ORIGINAL ARTICLE

Association between ACEI/ARB Usage and Occurrence of Metformin-associated Lactic Acidosis (MALA) in Diabetic Patients, A Case-control Study

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Background: Metformin-associated lactic acidosis (MALA), though not common, is a life-threatening complication of drug administration. An important precipitating cause of MALA is renal impairment, which can occur after angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB) usage.

Objective: To determine the association between ACEI/ARB usage and the development of MALA.

Materials and Methods: A 1: 5 matched case-control study among patients admitted to a medical intensive care unit with MALA. One hundred forty Controls were matched for age, sex, and metformin dose.

Results: Among 28 cases of MALA, 60.71% were female, the median (IQR) of patient age was 69.50 (61 to 76) years, and the median daily dose of metformin was 2,000 (1,500, 2,000) mg. All of them had acute kidney injury on admission. Initial and maximum serum lactate levels were 17.79 (11.28, 19.79) and 20.58 (16.24, 26.50) mmol/L, respectively, with an initial pH of 7.01 (6.94, 7.18). Mortality rate was 21.43%. The concomitant ACEI/ARB usage was not statistically different between cases (50%) and controls (54.29%) with an odds ratio of 0.84 (p=0.68, 95% CI 0.37 to 1.90).

Conclusion: ACEI/ARB usage was not associated with MALA occurrence.

Keywords: Metformin-associated lactic acidosis; MALA; Angiotensin-converting enzyme inhibitor; Angiotensin receptor blocker; ACEI; ARB; Diabetes mellitus

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Metformin was considered the first-line medication for type 2 DM and is still one of the most prescribed anti-diabetics worldwide[1], due to effective glycemic control, reasonable cost, and possible cardiovascular benefits[2,3]. Despite having a good safety profile, its potential adverse effect is lactic acidosis. The incidence of metformin-associated lactic acidosis (MALA) ranges from 5 to 47 per 100,000 patient-years[4-7]. Even though MALA is not common, it is associated with a significant mortality rate of up to 25% to 50%[8,9].

Since patients with MALA usually have certain risk factors such as renal impairment and dehydration[10] and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB) are the recommended antihypertensive agents in diabetic patients[11]. Thus, ACEI/ARB usage, which possibly causes acute kidney injury (AKI), is reported as a contributor to MALA occurrence[12,13]. However, there was a previous retrospective cohort study conducted in Thailand[14], which found that ACEI/ARB might be a protective factor against MALA (adjusted risk ratio of 0.31).

Owing to discordant results between the previous studies, this study aimed to further investigate potential risk factors of MALA and determine the association between ACEI/ARB usage and MALA.

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Materials and Methods

Study design and population

The present study was a case-control study conducted at the Srinagarind Hospital, Khon Kaen, Thailand. We enrolled all adult patients (≥18 years) with the diagnosis of MALA, who were admitted to the ICU between January 2015 and December 2022. MALA was defined if all the

following criteria were present: 1) diabetic patients currently on metformin; 2) metabolic acidosis (arterial blood gas pH <7.35); and 3) plasma lactate level >5 mmol/L or 45 mg/dL. Exclusion criteria were pregnancy, metformin usage due to medical conditions other than diabetes, and the presence of other causes that might elevate the lactate level such as infection, congestive heart failure, and seizure. Five controls, who were adult diabetic patients with current metformin therapy, were matched to every case based on sex, age, and metformin dose.

Variables

The medical records of the selected patients were reviewed for baseline demographic data, comorbidities, current medications, presenting signs and symptoms, acute illness severity indicators, laboratory tests, treatments including modes of dialysis, and outcomes. Comorbidities investigated were hypertension, chronic pulmonary disease (COPD, asthma), renal impairment (acute kidney injury, chronic kidney disease), hepatic dysfunction (cirrhosis, acute hepatitis), malignancy, coronary artery disease, and HIV infection. For current medications, the authors focused on prescriptions of metformin and other antidiabetic, antihypertensive, and non-steroidal anti-inflammatory drugs (NSAIDs), which potentially cause AKI. The severity of the disease was evaluated using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score on admission. Blood tests included serum blood urea nitrogen, creatinine, electrolytes, aspartate transaminase (AST), alkaline phosphatase (ALP), total bilirubin, prothrombin time, and international normalized ratio (INR), hemoglobin, lactate, and arterial blood gas.

Outcome

The study's primary endpoint was whether ACEI/ARB usage is associated with MALA occurrence. The secondary endpoint was to investigate other potential risk factors of MALA and to explore the factors associated with mortality.

Ethnic consideration and procedure

The present study was approved by the Ethics Committee of the Center for Ethics in Human Research, Khon Kaen University (HE641503), by the Helsinki Declaration. The information obtained from the study, including the patient's history, was kept confidential and took into account the patient's rights. The results are represented as an overview, not individual data. The present study is retrospective. However, there was no contact with patients and relatives for the patients' blood for further information. If the information is incomplete and needs more information besides the database of outpatient records, inpatient files, and laboratory information, it must be approved by the director or supervisor of each institution before accessing the information.

The authors collected data by reviewing medical records from the hospital information systems database (Health Object system) and inpatient log files. Patient demographic data, vital signs, laboratory results including lactate levels, severity scoring systems, diagnosis, treatment, and supportive modalities were collected. Shock types and lactic acidosis subtypes were then classified by the authors, case by case, afterward.

Sample size calculation

The authors assumed the prevalence of ACEI/ARB exposure in the case group and control group to be 0.8 and 0.5, respectively. A ratio of 1:5 was applied to the case versus control. It was calculated that 28 cases would be necessary to have a confidence of 95% and a power of 80%.

Statistical analysis

Results were expressed as mean ± standard deviation (SD) or as median interquartile range (IQR) for quantitative variables. Number (percentage, %) was used to describe qualitative data. The Chi-square test was used to analyze categorical variables. When appropriate, comparisons between groups were performed with a Student's t-test or a Mann-Whitney U test. Statistical analyses were performed using IBM SPSS Statistics, Version 26.0 (Armonk, NY: IBM Corp). A p-value <0.05 was considered significant.

Results

The authors identified 28 patients who were admitted to the ICU with a final diagnosis of MALA during the study period (Figure 1), 60.71% were female, the median (IQR) of patients' age was 69.50 (61 to 76) years, and a daily dose of metformin was 2,000 (1,500 to 2,000) mg. All of them had acute kidney injury on admission. Initial and maximum serum lactate levels were 17.79 (11.28 to 19.79) and 20.58

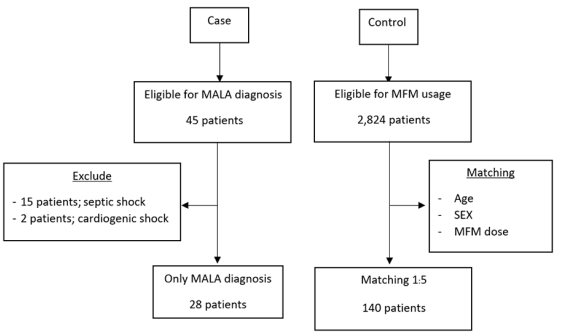

Figure 1. Recruitment flow between case and control patient.

(16.24, 26.50) mmol/L respectively with initial pH of 7.01 (6.94, 7.18).

A total of 140 controls were matched for age, sex, and metformin dose. Compared to controls, patients with MALA had more COPD (10.71% vs. 0.71%, p=0.002) and acute hepatitis (7.14% vs. 0%, p=0.001). The ACEI/ARB usage was not statistically different between cases and controls (50% vs. 54.29%, p=0.68) (OR 0.84, 95% CI 0.37 to 1.90) (Table 1).

Clinical presentations of MALA patients, the basic characteristics, comorbidities, and severity index (APACHE II, SOFA) were compared between survivors and non-survivors. Circulatory failure was noted in all non-survivors, and alteration of consciousness was more common. Initial

Table 1. Patient demographics and clinical characteristics

Factor	Case (n=28)	Control (n=140)	p-value
Basic characteristic			
Sex, male, n (%)	17 (39.28)	55 (39.29)	1.00
Age, median (IQR)	69.5 (61 to 76)	69 (61 to 76)	0.95
Creatinine, median (IQR)	8.33 (5.50 to 10.16)	0.9 (0.7 to 1.0)	<0.001
eGFR (/1.73 m^2), median (IQR)	5.87 (4.38 to 7.55)	76 (62 to 88)	<0.001
Underlying disease and comorbidity			
Hypertension, n (%)	19 (67.86)	96 (68.57)	0.94
COPD, n (%)	3 (10.71)	1 (0.71)	0.002
AKI, n (%)	28 (100)	0	<0.001
CKD, n (%)	9 (32.14)	25 (17.86)	0.09
Cirrhosis, n (%)	1 (3.57)	3 (2.14)	0.65
Acute hepatitis, n (%)	2 (7.14)	0	0.001
Solid tumor, n (%)	2 (7.14)	3 (2.14)	0.16
Coronary artery disease, n (%)	2 (7.14)	4 (2.86)	0.27
NSAIDs usage, n (%)	4 (14.29)	7 (5)	0.07
Diabetes drug usage			
Metformin, n (%)	28 (100)	140 (100)	1.00
Metformin dose (mg), median (IQR)	2,000 (1,500 to 2,000)	2,000 (1,500 to 2,000)	1.00
Sulfonylurea, n (%)	16 (57.14)	72 (51.43)	0.58
Glipizide, n (%)	14 (50)	67 (47.86)	0.84
Glibenclamide, n (%)	2 (7.14)	0	0.001
Glimepiride, n (%)	0	1 (0.71)	0.65
Gliclazide, n (%)	0	4 (2.86)	0.37
Pioglitazone, n (%)	5 (17.86)	40 (28.57)	0.12
DPP4 inhibitor, n (%)	3 (10.7)	22 (15.71)	0.50
Sitagliptin, n (%)	2 (7.14)	17 (12.14)	0.45
Alogliptin, n (%)	1 (3.57)	3 (2.14)	0.65
Vildagliptin, n (%)	0	1 (0.71)	0.65
Linagliptin, n (%)	0	1 (0.71)	0.65
SGLT2 inhibitor, n (%)	0	11 (7.86)	0.13
Empagliflozin, n (%)	0	7 (5)	0.23
Dapagliflozin, n (%)	0	3 (2.14)	0.43
Luseogliflozin, n (%)	0	1 (0.71)	0.65
Insulin, n (%)	3 (10.71)	13 (9.29)	0.81
ACEI/ARB usage, n (%)	14 (50)	76 (54.29)	0.68
Enalapril, n (%)	10 (35.71)	37 (26.43)	0.32
Ramipril, n (%)	0	1 (0.71)	0.65
Losartan, n (%)	4 (14.29)	33 (23.57)	0.49
Irbesartan, n (%)	0	2 (1.43)	0.53
Azilsartan, n (%)	0	2 (1.43)	0.53
Telmisartan, n (%)	0	2 (1.43)	0.53

and maximum lactate levels were not different between the two groups. However, AST and INR were higher in non-survivors (Table 2).

For treatment, non-survivors received a higher bolus dose of sodium bicarbonate ($NaHCO_3$) ($p<0.001$). All MALA patients underwent renal dialysis. The mode and dose of renal replacement therapy did not affect mortality (Table 3).

The mortality rate of MALA patients was 21.43% (Table 4). No association between ACEI/ARB usage and MALA was observed (COR 0.84, 95% CI 0.37 to 1.90) (Table 5). Nevertheless, the presence of COPD was a significant risk factor for MALA (COR 16.68, 95% CI 1.67 to 166.85).

Table 2. Clinical presentation of MALA patients (case group)

Factor	Death (n=6)	Alive (n=22)	p-value
Basic characteristic			
Sex, male, n (%)	1 (16.67)	10 (45.45)	0.20
Age, median (IQR)	75 (73.25 to 78.25)	62.50 (60.25 to 74.50)	0.07
Ideal body weight, median (IQR)	52 (45.25 to 52)	59 (48 to 60.75)	0.36
APACHE II score, median (IQR)	23.5 (21 to 26.3)	18.50 (18 to 24.75)	0.26
SOFA score, median (IQR)	8 (7.25 to 8.75)	4 (4 to 8)	0.18
Body temperature, median (IQR)	35.25 (35.20 to 35.83)	36.60 (36 to 36.60)	0.07
Pulse rate, median (IQR)	86 (76 to 98.25)	97 (83.75 to 108.50)	0.36
Respiratory rate, median (IQR)	26 (22.50 to 29.50)	21 (20 to 29)	0.41
Mean arterial pressure, median (IQR)	73.5 (68 to 76.75)	101.50 (65.25 to 97.75)	0.07
SpO_2, median (IQR)	99 (98.25 to 99.75)	100 (97.25 to 99.75)	0.77
Symptoms			
Hypoglycemia, n (%)	1 (16.67)	8 (36.36)	0.36
Circulatory failure, n (%)	6 (100)	12 (54.55)	0.04
Oliguria, n (%)	4 (66.67)	12 (54.55)	0.595
Alteration of consciousness, n (%)	4 (66.67)	5 (22.73)	0.04
Nausea and vomiting, n (%)	5 (83.33)	18 (81.82)	0.93
Diarrhea, n (%)	5 (83.33)	11 (50)	0.14
Underlying disease and comorbidity			
Hypertension, n (%)	4 (66.67)	15 (68.18)	0.94
COPD, n (%)	0	3 (13.64)	0.34
AKI, n (%)	6 (100)	22 (100)	1.00
CKD, n (%)	2 (33.33)	7 (31.82)	0.94
Cirrhosis, n (%)	1 (16.67)	0	0.05
Acute hepatitis, n (%)	1 (16.67)	1 (4.55)	0.31
Solid tumor, n (%)	0	2 (9.09)	0.44
NSAID usage, n (%)	1 (16.67)	3 (13.64)	0.85
Metformin dose (mg), median (IQR)	1,500 (1,125 to 1,875)	2,275 (1,700 to 2,357)	0.06
Initial laboratory			
Hemoglobin; gm, median (IQR)	10.10 (8.73 to 11.33)	10.60 (10.08 to 11.80)	0.36
AST; U/dL, median (IQR)	44.5 (39 to 62)	28.50 (24 to 36.75)	0.04
ALP; U/dL, median (IQR)	79 (69 to 81.50)	132.50 (57.25 to 82)	0.36
Total bilirubin; mg/dL, median (IQR)	0.65 (0.35 to 1.55)	0.50 (0.20 to 0.40)	0.18
INR, median (IQR)	2.04 (1.68 to 4.27)	1.05 (0.97 to 1.23)	0.006
Blood glucose; mg/dL, median (IQR)	187.50 (146.75 to 208.75)	93.50 (60.25 to 191)	0.07
BUN; mg/dL, median (IQR)	37.80 (31.18 to 46.08)	58.95 (57.40 to 82.23)	0.07
Creatinine; mg/dL, median (IQR)	4.66 (3.60 to 4.95)	6.59 (6.53 to 10.32)	0.07
pH, median (IQR)	7.09 (7 to 7.23)	7.10 (6.94 to 7.14)	0.36
HCO_3; mEq/L, median (IQR)	7.70 (4.08 to 11.25)	9.15 (3.60 to 9.03)	0.84
Initial lactate; mmol/L, median (IQR)	14.94 (11.37 to 23.23)	14.88 (11.54 to 19.43)	0.36
Maximum lactate; mmol/L, median (IQR)	24.85 (20.94 to 31.11)	20.02 (12.66 to 24.81)	0.36

Table 3. Treatment of MALA patients (case group)

Factor	Death (n=6)	Alive (n=22)	p-value
Supportive treatment			
Invasive mechanical ventilation, n (%)	5 (83.33)	12 (54.55)	0.20
Intravenous vasopressor, n (%)	6 (100)	12 (54.55)	0.04
Bicarbonate intravenous			
7.5% $NaHCO_3$ bolus, n (%)	6 (100)	20 (90.91)	0.44
7.5% $NaHCO_3$ bolus dose (meq), median (IQR)	289.90 (267.60 to 312.20)	178.40 (89.20 to 334.50)	<0.001
7.5% $NaHCO_3$ drip, n (%)	2 (33.3)	7 (31.82)	0.94
7.5% $NaHCO_3$ continuous dose, median (IQR)	0 (0 to 66.90)	0 (0 to 59.13)	0.14
Renal replacement therapy (RRT)			
IHD, n (%)	0	8 (36.36)	0.08
Continuous RRT (CRRT)	n=6	n=16	
CVVH, n (%)	3 (50)	9 (40.91)	0.89
CVVHD, n (%)	2 (33.33)	1 (4.55)	0.12
CVVHDF, n (%)	1 (16.67)	6 (27.27)	0.31
CRRT dose; ml/kg/hr, mean (SD)	29.5 (29, 33)	30 (30.5, 40)	0.31

Table 4. Mortality outcome

Factor	Result
Hospital mortality, n (%)	6 (21.43)
Hospital LOS, median (IQR)	11.50 (8 to 16.25)
ICU mortality, n (%)	5 (17.86)
ICU LOS, median (IQR)	5 (4 to 6.25)
28-day mortality, n (%)	6 (21.43)

Table 5. Crude Odds ratio (COR) and primary outcome

Factor	COR	95% CI
ACEI/ARB usage	0.84	0.37 to 1.90
COPD	16.68	1.67 to 166.85
Age ≥70 years	1.06	0.47 to 2.38
CKD	2.18	0.88 to 5.37
MFM usage ≥2,000 mg	1.34	0.59 to 3.07
NSAIDs usage	3.17	0.86 to 11.66

Discussion

Our observational study demonstrated that concomitant usage of ACEI/ARB was not associated with the development of MALA. This is supported by a previous cohort study, which showed that the risk of AKI after ACEI/ARB treatment was scant (adjusted RR 1.14 and 1.06 for ACEI and ARB, respectively)[15]. Furthermore, most patients in our study were on the same tolerable doses of ACEI/ARB for quite some time, unlike patients with new ACEI/ARB treatment or recently increased doses of ACEI/ARB, who are more at risk of AKI.

NSAIDs user seems to be more susceptible to MALA[14], though not statistically significant. This could be attributed to the retrospective nature of the study and the numerous over-the-counter medications in Thailand. Despite the insignificance of sulfonylurea usage, our study suggested that there was possibly an interaction between glibenclamide usage and MALA development. This might be a result of the pharmacokinetics of glibenclamide. Compared to other sulfonylureas, glibenclamide has a longer half-life and potential accumulation of its metabolites in patients with eGFR <60 mL/min/1.73 m^2. Therefore, glibenclamide is not recommended in patients with reduced renal function[16]. We presumed that glibenclamide usage in renal failure patients could precipitate MALA. Still, the mechanism was not known and needs further study.

AKI was present in all MALA cases, while CKD was not statistically different between cases and controls. This could be because all CKD patients in the present study had eGFR between 30 to 59 mL/min/1.73 m^2, which is approved to be safe by the FDA[17]. Our results underlined that metformin accumulation on account of renal failure is key in the pathophysiology of MALA. Although COPD, which is usually accompanied by hypoxemia, and acute hepatitis are both known risk factors for elevated plasma lactate levels, our results highlighted a stronger correlation of these factors to MALA incidence, compared to other studies.

The risks associated with unfavorable outcomes included circulatory failure, alteration of consciousness, and acute hepatitis with elevated AST and INR, but not lactate levels. The severity index, assessed with APACHE II score and SOFA score, was also higher in non-survivors. These findings were consistent with previous studies, which found that poor prognostic factors in MALA patients were shock state and high APACHE II score[18], and lactate levels had no prognostic value[19,20]. Seidowsky et al. also demonstrated that PT activity was the best predictive factor of death[21]. Thereby, acute liver dysfunction evaluated by PT or INR could be the other major prognostic factor in MALA.

Regarding treatment modalities, there was no correlation between types of renal replacement therapy and mortality. However, the higher dose of $NaHCO_3$ was associated with more fatal outcomes. This could be explained by either the more severe disease nature in non-survivors or the negative effects of $NaHCO_3$. Possible risks of $NaHCO_3$ administration included hypocalcemia, increased plasma CO_2, and intracellular acidification[22]. In the present day, the benefit of $NaHCO_3$ administration remains controversial in MALA.

In the present study, the mortality rate (21.43%) is lower than in previous reports. This may be the result of an improvement in ICU care, as well as our study design, which excluded patients with infection.

Our study had limitations due to an observational design with the recall bias by the study's design. Several unaccounted confounding factors may have played a role in the results. In addition, we could not evaluate serum metformin levels in our center. The suggestion for further prospective studies to improve the knowledge gap of ACEI/ARB titration dose can affect the occurrence of MALA. If the initiation and the titration of ACEI/ARB are not associated with MALA, this outcome could reassure physicians to start these medications without concern about AKI/MALA.

Conclusion

According to this study, ACEI/ARB usage was not associated with MALA occurrence. The tolerable dose of ACEI/ARB can be safely prescribed together with metformin. However, serum creatinine and eGFR should be monitored in the setting of ACEI/ARB initiation or titration, concerning AKI.

What is already known on this topic?

ACEI/ARB are the recommended antihypertensive agents in diabetic patients[11]. Thus, ACEI/ARB usage, which possibly causes acute kidney injury (AKI), is reported as a contributor to MALA occurrence[12,13].

What this study adds?

After analyzing the association between ACEI/ARB usage and MALA occurrence by case-control study, the findings support and encourage continued use of ACEI/ARB in hypertensive patients with diabetic patients for non-occurring complications risk as MALA.

Conflicts of interest

The authors declare no conflict of interest.

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ความสัมพันธ์ระหว่างการใช้ยา Angiotensin converting enzyme inhibitor (ACEI) หรือ ยา Angiotensin receptor blocker (ARB) กับการเกิดภาวะเลือดเป็นกรดแล็กติกจากการใช้ยาเมทฟอร์มินในผู้ป่วยเบาหวาน

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ภูมิหลัง: การรักษาด้วยยาเมทฟอร์มินมีภาวะแทรกซ้อนที่สำคัญคือภาวะเลือดเป็นกรดแล็กติก ซึ่งมีอุบัติการณ์ต่ำแต่มีอัตราการตายที่สูง ปัจจัยหลักคือภาวะไตวายฉับพลันซึ่งสามารถเกิดจากยากลุ่ม ACEI/ARB ที่ใช้ร่วมรักษาความดันโลหิตสูง และอาจสัมพันธ์กับการเกิดภาวะเลือดเป็นกรดแล็กติกจากการใช้ยาเมทฟอร์มินในผู้ป่วยเบาหวานได้

วัตถุประสงค์: เพื่อหาความสัมพันธ์ระหว่างใช้ยากลุ่ม ACEI/ARB กับการเกิดภาวะเลือดเป็นกรดแล็กติกจากการใช้ยาเมทฟอร์มิน

วัสดุและวิธีการ: เป็นการศึกษาโดยมีกลุ่มควบคุมโดยกำหนดอัตราส่วนกลุ่มโรค 1 ส่วน ต่อกลุ่มควบคุม 5 ส่วน ซึ่งกลุ่มโรคเป็นผู้ป่วยวิกฤตอายุรกรรมที่มีภาวะเลือดเป็นกรดแล็กติกจากการใช้ยาเมทฟอร์มินจำนวน 28 คน ส่วนกลุ่มควบคุมเป็นผู้ป่วยโรคเบาหวานที่ได้รับยาเมทฟอร์มินโดยมีการสุ่มกำหนดเพศ ช่วงอายุ และขนาดยาเมทฟอร์มิน จำนวน 140 คน

ผลการศึกษา: กลุ่มโรค 28 คน เป็นเพศหญิงร้อยละ 60.71 มีอายุเฉลี่ยค่า 69.50 (61 ถึง 76) ปี ได้รับยาเมทฟอร์มินเฉลี่ย 2,000 (1,500 ถึง 2,000) มิลลิกรัมต่อวัน ได้รับยากลุ่ม ACEI/ARB ร้อยละ 50 มีภาวะไตวายฉับพลันร้อยละ 100 ระดับกรดแล็กติกในเลือดแรกรับและระดับสูงสุดเฉลี่ย 17.79 (11.28 ถึง 19.79) และ 20.58 (16.24 ถึง 26.50) มิลลิโมล/ลิตรตามลำดับ ความเป็นกรดในเลือดแรกรับเฉลี่ย 7.01 (6.94 ถึง 7.18) อัตราการตายร้อยละ 21.43 ไม่พบความสัมพันธ์ระหว่างการใช้ยากลุ่ม ACEI/ARB กับการเกิดภาวะเลือดเป็นกรดแล็กติกจากการใช้ยาเมทฟอร์มินในผู้ป่วยเบาหวานอย่างมีนัยสำคัญทางสถิติ กลุ่มโรคร้อยละ 50 กลุ่มควบคุมร้อยละ 54.29 ความเสี่ยง Odds ratio of 0.84 (p=0.68, 95% CI 0.37 ถึง 1.90)

สรุป: ไม่พบความสัมพันธ์ระหว่างการใช้ยากลุ่ม ACEI/ARB กับการเกิดภาวะเลือดเป็นกรดแล็กติกจากการใช้ยาเมทฟอร์มินในผู้ป่วยเบาหวาน