Lactic acidosis associated with metformin in diabetic patients with chronic kidney disease: a multicentre case-control study using electronic health records

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Abstract

Background

Several studies have assessed the risk of lactic acidosis with metformin use. However, data of this association in patients with renal impairment are still scarce and controversial. Our aim was therefore to assess the association between metformin and lactic acidosis in Spanish type 2 diabetic patients with chronic kidney disease.

Methods

A case-control study (ALIMAR-C2) was performed using the electronic health records from hospitals linked to their corresponding primary healthcare regions. The cases were adult (≥ 18 years) diabetic patients with chronic kidney disease, admitted to seven Spanish hospitals from 2010 to 2016. Ten controls (≥ 18 years, diabetic patients with chronic kidney disease) per case were selected from the population within the same primary healthcare region of the hospital cases. The patients' hospital health records were linked to their corresponding primary healthcare information. Analyses included multivariable logistic regression and adjustment for potential confounders.

Results

Our study included 126 cases and 1,260 matched controls. The current use of metformin and administration at high doses (> 2 g) were associated with lactic acidosis (adjusted OR: 1.92, 95% CI: 1.21–3.03; OR: 3.13, 95% CI: 1.63–6.01, respectively). The estimated case fatality rate was 46.8% (95% CI: 38.3–55.5%). An increased risk of lactic acidosis was observed in patients with mild to moderate renal impairment (OR: 3.41, 95% CI: 1.48–7.85). As an unexpected finding, diuretic drugs use was also associated with lactic acidosis (OR: 2.73, 95% CI: 1.67–4.46).

Conclusions

Metformin was associated with an increased risk of lactic acidosis in patients with type 2 diabetes mellitus and chronic kidney disease. New data is needed to confirm the association between diuretic drugs and lactic acidosis in this group of patients.

Background

Metformin is the initial drug treatment for adults with type 2 diabetes mellitus (DM2) but has been associated with lactic acidosis (LA), a very rare and life-threatening adverse event, especially in patients with renal disease [1, 2]. The safety evidence supporting its use in these patients remains controversial and scarce.

In 2016 the regulatory authorities of the Food and Drug Administration (FDA) and European Medicines Agency (EMA) carried out safety reviews, concluding that metformin can be used in patients with mild to moderate kidney impairment (stage 3a and stage 3b; estimated glomerular filtration rate [eGFR] 30–59 mL/min) but still warned against its use in cases of severe renal impairment (stage 4 and stage 5; eGFR < 30 mL/min) [3, 4]. Additionally, a recent large cohort study showed that metformin does not appear to increase the risk of lactic acidosis in such patients while metformin should be used with caution in patients with severe renal impairment [5]. It is noteworthy that, prior to the aforementioned regulatory authorities' guidelines, observational studies had already shown an increased incidence of LA in patients exposed to metformin in parallel to the degree of impairment of renal function [6], as well as an increased risk of LA in patients with eGFR < 60 mL/min, mainly due to the higher risk in patients with eGFR < 45 mL/min [7].

Prescribing metformin for people with renal impairment continues to be a matter of debate today, especially in patients with severely reduced kidney function. As a consequence, there is still considerable variation between the different international prescribing guidelines for metformin. The aim of this case-control study (ALIMAR-C2), using electronic health records from hospitals linked to their corresponding primary healthcare regions, was therefore to assess the association between metformin and LA in Spanish patients with DM2 and reduced kidney function.

Methods/design

Study design and setting

We conducted a multicentre case-control study using data from 2010 to 2016, obtained from the electronic health records of seven hospitals and their primary healthcare institutions geographically located in two regions of Spain (Madrid and Catalonia). The study methodology has been described elsewhere [8]. The administrative, clinical and laboratory records from the data warehouses (DWs) of Catalan hospitals were linked with the primary healthcare data compiled in SIDIAP (Information System for Research in Primary Care) which contains pseudonymised clinical information from all the primary healthcare centres of the Institut Català de la Salut (ICS) [9]. Bellvitge University Hospital is the only hospital in which a DW integrates both clinical practice and primary healthcare data. In Madrid, the clinical data obtained from different sources and information systems integrated within the hospitals were linked to the Primary Healthcare Electronic Health Record (AP-Madrid) which contains data from all the primary healthcare centres within the Servicio Madrileño de Salud (SERMAS).

Study population

We identified all patients admitted to the hospital with a diagnosis of LA (pH < 7.35 and plasmatic lactic acid concentration > 5 mM/L within the first 24 and 72 hours after admission, respectively) from 2010 to 2016. The date of admission was used as the index date. The inclusion criteria were as follows: (1) at least 18 years of age, (2) hospital or primary healthcare diagnosis of DM2 before the index date, (3) chronic kidney disease (CKD) stage 3a (mild-moderate), 3b (moderate-severe) or 4 (severe) of the Kidney

Disease Improving Global Outcomes (KDIGO) classification [10] during the 2-year period before the index date (excluding the previous 2 weeks), taking into account data from the primary healthcare database, and (4) availability of any information recorded on the primary healthcare database within a 1-year period before the index date. We excluded cases with: (1) diabetic ketoacidosis during the current in-hospital stay; (2) hospital or primary healthcare diagnosis of type 1 diabetes mellitus, human immunodeficiency virus disease or solid organ transplant before the index date; (3) hospital or primary healthcare diagnosis of malignant neoplasm (except skin cancer other than melanoma; including pheochromocytoma) within a 5-year period before the index date [8]. In Catalonia, patients not registered in the hospital referral area were also excluded.

Furthermore, people assigned to the hospital's primary healthcare region were chosen for the control group and matched in a ratio of 10:1 by age, gender, CKD stage and year of admission. They were at least 18 years old, had DM2 diagnosed before the index date and a CKD stage as defined for the cases. Additionally, they had information recorded on the primary healthcare database within a 1-year period before the index date. We excluded controls with: (1) type 1 diabetes mellitus, human immunodeficiency virus disease or a solid organ transplant before the index date; (2) malignant neoplasm (except skin cancer other than melanoma; including pheochromocytoma) within a 5-year period before the index date, and (3) patients not resident in the area of study.

Measurements

The hospital databases provided information on the patients' characteristics, including age and gender, hospital course data (admission date, in-hospital death, admission to critical care unit), laboratory test data (values and dates for lactic acid and haemoglobin concentration, and pH). The primary healthcare databases provided laboratory test data (values and dates for serum creatinine and haemoglobin concentration), and information on the drugs prescribed (anatomical therapeutic chemical [ATC] codes; prescription dates for metformin, other non-insulin antidiabetic drugs [NIADs], insulin, diuretics [high ceiling: furosemide, torasemide; low ceiling: hydrochlorothiazide, chlortalidone, xipamide, indapamide; potassium-sparing diuretics: spironolactone, eplerenone], renin-angiotensin system [RAS] inhibitors, and non-steroidal anti-inflammatory drugs [NSAIDs]; National Drug Code [NDC]; and prescribed posology for metformin). In the case of drug combinations, each drug was classified in its corresponding ATC group with a record of the drug's dosage in the combination. Additionally, diagnosis dates and codes (International Classification of Diseases, 9th and 10th revisions [ICD-9, ICD-10], and International Classification of Primary Care, 2nd revision [ICPC-2]) were obtained from both the hospital and primary healthcare databases. Renal function was estimated using serum creatinine data between 2 years and 2 weeks before the index date. The eGFR was calculated using the CKD-Epidemiology equation and stage according to the KDIGO classification (≥ 90, 60–89 45–59, 30–44, < 30 mL/min/1.73 m^2) [11]. In the case of eGFR estimates resulting in different CKD stages for an individual patient across the 2-year period, the worst CKD stage closest to the index date was assigned to this patient when this was not followed by a better stage. Detailed information regarding the variables has been described previously [8].

Exposure definition

Exposure to metformin, other NIADs and insulin was defined as current use (prescription within a 30 day-period before the index date) or global use (prescription within a 365 day-period before the index date). We would like to point out that global use was defined in the statistical analysis plan.

The length of the exposure was defined as the time between the start and end prescription dates. A gap in drug prescription of ≤ 30 consecutive days was not considered as discontinued exposure. The prescribed daily dose of metformin was calculated according to the posology recorded by the prescriber and the strength corresponding to the NDC, and was categorised into < 1 g, 1–2 g, and > 2 g. Exposure to diuretics, RAS inhibitors and NSAIDs were defined as prescriptions during the 30 day-period before the index date.

Statistical analysis

Baseline characteristics were summarised for cases and controls using standard descriptive statistics and a descriptive comparative analysis was carried out.

Conditional logistic regression was used to control for matches on age, gender, renal stage and year of index date. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) were estimated to assess the risk of LA associated with metformin. The following drugs competed with metformin: alpha glucosidase inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors, insulins and analogues, other blood glucose lowering drugs, sulfonylureas, thiazolidinediones, glucagon-like peptide 1 (GLP1) receptor agonists, NSAIDs, potassium-sparing diuretics, high ceiling diuretics, low ceiling diuretics and RAS inhibitors.

A stepwise procedure was used to select the baseline covariates to be included in the adjusted models. The variables selected were: alcohol use, liver disease, acute myocardial infarction, arterial peripheric arteriopathy, heart failure, chronic respiratory disease, dementia, seizures, gastroenteritis and dehydration.

Subgroup analyses were performed according to the daily dose of metformin, current and global use, and also the CKD stage.

Additionally, the overall case fatality rate of LA as well as the case fatality rate stratified by CKD stage were calculated from the number of deaths among cases and the total number of cases.

The possibility of detection bias was studied by analysing the frequency of determination of plasmatic lactate levels in patients with metabolic acidosis according to the status of metformin exposure. This analysis was performed with data from two of the participating hospitals in a sample of episodes of urgent hospital admission with pH < 7.35 during the first 24 hours. An OR with its 95% CI for each hospital was provided.

All statistical analyses were performed with R statistical package version 3.6.0.

Results

Among the 1,619,481 patients admitted to hospital between January 2010 and December 2016, 126 cases were identified (Figure 1). Table 1 shows the demographic and clinical characteristics of the study population. 35 of them were admitted to critical care unit (admission rate: 27.8%, 95% CI: 20.7-36.2%). A total of 59 out of 126 cases died from any cause during hospitalisation (case fatality rate: 46.8%, 95% CI: 38.3-55.5%), of which 22 (37.3%, 95% CI: 26.5-50.0%) died in critical care units. The characteristics of the dead patients are described in Additional File 1: Table 1. According to CKD stage, the case fatality rates were 48.0% in stage 3a and stage 3b (95% CI: 34.8-61.5% and 95% CI: 34.8-61.5%, respectively) and 42.3% in stage 4 (95% CI: 25.5-61.1%).

LA cases showed statistically significant higher morbidity than controls in acute myocardial infarction (23.8% vs 12.6%), peripheral arterial disease (24.6% vs 15.4%), heart failure (38.1% vs 26.7%), seizures (4% vs 1.3%), dehydration (6.3% vs 1.8%), chronic alcoholism (13.5% vs 6.2%) and acute alcohol intoxication (2.4% vs 0%).

Table 2 shows the OR for association between LA and different drugs. Compared with no use, current use of metformin was associated with a higher risk of LA (OR: 1.92, 95% CI: 1.21-3.03). A dose-effect trend was observed, although the increase in risk was statistically significant only for the higher dosage category (>2g) (Table 3). Similar results were found for global use of metformin (see Additional File 2: Table 2 and Additional File 3: Table 3).

Subgroup analysis according to the CKD stage showed that current use of metformin was associated with LA in patients with mild-moderate renal impairment (stage 3a; OR 3.41, 95% CI 1.48-7.85; Table 4). However, this association was not found in patients with severe renal impairment (stage 4).

In the analysis by different drugs (Table 2 and Additional File 2: Table 2), neither the current use nor global use of other hypoglycaemic drugs, nor current use of NSAIDs or RAS inhibitors was associated with LA. However, the current use of diuretics was associated with LA (OR: 2.73, 95% CI: 1.67 - 4.46). The risk of LA by a classification of the diuretics is shown in Table 2. The subgroup analysis according to CKD stage showed an association with a higher risk of LA for high ceiling diuretics in CKD stage 3b, for low ceiling diuretics in CKD stage 3a, and for potassium sparing diuretics in CKD stages 3b and 4 (Table 5).

Acidosis lactic detection bias was not found in any of the two hospitals studied (Hospital 1 (Catalonia): OR 0.95, 95% CI 0.70-1.28; Hospital 2 (Madrid): OR 1.07, 95% CI 0.69-1.67). Patients with metabolic acidosis admitted via the emergency department who were metformin users did not show a higher risk of their plasmatic lactate levels being determined than non-metformin users.

Discussion

To our knowledge, this multicentre case-control study on LA is one of the largest studies published to date and it is noteworthy that LA was defined based on objective parameters (laboratory tests: pH value and lactic acid level). The use of metformin was associated with a higher risk of LA in diabetic patients with chronic kidney disease, especially in patients on a higher dose of metformin. Unexpectedly, LA was also associated with diuretics use.

The use of metformin for DM2 in patients with reduced kidney function remains controversial and data on safety in this population is scarce. The prescription of metformin for people with renal impairment continues to be a matter of debate, especially with this type of patient [3,4]. Our findings have shown that a current use of metformin increases the risk of lactic acidosis (OR: 3.41, 95% CI: 1.48-7.85) in patients with mild-moderate CKD (stage 3a; eGFR: 45–59 mL/min). These findings are partly in line with the results described in a UK population cohort study on the same group of patients (adjusted HR: 6.06, 95% CI: 1.37-27.10) [7]. Conversely, metformin use has not been associated with an increased risk of LA in other studies [5] [12] [13]. It should be noted that recommendations on the use of metformin in patients with CKD are based on observational studies, which could represent a limitation for its endorsement [3,4]. A channelling bias may be the consequence of the restricted use of metformin with patients at CKD stage 3 or 4, whereas patients with reduced eGFR may have been more likely to receive metformin therapy, if they were healthier [13]. This might explain the mixed opinions regarding metformin use in clinical guidelines [14]. Our findings suggest that a higher dose of metformin is associated with a higher risk of LA, in line with other findings that have shown an increased risk with high daily exposure to metformin in patients with CKD (adjusted HR: 13.0, 95% CI: 2.36-72.0) [7]. In brief, based on our results, the use of metformin in DM2 and CKD patients should be carried out with caution.

Current diuretics use was unexpectedly found to be associated with a higher risk of LA and this association was also observed in the analysis by diuretic type. To our knowledge, this is the first time such a finding has been reported. In order to find an explanation, we performed a *post hoc* analysis excluding patients with heart failure (38% of our analysis population), given that these patients are usually treated with diuretics. The risk association between diuretics and LA was still present (see Additional File 4: Table 4). Another factor studied in order to explain this association was the effect of dehydration as diuretics may negatively affect renal performance, especially in dehydrated patients. However, only 8 patients suffered from dehydration. Such a low number of patients with dehydration

cannot contribute to an explanation of the association found between diuretics and LA. In fact, although we believe this finding may be misleading, future studies are required to study this association.

Half our cases died. According to the evidence available [15], this high morbidity rate is to be expected. The low admission rate to critical care units is consistent with the admission criteria; the patients who were not admitted were older and had a worst diagnosis than those who were admitted (see Additional File 1: Table 1).

This study has some limitations. First, there were differences regarding the data stored in the electronic databases. Likewise, different diagnosis coding systems were used. However, this is an inherent limitation to studies based on databases. Second, we had not taken into account changes in eGFR over time. However, only one recent study has taken this methodological consideration into account [12] and, moreover, earlier evidence has demonstrated consistency without its use. Third, exposure could be overestimated as the analysis was carried out according to drug prescriptions and not to the dispensation or actual intake of the drug. Nevertheless, this situation would be the same for both cases and controls and, consequently, the potential overestimation is not expected to have a significant effect on the results. Fourth, although the channelling bias was not taken into account, a detection bias analysis was planned in the protocol. Over-diagnosis of LA in metformin users was not observed despite the longstanding assumption that metformin may be associated with lactic acidosis.

In brief, in this study metformin was associated with an increased risk of lactic acidosis in patients with type 2 diabetes mellitus with chronic kidney disease. New data is needed to confirm the association between diuretic drugs and lactic acidosis in this group of patients.

Abbreviations

CKD: chronic kidney disease; CMBD: basic minimum set of data; CREC: Clinical Research Ethics Committee; DM2: type 2 diabetes mellitus; eGFR: expected glomerular filtration rate; DPP-4: dipeptidyl peptidase 4; EMR: electronic medical record; ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; ER: Emergency Room; GLP1: glucagon-like peptide 1; KDIGO: Kidney Disease Improving Global Outcomes; LA: lactic acidosis; NIAD: non-insulin antidiabetic drug; NSAID: non-steroidal anti-inflammatory drug; PHC: primary healthcare; RAS: renin-angiotensin system; SAP BO: Systems, Applications and Products in Data Processing Business Objects.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the CRECs of all participant centres (study code in the coordinating centre [Hospital Universitari de Bellvitge] CREC: EPA032/16; [Hospital Germans Trias i Pujol] CREC: PI-16-120 ; [Hospital Clínic de Barcelona] CREC: HCB/2019/0528; [Hospital Universitari Vall d'Hebron] CREC: EPA(AG)55/2016(4967); [Hospital de la Santa Creu i Sant Pau] CREC: 16/156(OBS); [Hospital Universitario Ramón y Cajal] CREC: ALIMAR-C2; [Hospital Universitario Fundación Jiménez Díaz] CREC: EOH 2016-37; [Hospital Clínico San Carlos] CREC: 16/326-E; [Institut Universitari d'Investigació en Atenció Primària (IDIAP) Jordi Gol] CREC: P16/105, and [Gerencia Asistencial de Atención Primaria] CREC:43/16. All CRECs accept a waiver for participant consent, taking into account the characteristics of the study.

The ALIMAR-C2 study was entered in the European Union electronic Register of Post-Authorisation Studies (EU PAS Register Number: EUPAS13969, June 2016) and received approval from the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (http://www.encepp.eu/encepp/viewResource.htm?id=14215).

Regarding the data contained in the databases, and according to Spanish legislation on the confidentiality and protection of data (Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales), data included in this study consist of the identification of incident cases of LA in hospitals and some specific information from primary healthcare. In order to link this information, the same identity code is needed for each patient. A coding system was used to link this information while keeping the identity of the patients anonymous.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

SV is the principal investigator. CP was actively involved in the conception and design of the study. MA, MM, RM, and AG are members of the coordinating group and were also involved in the conception and design of the study.

MA, SV, CP, AG, OP and RM drafted the manuscript. All authors made contributions to the design of the study, critically reviewed the manuscript and approved the final version.

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Tables

Table 1. Demographic and clinical characteristics of cases and controls

	Cases	Controls	p-value
Participants, n (%)	126 (100%)	1260 (100%)	
Age mean (SD), years	78.8 (9.1)	79.1 (9.2)	0.828
Female gender, n (%)	67 (53.2)	670 (53.2)	1.000
Chronic kidney disease stage, (current) n (%)			
3a	50 (39.7)	500 (39.7)	1.000
3b	50 (39.7)	500 (39.7)	
4	26 (20.6)	260 (20.6)	
Index date(year)			1.000
2011	6 (4.8)	60 (4.8)	
2012	17 (13.5)	170 (13.5)	
2013	16 (12.7)	160 (12.7)	
2014	33 (26.2)	330 (26.2)	
2015	32 (25.4)	320 (25.4)	
2016	22 (17.5)	220 (17.5)	
Antidiabetic drugs, number (%)			<0.001
0	32 (25.4)	629 (49.9)	
1	51 (40.5)	382 (30.3)	
2	32 (25.4)	178 (14.1)	
≥3	11 (8.7)	71 (5.7)	
Comorbidities, n (%)			
Acute myocardial infarction	30 (23.8)	159 (12.6)	0.001
Hypertension	111 (88.1)	1159 (92.0)	0.182
Dyslipidemia	82 (65.1)	791 (62.8)	0.679
Peripheral arterial disease	31 (24.6)	194 (15.4)	0.011
Cerebrovascular disease	42 (33.3)	318 (25.2)	0.062
Heart failure	48 (38.1)	336 (26.7)	0.009
Dementia	20 (15.9)	132 (10.5)	0.089
Seizures	5 (4.0)	16 (1.3)	0.048
Chronic respiratory disease	43 (34.1)	430 (34.1)	1.000
Chronic liver disease			
Mild	11 (8.7)	72 (5.7)	0.245
Moderate-severe	18 (14.3)	93 (7.4)	0.011
Connective tissue disease	9 (7.1)	64 (5.1)	0.436
Gastro duodenal ulcer	6 (4.8)	65 (5.2)	1.000
Vomiting, diarrhea or gastroenteritis	10 (7.9)	167 (13.3)	0.118
Dehydration	8 (6.3)	23 (1.8)	0.003
Alcoholism	17 (13.5)	78 (6.2)	0.004
Acute alcohol intoxication	3 (2.4)	0 (0.0)	<0.001

Table 2. Odds ratios for lactic acidosis (current use)

	Cases n (%)	Controls n (%)	OR $_{crude}$ (95%CI)	p-value	OR $_{adj}$ (95%CI)*	p-value
Metformin	62 (49.2)	370 (29.4)	2.91 (1.91-4.43)	<0.001	1.92 (1.21-3.03)	0.01
Hypoglycaemic drugs						
Alpha glucosidase inhibitors	1 (0.8)	8 (0.6)	1.25 (0.16-9.99)	0.83	0.99 (0.12-8.54)	0.99
DPP-4 inhibitors	14 (11.1)	119 (9.4)	1.21 (0.66-2.23)	0.53	0.83 (0.42-1.62)	0.58
Insulins and analogues	36 (28.6)	247 (19.6)	1.71 (1.11-2.63)	0.01	1.12 (0.69-1.81)	0.66
Sulfonylureas	26 (20.6)	133 (10.6)	2.36 (1.44-3.86)	0.00	1.57 (0.90-2.73)	0.11
Thiazolidinediones	1 (0.8)	9 (0.7)	1.11 (0.14-8.77)	0.92	0.88 (0.10-7.86)	0.91
GLP1-receptor agonists	1 (0.8)	4 (0.3)	2.5 (0.28-22.37)	0.41	2.36 (0.21-26.0)	0.48
Other, excluding insulins	10 (7.9)	68 (5.4)	1.55 (0.76-3.17)	0.23	1.87 (0.84-4.16)	0.13
Diuretics						
High ceiling	62 (49.2)	301 (23.9)	3.64 (2.42-5.47)	<0.001	2.60 (1.60-4.21)	<0.001
Low ceiling	42 (33.3)	293 (23.3)	1.83 (1.18-2.83)	0.01	1.96 (1.20-3.20)	0.01
Potassium-sparing	24 (19.0)	64 (5.1)	4.48 (2.67-7.51)	<0.001	2.62 (1.38-4.98)	<0.01
Nonsteroidal anti-inflammatory drugs	9 (7.1)	75 (6.0)	1.23 (0.59-2.55)	0.59	1.04 (0.45-2.37)	0.93
Renin-angiotensin system inhibitors	56 (44.4)	404 (32.1)	1.87 (1.24-2.81)	<0.001	1.42 (0.90-2.23)	0.13

*Adjusted for age, gender, renal stage, year of index date, alcohol use, liver disease, acute myocardial infarction, arterial peripheric arteriopathy, heart failure, chronic respiratory disease, dementia, seizures, vomiting, diarrhea or gastroenteritis, dehydration, and other current treatments.

DPP-4: dipeptidyl peptidase 4; GLP1: glucagon-like peptide 1.

Table 3. Odds ratio for lactic acidosis stratified by metformin daily dose (current use)

	Cases	Controls	OR$_{crude}$ (95%CI)	p-value	OR $_{adj}$ (95%CI)*	p-value
Missing	0 (0.0)	3 (0.4)				
Non-use**	55 (43.7)	808 (64.1)	Ref		Ref	
<1 g	14 (22.6)	109 (29.7)	2.43 (1.26-4.68)	<0.01	1.34 (0.66-2.74)	0.42
1-2 g	24 (38.7)	182 (49.6)	2.47 (1.39-4.40)	<0.001	1.53 (0.80-2.93)	0.20
>2 g	24 (38.7)	76 (20.7)	5.29 (2.97-9.42)	<0.0001	3.13 (1.63-6.01)	<0.001

*Adjusted for age, gender, renal stage, year of index date, alcohol use, liver disease, acute myocardial infarction, arterial peripheric arteriopathy, heart failure, chronic respiratory disease, dementia, seizures, vomiting, diarrhea or gastroenteritis, dehydration, and other current treatments. **The 'Non-use' level refers to patients who have not been exposed to metformin.

Table 4. Odds ratio for lactic acidosis according to chronic kidney disease stage

	Cases N (%)	Controls N (%)	OR_{crude} (95%CI)	p-value	OR_{adj} (95%CI)*	p-value
Metformin current use						
CKD stage						
Stage 3a	33 (26.2)	193 (15.3)	4.69 (2.23-9.87)	<0.001	3.41 (1.48-7.85)	<0.001
Stage 3b	24 (19.1)	144 (11.4)	2.54 (1.35-4.77)	<0.01	1.97 (0.95-4.10)	0.07
Stage 4	5 (4.0)	33 (2.6)	1.64 (0.58-4.66)	0.35	0.37 (0.07-2.06)	0.26

CKD: chronic kidney disease.

***** Model CKD stage 3a adjusted for all diagnosis and other current treatments (except for alpha glucosidase inhibitors and thiazolidinediones, due to lack of sample. Model CKD stage 3b adjusted for all diagnosis and other current treatments (except for glucagon-like peptide 1-receptor agonists due to lack of sample). Model CKD stage 4 adjusted for all diagnosis and other current treatments (except for alpha glucosidase inhibitors, thiazolidinediones, and glucagon-like peptide 1-receptor agonists due to lack of sample).

Table 5. Odds ratio for lactic acidosis regarding current use of diuretics stratified by chronic kidney disease stage

	Cases	Controls	OR_{crude} (95%CI)	p-value	OR_{adj} (95%CI)*	p-value
High ceiling diuretics						
CKD stage 3a	19	75	3.78 (1.97-7.26)	<0.001	2.24 (0.92-5.44)	0.07
CKD stage 3b	29	149	3.58 (1.92-6.67)	<0.001	2.71 (1.28-5.77)	0.01
CKD stage 4	14	77	3.50 (1.37-8.93)	0.01	3.59 (0.90-14.3)	0.07
Low ceiling diuretics						
CKD stage 3a	22	129	2.67 (1.38-5.17)	<0.001	2.66 (1.17-6.03)	0.02
CKD stage 3b	15	140	1.12 (0.56-2.24)	0.746	1.45 (0.66-3.19)	0.35
CKD stage 4	5	24	2.45 (0.81-7.36)	0.111	2.28 (0.43-12.07)	0.33
Potassium-sparing diuretics						
CKD stage 3a	8	27	3.36 (1.43-7.91)	0.01	1.47 (0.45-4.83)	0.53
CKD stage 3b	10	29	4.16 (1.88-9.21)	<0.001	3.37 (1.21-9.38)	0.02
CKD stage 4	6	8	9.74 (2.92-32.49)	<0.001	22.36 (3.24-154.14)	<0.01

CKD: chronic kidney disease.

***** Model CKD stage 3a adjusted for all diagnosis and other current treatments (except for alpha glucosidase inhibitors and thiazolidinediones due to lack of sample). Models CKD stage 3b and stage 4 adjusted for all diagnosis and other current treatments (except for glucagon-like peptide 1-receptor agonists due to lack of sample).

Figures

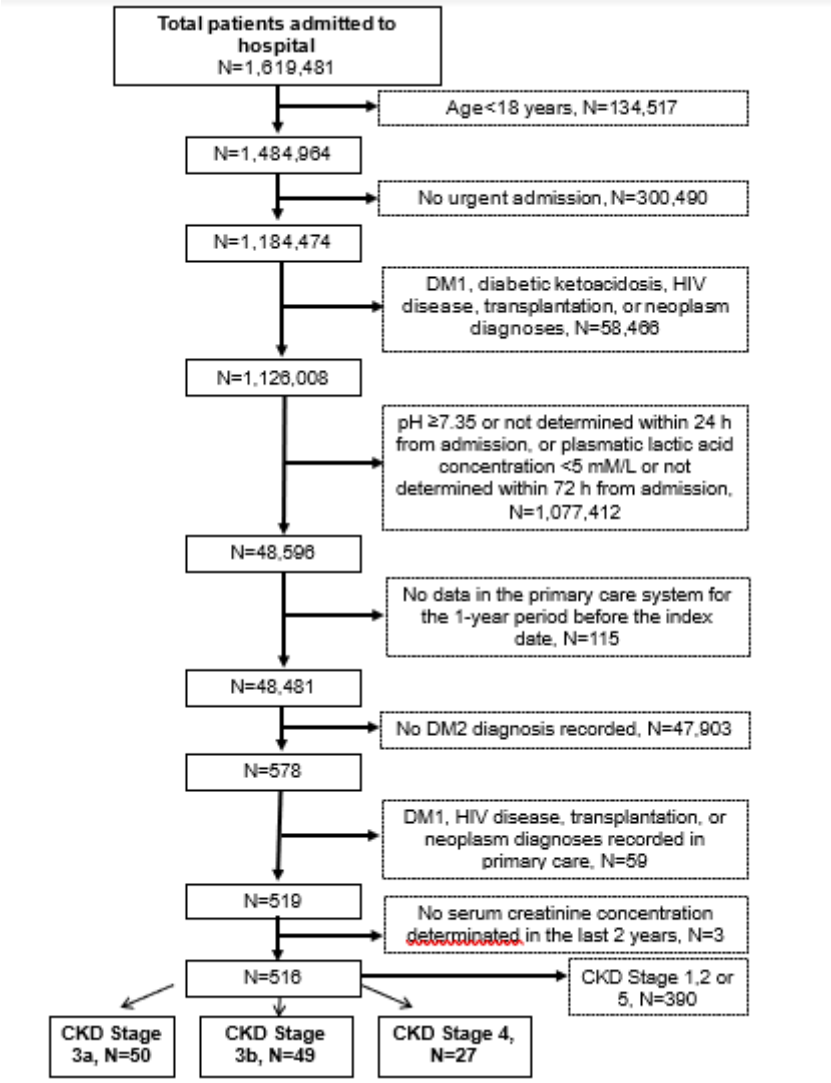

Figure 1

Flowchart of selection of cases. CKD: chronic kidney disease; DM1: type 1 diabetes mellitus; DM2: type 2 diabetes mellitus; HIV: human immunodeficiency virus.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEChecklistLAmetforminCC.docx
- SupplementaryTable4heartfailure.docx
- SupplementaryTable3ORglobaluseLAmetforminCC.docx
- SupplementaryTable2ORuseLAmetforminCC.docx
- SupplementaryTable1fatalitycasecharacteristicsCC.docx