practitioners (GPs). GPs play a key role in the U.K. health care system; they are responsible for primary health care and specialist referrals. Patients are semipermanently affiliated with a practice that centralizes the medical information from the GPs, specialist referrals, and hospitalizations. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes since 1987 (www.CPRD.com).

Study Population

All patients with at least one prescription for a NIAD and age >18 years during the period of valid CPRD data collection were enrolled. For this study, data collection started in April 2004, with the introduction of the Quality and Outcomes Framework, and ended in August 2012. The first NIAD prescription after the start of data collection defined the index date. Patients with a record for renal transplant or dialysis during the study period were excluded (n = 152 among metformin users; n = 234 among nonusers).

Exposure

Exposure to metformin and/or other NIADs was assessed in a time-dependent manner. For this purpose, total follow-up of each individual was divided into small time intervals. The length of a time interval was based on NIAD prescriptions: a time interval starts with a NIAD prescription and ends 1 day before the next NIAD prescription. If the length of a time interval exceeded 90 days, the interval was further divided into separate 90-day intervals. This approach minimizes exposure misclassification. For each time interval, the exposure to metformin was assessed as *1*) current metformin use (at least one metformin prescription in the 3 months before the start of a time interval); *2*) recent metformin use (a most recent metformin prescription between 3 and 6 months before the start of a time interval); *3*) past metformin use (a most recent metformin prescription >6 months before the start of a time interval); and *4*) never metformin use (no metformin prescription at any time before the start of a time interval).

As a consequence, a patient could move between never, current, recent, and past metformin use. A past user could become a current metformin user again in the event of a new metformin prescription. Current metformin users were stratified according to their cumulative metformin exposure in the previous year (<730 g [<365 × 2 g] and ≥730 g) and their most recent prescribed daily metformin dose (≤2 g and >2 g).

Renal Function

For current metformin users, we evaluated the most recently recorded renal function 1 week to 1 year before to the start of an interval. Renal function was evaluated by reviewing laboratory test data (eGFR [MDRD] where possible), and CPRD READ codes (stages of

chronic kidney disease). In the event of multiple eGFR values on the same day, the mean value was used. CPRD READ codes were prioritized if there was a laboratory test on the same day as recording.

Outcomes

Patients were followed up from the index date to either the end of data collection, the date the patient transferred out of the practice area, the patient's death, or an event of lactic acidosis or elevated lactate concentrations.

Lactic acidosis or elevated lactate concentrations were evaluated either by a CPRD READ code for lactic acidosis or by a record of plasma lactate concentration of >5 mmol/L, whichever came first. In the event of multiple laboratory tests for lactate concentrations on the same day, the lowest value was used. In a sensitivity analysis, the highest value was used instead of the lowest value. CPRD READ codes for lactic acidosis were prioritized if there was a laboratory test on the same day as recording.

Potential Confounders

The presence of risk factors for lactic acidosis during metformin use was assessed by reviewing the computerized medical records before the start of an interval. Risk factors that were considered in this study included age, sex, smoking status, BMI, alcohol use, hemoglobin A_{1c} (HbA_{1c}), and a history of asthma/chronic obstructive pulmonary disease, chronic liver disease, heart failure, and/or sepsis (12,23–25). We further considered a prescription in the previous 6 months for drugs that may have influenced renal function (including nonsteroidal anti-inflammatory drugs, renin-angiotensin-aldosterone system inhibitors, loop diuretics, thiazide diuretics, β-blockers, statins, and systemic calcineurin inhibitors).

Data Analysis

Cox regression analysis compared hazard rates of lactic acidosis or elevated lactate concentrations in current metformin users versus NIAD users who had never used metformin (SAS software version 9.2). Confounders were entered into the final model if they independently changed the β-coefficient for current metformin use by at least 5%. The main association for possible interactions with any of the risk factors was tested. Current metformin users were further stratified according to renal function and metformin dose.

RESULTS

Table 1 displays the baseline characteristics of NIAD users who were either current metformin users (n = 223,968) or nonusers (n = 34,571). The mean duration of follow-up was 4.3 years for metformin users and 4.9 years for nonusers. Metformin users were younger (60.1 years) than nonusers (67.8 years). No substantial difference in sex distribution was observed. The proportion of metformin users with stage 4 or 5 chronic kidney disease (eGFR <30 mL/min/1.73 m^2) was lower than that

Table 1—Baseline characteristics of current metformin users and nonusers among patients using NIADs

Characteristics	Current metformin users (N = 223,968)	Nonusers (N = 34,571)
Follow-up, years (mean [SD])[a]	4.3 (2.8)	4.9 (3.0)
Female sex	105,561 (47.1)	15,007 (43.4)
Age, years (mean [SD])	60.1 (14.8)	67.8 (14.5)
18–49	51,394 (22.9)	4,221 (12.2)
50–59	49,018 (21.9)	4,997 (14.5)
60–69	59,363 (26.5)	7,899 (22.8)
70–79	45,689 (20.4)	9,558 (27.6)
≥80	18,504 (8.3)	7,896 (22.8)
Most recent renal function (mL/min/1.73 m^2) in the previous year[b]		
<30	586 (0.3)	955 (2.8)
30–59	29,742 (13.3)	7,436 (21.5)
≥60	132,344 (59.1)	14,235 (41.2)
Unknown	61,296 (27.4)	11,945 (34.6)
Smoking status		
Current smoker	45,258 (20.2)	6,848 (19.8)
Former smoker	66,485 (29.7)	9,706 (28.1)
Never smoker	111,137 (49.6)	17,387 (50.2)
Unknown	1,088 (0.5)	630 (1.8)
BMI, kg/m^2 (mean [SD])	31.6 (6.6)	27.6 (5.7)
<20.0	2,259 (1.0)	1,502 (4.3)
20.0–24.9	25,816 (11.5)	9,777 (28.3)
25.0–29.9	71,071 (31.7)	12,205 (35.3)
30.0–34.9	63,622 (28.4)	5,647 (16.3)
≥35.0	55,885 (25.0)	3,176 (9.2)
Unknown	5,315 (2.4)	2,264 (6.5)
Alcohol use		
Yes	147,319 (65.8)	20,861 (60.3)
No	64,408 (28.8)	10,363 (30.0)
Unknown	12,241 (5.5)	3,347 (9.7)
History of disease		
Asthma/COPD	36,670 (16.4)	5,309 (15.4)
Chronic liver disease	3,511 (1.6)	733 (2.1)
Heart failure	8,794 (3.9)	2,879 (8.3)
Sepsis	2,827 (1.3)	488 (1.4)
Drug use within 6 months with potential influence on renal function		
NSAIDs	40,147 (17.9)	5,435 (15.7)
RAAS inhibitors	91,230 (40.7)	12,151 (35.1)
Loop diuretics	21,874 (9.8)	5,468 (15.8)
Thiazide diuretics	40,538 (18.1)	5,497 (15.9)
β-Blockers	40,090 (17.9)	6,534 (18.9)
Statins	99,990 (44.6)	14,070 (40.7)
Systemic calcineurin inhibitors	316 (0.1)	255 (0.7)

Data are n (%) unless otherwise indicated. COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug; RAAS, renin-angiotensin-aldosterone system. [a]Time represents valid follow-up time for patients using metformin and control patients not using metformin. [b]Proportion of renal function originating from READ codes: 3.6%, and 96.4% from laboratory test events.

of NIAD users (0.3% and 2.8%, respectively). Heart failure was less prevalent among the metformin users compared with the nonusers (3.9% and 8.3%, respectively). Age was strongly correlated with worsening of glomerular filtration rate (GFR): patients younger than 50 years old had a GFR of 96 mL/min/1.73 m^2, those aged 50–64 years had a GFR of 84 mL/min/1.73 m^2, patients aged 65–79 years had a GFR of 70 mL/min/1.73 m^2, and the lowest GFR (59 mL/min/1.73 m^2) was seen in patients aged 80 years and older (data not shown). Patients suffering from lactate acidosis or elevated lactate concentrations had a median age of 72 years (75% were older than 60 years of age).

Table 2 shows that the incidence rate of lactic acidosis or elevated lactate concentrations was 7.4 events per 100,000 person-years among current metformin users versus 2.2 events per 100,000 person-years among nonusers. Of a total of 68 events of lactic acidosis or elevated lactate concentrations, 50 (74%) originated from a READ code for lactic acidosis, whereas 18 (26%) were derived from an elevated plasma lactate concentration. Three events had both a READ record for lactic acidosis and a positive laboratory test. Current metformin users had a fourfold risk compared with NIAD users who had never used metformin, but this increase was not statistically significant (adjusted hazard ratio [AHR] 4.03 [95% CI 0.97–16.8]). The risk among recent or past users of metformin also was nonsignificantly increased. None of the results were influenced by our sensitivity analysis, which used the highest value (instead of the lowest value) in the event of multiple lactate concentrations on the same day.

The different strata of current metformin users (compared with NIAD users who had never used metformin) showed the following increases in the risk of lactic acidosis or elevated lactate concentrations. *1*) The risk in those with a most recent renal function <60 mL/min/1.73 m^2 was significantly higher than the risk in never users (AHR 6.37 [95% CI 1.48–27.5]), whereas the risk in current users with renal function ≥60 mL/min/1.73 m^2 (AHR 2.87 [95% CI 0.67–12.3]) was not. *2*) In an additional analysis, we looked at an eGFR cut point of 45 mL/min/1.73m^2. Current metformin users with an eGFR of ≥45 mL/min/1.73 m^2 had an AHR for lactic acidosis or elevated lactate concentrations of 3.16 (95% CI 0.75–13.3), whereas those with poorer renal function (eGFR <45 mL/min/1.73 m^2) had an AHR of 6.74 (95% CI 1.34–33.8). Among metformin users with a recorded eGFR value, 14% of all lactic acidosis or elevated lactate concentrations occurred among those with an eGFR of <45 mL/min/1.73 m^2. *3*) The risk in those with a cumulative exposure to metformin of ≥730 g in the previous year (AHR 6.14 [95% CI 1.35–28.0]) was significantly increased; this was not the case in those with an exposure <730 g (AHR 3.69 [95% CI 0.88–15.5]). *4*) The risk in those with a recent prescribed daily dose of >2 g of metformin (AHR 6.40 [95% CI 1.35–30.3]) was significantly increased; this was not the case in those with a dose of ≤2 g of metformin (AHR 3.78 [95% CI 0.90–15.8]).

When the strata in analyses 3 and 4 were substratified by renal function, the risk in metformin users with renal function <60 mL/min/1.73 m^2 consistently showed a significant increase; this was not seen in those with renal function ≥60 mL/min/1.73 m^2 (Table 3). Compared with never users, there was an almost 12-fold risk in the substratum with reduced renal function and a cumulative exposure to ≥730 g of metformin in the preceding year (AHR 11.8 [95% CI 2.27–61.5]) and a 13-fold increase in the substratum with reduced renal function and recent exposure to >2 g of metformin/day (AHR 13.0 [95% CI 2.36–72.0]).

CONCLUSIONS

The risk of lactic acidosis or elevated lactate concentrations was increased

Table 2—Risk of lactic acidosis or elevated lactate concentrations in current, recent, and past metformin users compared with never users of metformin

	Risk of lactic acidosis or elevated lactate concentration			
Metformin use	Person-years, *n*	Events, *n*	Age-/sex-adjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Never use	91,287	2	Reference	Reference
Past use	212,007	9	1.94 (0.42–8.97)	2.25 (0.48–10.5)
Recent use	40,526	2	2.25 (0.32–16.0)	2.99 (0.42–21.5)
Current use	743,151	55	3.38 (0.82–13.8)	4.03 (0.97–16.8)
Substratification of current users by most recent renal function (mL/min/1.73 m^2) in the previous year[b]				
≥60	547,731	29	2.42 (0.58–10.1)	2.87 (0.67–12.3)
<60	126,881	21	7.56 (1.77–32.2)	6.37 (1.48–27.5)
30–59[c]	124,275	19	7.09 (1.98–27.9)	5.94 (1.55–24.7)
45–59	89,976	13	6.60 (1.49–29.2)	6.06 (1.37–27.1)
30–44	25,450	5	7.98 (1.61–39.6)	5.47 (1.05–28.5)
<30	2,605	2	35.1 (4.90–249)	25.7 (3.57–185)
≥45	644,861	43	3.30 (0.79–13.8)	3.16 (0.75–13.3)
<45	29,751	7	8.97 (1.85–43.4)	6.74 (1.34–33.8)
Unknown	68,539	5	3.33 (0.65–17.2)	4.51 (0.85–23.8)

Current metformin users are stratified by renal function. [a]Adjusted for age, sex, BMI, a history of heart failure, and use of renin-angiotensin-aldosterone system inhibitors and other NIADs/insulin in the previous 6 months. Chronic liver disease and sepsis were not included in the final model because there were too few exposed patients. [b]Renal function records in the previous week are excluded. [c]This substratum included 8,849 person-years, with one event that could not be subdivided further because the patient only had a READ code for chronic kidney disease stage 3 (30–59 mL/min/1.73 m^2).

Table 3—Risk of lactic acidosis or elevated lactate concentration in current metformin users stratified by cumulative exposure or recent daily exposure to metformin and further stratified by renal function

	Risk of lactic acidosis or elevated lactate concentration			
Metformin use	Person-years, *n*	Events, *n*	Age-/sex-adjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Never use	91,287	2	Reference	Reference
Current use	743,151	55	3.38 (0.82–13.8)	4.03 (0.97–16.8)
Substratification of current users by cumulative exposure to metformin in the previous year and renal function[b]				
<730 g of metformin/year	628,644	43	3.12 (0.76–12.9)	3.69 (0.88–15.5)
Renal function ≥60 mL/min/1.73 m^2	460,012	23	2.28 (0.54–9.65)	2.73 (0.63–11.9)
Renal function <60 mL/min/1.73 m^2	108,561	16	6.72 (1.55–29.2)	5.54 (1.26–24.4)
Unknown	60,071	4	3.03 (0.56–16.5)	4.25 (0.76–23.7)
≥730 g of metformin/year	114,506	12	4.78 (1.07–21.4)	6.14 (1.35–28.0)
Renal function ≥60 mL/min/1.73 m^2	87,719	6	3.12 (0.63–15.4)	3.94 (0.78–20.0)
Renal function <60 mL/min/1.73 m^2	18,320	5	12.4 (2.42–64.1)	11.8 (2.27–61.5)
Unknown	8,468	1	5.38 (0.49–59.3)	6.96 (0.62–78.0)
Substratification of current users by most recent prescribed daily dose of metformin and renal function[b]				
≤2 g of metformin/day	658,391	46	3.19 (0.77–13.1)	3.78 (0.90–15.8)
Renal function ≥60 mL/min/1.73 m^2	483,674	24	2.27 (0.54–9.58)	2.71 (0.63–11.7)
Renal function <60 mL/min/1.73 m^2	113,530	17	6.84 (1.58–29.6)	5.66 (1.29–24.8)
Unknown	61,187	5	3.73 (0.72–19.2)	5.19 (0.98–27.4)
>2 g of metformin/day	84,759	9	4.85 (1.05–22.4)	6.40 (1.35–30.3)
Renal function ≥60 mL/min/1.73 m^2	64,057	5	3.56 (0.69–18.4)	4.59 (0.87–24.3)
Renal function <60 mL/min/1.73 m^2	13,350	4	13.7 (2.51–74.7)	13.0 (2.36–72.0)
Unknown	7,352	0		

[a]Adjusted for age, sex, BMI, a history of heart failure, and use of renin-angiotensin-aldosterone system inhibitors and other NIADs/insulin in the previous 6 months. Chronic liver disease and sepsis were not included in the final model because there were too few exposed patients.
[b]Substratification by most recent renal function in the previous year; renal function records in the previous week excluded.

sixfold in current metformin users with reduced renal function (Table 2); it increased further to 12- or 13-fold in substrata with high cumulative exposure to metformin in the preceding year or with recent high daily exposure to metformin (Table 3).

Our crude incidence rate of lactic acidosis or elevated lactate concentrations—7.4 events per 100,000 person-years—among current metformin users corresponds well with the range of one to nine cases of lactic acidosis per 100,000 patient-years among metformin users that emerged from previous studies (7,10,12,26). Higher incidences of 47 to 57 cases per 100,000 patient-years also have been reported, but this is probably due to differences in study design (11,27). Ekström et al. (21) assessed whether different degrees of renal function affect the safety of metformin use in a cohort study comprising more than 51,000 patients with type 2 diabetes. To evaluate the occurrence of lactic acidosis, they used a composite end point that included a diagnosis of acidosis, shock, acute renal failure, and serious infections. When metformin use was compared with any other treatment, the risk of acidosis/serious infection was not significantly increased in patients with an eGFR ≤60 mL/min/1.73 m^2.

In contrast with these negative findings, we found that reduced renal function or high cumulative or daily exposure to metformin (all of which can lead to higher concentrations of metformin) were associated with an increased risk of lactic acidosis or elevated lactate concentrations. That the risk was further increased when both reduced renal function and a high intake of metformin were present is of particular interest. This lends support to the supposition that high concentrations of metformin may increase the risk of lactic acidosis during metformin use.

A major strength of our study is that it was conducted over a long observation period in a large database representative of the U.K. population in general practice, which offers the possibility to correct for smoking and BMI. The database's information on drug exposure and diagnoses has been validated and proven to be of high quality (12). Another strength is that we not only separately evaluated the influence of renal function and the level of metformin intake, but also did so in combination.

Like most observational studies, our study is not without limitations. First, there is the potential issue of the selection and inaccurate estimation of our outcome measure. The inclusion of patients with a lactate concentration >5 mmol/L (26% of our cases) may have resulted in an overestimate compared with lactic acidosis during metformin use alone, since elevated lactate concentrations do not necessarily signify a diagnosis of lactic acidosis (28). Furthermore, in a previous study of the same CPRD database (General Practice Research Database) that we used, 7 of 14 patients with a READ code of lactic acidosis were excluded after a manual review of their medical record (12). This may have resulted in a nondifferential misclassification of the outcome, which might overestimate the incidence rates of lactic acidosis, although it is unlikely to affect the relative risk of lactic acidosis with metformin use among patients with decreased renal function. However, our period of observation (2004–2012) was different from

the study period used by Bodmer et al. (1994–2005) and started with the year in which the so-called Quality and Outcomes Framework was introduced in the U.K. (29). The potential risk of differential underrecording among nonusers should also be considered. Because of the longstanding assumption that metformin may be linked to lactic acidosis, the lactate concentrations of metformin users may have been measured and recorded more selectively, particularly in those with reduced renal function. Nondifferential underrecording of lactic acidosis in the CPRD database may also have occurred; the presenting features of lactic acidosis are often vague (28), and GPs may not always have transferred lactic acidosis in a hospital discharge letter to their own records by means of the appropriate READ code. A counterargument against such underrecording is, of course, that lactic acidosis is a serious event that is likely to draw sufficient clinical attention. Mild elevations of lactate concentrations can be caused by a large number of pathologic conditions, ethanol, and drugs. Since we were not able to identify the exact cause of lactic acidosis, we were not able to exclude these events.

A second limitation is that we could not retrieve adequate information about all potentially relevant risk factors for lactic acidosis during metformin use. We based our classification of renal function on a READ code or a single eGFR value; we pragmatically accepted this latter value so long as it was not more than 1 year old (based on the argument that clinical guidelines often recommend annual monitoring of renal function). This may have increased the risk of including outdated information. In spite of our liberal choice, we could not retrieve renal function data for 27.4% and 34.6% of the current metformin users and nonusers, respectively (Table 1). Finally, we were not able to analyze the effect of acute decreases in GFR on the risk of lactic acidosis or elevated lactate concentrations.

In conclusion, our study suggests that the risk of lactic acidosis or elevated lactate concentrations is significantly increased in patients with mild to moderate renal insufficiency and that this risk is further increased in long-term heavy metformin users. Although these findings are not conclusive, they are consistent with current recommendations in the literature to adequately monitor the renal function of metformin users and to adjust the dose of metformin, if necessary, if the eGFR falls below 60 mL/min/1.73 m^2 (3,17,18). This should be confirmed in future research, preferably in a study in which lactate concentrations, renal function, and metformin exposure are frequently assessed and in which all potential risk factors are accurately determined and recorded.

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