



# A Claims Database Analysis of Dose-Dependency of Metformin and Incidence of Lactic Acidosis in Japanese Patients with Type 2 Diabetes

Yoshio Nagai · Kiyoyasu Kazumori · Tomomi Takeshima ·  
Kosuke Iwasaki · Yasushi Tanaka

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## ABSTRACT

**Introduction:** Patients with type 2 diabetes (T2D) in Japan are prescribed a lower dose of metformin than their counterparts in Western countries due to concerns for the risk of lactic acidosis incidence. Here we report our study on the association between high-dose metformin administration and the incidence of lactic acidosis in Japanese patients with T2D.

**Methods:** A Japanese claims database (April 2008–November 2018) was analyzed. Factors associated with the incidence of lactic acidosis were first identified from the database records by conducting a case–control study, and these were then used as confounding factors in

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Y. Nagai  
Department of Medicine, Metabolism and  
Endocrinology, St. Marianna University School of  
Medicine, Kanagawa, Japan

K. Kazumori (✉)  
Medical Affairs, Sumitomo Dainippon Pharma Co.,  
Ltd., Tokyo, Japan  
e-mail: kiyoyasu-kazumori@ds-pharma.co.jp

T. Takeshima · K. Iwasaki  
Milliman Inc, Tokyo, Japan

Y. Tanaka  
Diabetes Center, Yokohama General Hospital,  
Kanagawa, Japan

subsequent analyses. The association between high-dose metformin administration ( $\geq 1000$  mg/day) and the incidence of lactic acidosis was compared with that between low-dose metformin ( $< 1000$  mg/day) or no metformin administration and lactic acidosis incidence by using the following approaches: a logistic regression analysis hypothesizing that metformin-associated lactic acidosis is short term; a time-dependent proportional hazard model hypothesizing that the influence of metformin is cumulative; and a case–control study in which lactic acidosis incidence was the case and metformin administration within 3 months prior to the incidence of lactic acidosis (or corresponding date for the control) was the exposure.

**Results:** Prescriptions for biguanide and vitamin B complex and volume depletion were identified as factors associated with the incidence of lactic acidosis. The incidence rate was higher in patients prescribed metformin than in those not receiving metformin; however, it was not higher in those prescribed high-dose metformin compared to those prescribed low-dose metformin. The estimated regression coefficient for high-dose metformin administration was 0.816 ( $p < 0.001$ ); this was not higher than those for low-dose metformin (1.047), vitamin B complex (2.725) and volume depletion (3.301). The time-dependent proportional hazard analysis did not indicate any effect of metformin prescription.

**Conclusion:** The results suggest an association between metformin administration and the incidence of lactic acidosis, but an increase in the incidence rate of lactic acidosis was not observed in those patients receiving high-dose metformin compared to those receiving low-dose metformin.

**Keywords:** Case–control study; Claims database; Dose increased; Hypovolemia; Lactic acidosis; Metformin; Time-dependent proportional hazard model; Type 2 diabetes; Vitamin B complex

### Key Summary Points

#### Why carry out this study?

Patients with type 2 diabetes (T2D) in Japan are prescribed a lower dose of metformin than their counterparts in Western countries due to concerns for the risk of lactic acidosis incidence.

Lactic acidosis is considered to be the most serious side effect of metformin, and the package inserts of metformin mention the possibility of serious lactic acidosis in patients with risk factors, such as renal or hepatic dysfunction, and older age. However, no association of metformin administration with lactic acidosis has been reported.

We examined whether high-dose metformin administration ( $\geq 1000$  mg/day) increases the risk of incidence of lactic acidosis in patients with T2D using Japanese claims database. We also investigated the factors associated with the incidence of lactic acidosis in these patients.

#### What was learned from the study?

The incidence rate of lactic acidosis was not higher in patients prescribed high-dose metformin than in those on low-dose metformin.

The estimated regression coefficient in the logistic regression for the incidence of lactic acidosis was positive for high-dose metformin administration, but it was not higher than that for low-dose metformin administration; factors identified as those associated with the incidence of lactic acidosis were prescriptions for vitamin B complex and diagnosis of volume depletion.

The results suggest an association of metformin administration with the incidence of lactic acidosis incidence; however, an increase in the incidence rate was not observed among patients administered high-dose metformin compared with low-dose metformin.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13746808>.

## INTRODUCTION

For a long time, metformin has been used at a lower dose in Japan than in European countries and the USA despite evidence on its dose-dependent hypoglycemic effect [1, 2]. The validity and safety of high-dose metformin have been demonstrated in large-scale clinical studies, including the UK Prospective Diabetes Study (UKPDS) [3]. In the clinical guidelines of Western countries, metformin is a first-line hypoglycemic drug used for managing type 2 diabetes (T2D) [4]. However, owing to multiple reports of deaths overseas in the 1970s due to lactic acidosis associated with the use of phenformin, regulatory authorities in Japan placed restrictions on the maximum dosage of metformin which, like phenformin, belongs to the

biguanide class of drugs. In 2010, the recommended dosage levels of metformin were revised in Japan, with the normal maintenance dose increased to 750–1500 mg/day and the maximum prescription dose increased to 2250 mg/day. However, the average daily prescription dose has continued to be at < 1000 mg/day in many patients in clinical settings [5, 6].

Lactic acidosis is considered to be the most serious side effect of metformin [7, 8], and the package inserts of metformin describe the possibility of serious lactic acidosis in patients with risk factors, such as renal or hepatic dysfunction and older age [9]. Lactic acidosis is a disease with poor prognosis and is a form of metabolic acidosis caused by the build-up of lactic acid in the blood as a result of the overproduction of lactate or its decreased metabolism [10]. However, to our knowledge, there have been no reports to date of an association of metformin administration with lactic acidosis and an elevated risk in patients having comorbidities, such as renal impairments. For example, some meta-analyses studies have reported that there is no evidence associating metformin administration with an increase in lactic acid level and incidence of lactic acidosis [11, 12]. It has also been reported that the incidence rate of lactic acidosis in patients using metformin ranges from 3.3 to 9.7 per 100,000 person-years, which is comparable to that of patients who do not use metformin, which ranges from 4.8 to 9.9 per 100,000 person-years [11–14]. The majority of the cases in which the incidence of lactic acidosis has been associated with the use of a biguanide are those noted as an administration contraindication or careful administration [10, 15]. In 1972, the *Lancet* published an article that indicated an association between metformin administration and incidence of lactic acidosis; the same article also highlighted a possible contraindication of metformin in diabetic patients with chronic kidney disease, but not in those without such comorbidities [16].

The association between the dose of metformin and incidence of lactic acidosis has not

been elucidated in patients with T2D in clinical practice in Japan. A Japanese cohort study using a claims database provided by Medical Data Vision Co., Ltd. (MDV; Tokyo, Japan; the same database as used in the present study) for the period January 2010 to August 2014 reported that the incidence of lactic acidosis was not associated with metformin administration in patients with T2D treated with antidiabetic drugs, including those with comorbidity of chronic hepatic or renal disease [17]. In this study, the dose of metformin administered to the patients who developed lactic acidosis was in a range of 500–1000 mg/day. Also, the authors of this study concluded that chronic renal disease appeared to be a risk factor of lactic acidosis regardless of the dose of metformin administered. In another Japanese observational study conducted in a hospital, 290 metformin-treated patients with an average age of  $59.3 \pm 11.3$  years were examined [18]. The lactate levels were found to be significantly higher in those patients receiving  $\geq 1000$  mg/day of metformin than in those receiving < 1000 mg/day of metformin, and the lactate levels were found to be unaffected by patient age or kidney function [18]. Notably, no patient developed lactic acidosis during the observational period in that study.

The lower metformin dose administered in Japan compared to other countries may lead to insufficient glycemic control in patients on metformin monotherapy. However, concern about the incidence of lactic acidosis is one of the main reasons for choosing low-dose metformin. Therefore, if it can be demonstrated that an increased dose of metformin is not associated with an (increased) incidence of lactic acidosis, then it may be possible to facilitate the administration of a sufficient dose of metformin for glycemic control. In the study reported here, we examined whether high-dose metformin administration ( $\geq 1000$  mg/day) increases the risk of incidence of lactic acidosis in patients with T2D by using a Japanese claims database. We also investigated the factors

associated with the incidence of lactic acidosis in these patients.

## METHODS

### Study Design

The aim of this study was to determine whether the risk of incidence of lactic acidosis is higher in patients prescribed high-dose metformin than in those prescribed low-dose metformin ( $\geq 500$  and  $< 1000$  mg/day) or no metformin at all. We first identified the factors associated with the incidence of lactic acidosis by conducting a case–control study in which the incidence of lactic acidosis was the case (study 1). The factors thus identified were then used as the confounding factors and adjusted in patients for comparing the risk of incidence of lactic acidosis.

The effects of high-dose metformin administration on the incidence of lactic acidosis were investigated using three approaches. First, we conducted a study with the hypothesis that the influence of metformin on the incidence of lactic acidosis is short term, in which we compared the incidence rates for each month (study 2). Secondly, we conducted a study with the hypothesis that the influence of metformin on the incidence of lactic acidosis is cumulative, in which a time-dependent proportional hazard model was used (study 3). Thirdly, we conducted a case–control study, in which the incidence of lactic acidosis was the case and metformin administration within 3 months prior to the incidence of lactic acidosis (or corresponding date for the control) was the exposure (study 4).

The incidence of lactic acidosis was defined as a hospitalization record with the first diagnosis of lactic acidosis, as indicated by the disease name ‘lactic acidosis.’

### Data Source

We used a claims database (April 2008–November 2018) provided by MDV that contains data from Diagnosis Procedure

Combination (DPC) hospitals, which are Japanese acute care hospitals that have adopted the DPC/Per-Diem Payment System [19]. The database contained data from 28,400,000 patients in 385 hospitals, which accounts for 22% of acute medical institutions as of August 2019. The database includes the records of all patients who visited the affiliated DPC hospitals, regardless of the age of the patient and the type of health insurance; however, records from other medical institutions are not included.

The observation period for each patient was defined as the period between the first and last date of any medical intervention recorded in the database. The date of first diagnosis of each disease was recorded as ‘FromDate’, irregardless of whether the date fell within or outside the observation period; thus, the earliest ‘FromDate’ was defined as the date of first diagnosis of each disease in this study. Notably, in this study, a definite diagnosis, but not a suspicious diagnosis, was considered as diagnosis.

### Definition of Patients

We defined patients with T2D as those (1) having records of diagnosis of T2D defined by International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10) codes E11 (T2D) or E14 (unspecified diabetes) [20]. It should be noted that the diagnosis of T2D was often coded as E14 in the database; thus the code E14 was also included here to define patients with T2D; (2) age  $\geq 18$  years at the time of the first diagnosis of T2D; (3) not having records of type 1 diabetes (defined as ICD-10 code E10); (4) not having records of diagnosis of lactic acidosis defined by the disease name ‘lactic acidosis’ before the first metformin administration (metformin administration was defined using any prescription record with the generic name of metformin or metformin hydrochloride; and (5) not having any records of diagnosis of diseases associated with mitochondrial disease, such as mitochondrial diabetes and encephalomyopathy. The exclusion of patients with the abovementioned diseases was applied because these diseases are likely to induce lactic acidosis.

For study 1, patients identified as having a diagnosis of lactic acidosis were identified for the case group. The control group comprised patients extracted from the database who were matched to those in the case group by sex, birth year, the start (year, month) of the observation period and the end (year, month) of the observation period, but without any reported incidence of lactic acidosis. In study 2, patients were evaluated on the basis of months (patient-month) and divided into the following three groups on the basis of the status of metformin prescription in each of the corresponding months: (1) high-dose metformin group: the month in which  $\geq 1000$  mg/day of metformin was administered at least once; (2) low-dose metformin group: the month in which  $\geq 500$  mg/day, but not  $\geq 1000$  mg/day, metformin was administered at least once and (3) no metformin group: month without metformin administration. In study 3, patients who had received metformin at least once and with  $\geq 3$  months of observation period before the first metformin administration were identified, and then those who were prescribed  $< 500$  mg/day of metformin were excluded. For study 4, patients with a reported incidence of lactic acidosis were identified for the case group. The control group comprised patients extracted from the database who were matched to those in the case group by sex, birth year, the start (year, month) of observation period and the end (year, month) of the observation period, but without any reported incidence of lactic acidosis, and the existence of confounding factors selected in study 1 during the 3 months before the index date was examined.

### Outcomes and Statistical Analysis

In study 1, factors associated with the incidence of lactic acidosis were explored from the following factors during 3 months before the index date: diagnoses as the first three digits of the ICD-10 codes; drugs as the first 4 digits of the Anatomical Classification (ATC) of Pharmaceutical Products by the European Pharmaceutical Market Research Association [21];

operations according to the names of procedures containing words indicating operation with the medical care identifying code 50, i.e. operation, the use of a contrast agent defined by the name of the procedure including the words 'contrast agent' and the use of intensive care unit defined by the name of procedure containing the words 'intensive care unit.' The logistic regression analysis was performed with the above-mentioned factors as explanatory variables and the incidence of lactic acidosis as the explained variable, and adopted the stepwise method. The significance of the difference was assessed on the basis of  $p < 0.05$ . The index date was defined as the date of the incidence of lactic acidosis for the case group, and the date corresponding to the index date was used in the matched patients in the control group.

In study 2, the following two methods were used to compare the incidence rates of lactic acidosis for each group in each observation month. In study 2-1, the incidence rate as patient-months was calculated for all patient-months and for each quantile of patient-months classified by the propensity scores by the groups. The propensity scores were developed using a logistic regression model to predict an order value corresponding to the following order: high-dose metformin group, low-dose metformin group and no metformin group. In the predictive models, the following explanatory variables were selected as confounding factors for the incidence of lactic acidosis: age, sex (1: men, 2: women), seasons (spring: March–May, summer: June–August, autumn: September–November, which were used as dummy variables; 1: yes, 0: no, for each season) and the existence of the factors selected by study 1. The average treatment effect was estimated between two groups to assess the differences between the groups. The statistical significance of the difference was evaluated on the basis of 95% confidence intervals (95% CIs) calculated using the Wald method.

As Study 2-2, a logistic regression analysis was conducted to evaluate the contribution of metformin dose to the incidence of lactic acidosis. A dummy variables (1: yes, 0: no) expressing the presence or absence of incidence of lactic acidosis was used as explained variable.

The same confounding factors as those for the development of propensity scores for study 2-1 and variables of the low-dose metformin (1: with administration of low-dose metformin at least once and no high-dose metformin in the corresponding month, 0: others) and high-dose metformin (1: with administration of high-dose metformin at least once, 0: others) were used as explanatory variables.

In study 3, a time-dependent proportional hazard regression analysis was conducted to evaluate the association of confounding factors, including the cumulative effect of a metformin prescription, with the incidence of lactic acidosis. Age, sex (1: men, 2: women) and the existence of the factors selected in study 1 during the 3 months before the first prescription of metformin were used as explanatory variables, and a prescription of low-dose metformin (1: prescribed low-dose metformin, 0: others) and of high-dose metformin (1: prescribed high-dose metformin, 0: others) were used as time-dependent explanatory variables. The explained variable was time (in months) to the incidence of lactic acidosis.

In study 4, the number of patients who received either high-dose metformin or low-dose metformin during the 3 months before the index date were determined for each group, and then the odds ratios were obtained as high-dose metformin versus low-dose metformin, low-dose metformin versus no metformin and high-dose metformin versus no metformin. For the case group, the index date was defined as the date of the incidence of lactic acidosis and the date corresponding to the index date of the matched patient in the case group.

The analyses were conducted using SAS ver. 9.4 (SAS Institute, Cary, NC, USA) and Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA).

### Compliance with Ethics Guidelines

The study was approved by the ethics committee of St. Marianna University School of Medicine (No. 4407). As the study only involved analysis of pre-existing data in databases, written informed consent from the study

participants was not required. Clinical trial registration was not required for this study because it was not a prospective study and did not involve any intervention.

## RESULTS

### Factors Associated With Lactic Acidosis Incidence

The total number of patients in study 1 were 1401 (including both the case and control groups). The mean age  $\pm$  standard deviation (SD) was  $69.98 \pm 13.69$  years, and the percentage of women was 35.19%.

The factors identified as being associated with the incidence of lactic acidosis were ICD-10 code E86 and ATC codes A10J and A11E (Table 1). Because the prescription of biguanide antidiabetics with the ATC code A10J included the prescription of metformin, we used the diagnosis of volume depletion, with ICD-10 code E86, and the prescription of vitamin B complex, with ATC code A11E, as the confounding factors for subsequent studies.

**Table 1** Factors that were significantly different between the case and control groups

Factors	Explanation
ICD-10 code E86	Volume depletion—dehydration, hypovolemia, extracellular fluid volume depletion and abnormally decreased volume of circulating fluid (plasma) in the body
ATC code A10J	Biguanide antidiabetics (including metformin)
ATC code A11E	Vitamin B complex, including combinations

*ATC* Anatomical Classification, *ICD-10* International Statistical Classification of Diseases and Related Health Problems, 10th revision

**Table 2** Target patient population for the analysis and the patient characteristics

Group	Number of patient-months	Age <sup>a</sup> (years)	Women (%)	Code E86 <sup>b</sup> (%)	Code A11E <sup>c</sup> (%)
HD metformin group	3,125,753	60.40 ± 11.66	37.99	1.06	0.18
LD metformin group	4,093,378	65.69 ± 11.43	40.13	1.42	0.26
No metformin group	83,902,106	69.04 ± 12.80	43.05	1.73	0.29

HD high-dose, LD low-dose

<sup>a</sup> Average ± standard deviation (SD)

<sup>b</sup> Percentage of patient-months with ICD-10 code E86 (volume depletion)

<sup>c</sup> Percentage of patient-months with ATC code A11 (vitamin B complex)

**Table 3** Incidence rate of lactic acidosis

Incidence rate of lactic acidosis before adjustment for confounding factors	Number of patient-months	Number of incidences of lactic acidosis (patient-months)	Incidence rate of lactic acidosis (95% CI lower limit, upper limit) (patient-months/100,000 patient-months)
HD metformin group	3,125,753	136	4.35 (3.65, 5.15)
LD metformin group	4,093,378	243	5.94 (5.21, 6.73)
No metformin group	83,902,106	1,834	2.19 (2.09, 2.29)
Comparison between the groups after adjustment for confounding factors			Difference in the incidence rate of lactic acidosis between groups (95% CI lower limit, upper limit) (patient-month/100,000 patient-months)
HD metformin group vs. LD metformin group			− 1.69 (− 2.77, − 0.61)
LD metformin group vs. no metformin group			3.55 (2.77, 4.32)
HD metformin group vs. no metformin group			2.14 (1.09, 3.19)

HD high-dose, LD low-dose

### Short-Term Effects of Metformin Administration on Incidence of Lactic Acidosis

Table 2 presents the number of patient-months and the characteristics of the target patient population in each group for the analysis. The mean age and percentage of women (69.04 ± 12.80 years and 43.05%, respectively) were the highest in the no metformin group. The percentages of patient-months with the diagnosis of volume depletion (1.73%) and vitamin B complex administration (0.29%) were also highest in the no metformin group.

In study 2–1, the incidence rate of lactic acidosis was highest in the low-dose metformin group, 5.94 (95% CI 5.21–6.73) patient-months/100,000 patient-months, followed by the high-dose metformin group, 4.35 (95% CI 3.65–5.15) patient-months/100,000 patient-months and the no metformin group, 2.19 (95% CI 2.09–2.29) patient-months/100,000 patient-months (Table 3). In those patients who developed lactic acidosis, the mean age in the no metformin group (69.9 ± 15.0 years) was higher than that in the other groups prescribed metformin (low-dose: 64.4 ± 11.6 years; high-dose 58.7 ± 12.3 years), and the percentage of patients diagnosed with volume depletion and

**Table 4** Regression coefficient of each parameter in the logistic regression analysis

Parameter <sup>a</sup>	Regression coefficient	Standard error	<i>p</i> value
Age	− 0.004	0.002	0.010
Sex	− 0.305	0.044	< 0.001
HD metformin	0.816	0.090	< 0.001
LD metformin	1.047	0.069	< 0.001
E86	3.301	0.047	< 0.001
A11E	2.725	0.070	< 0.001
Spring	− 0.027	0.063	0.673
Summer	0.021	0.061	0.728
Autumns	0.056	0.061	0.354

<sup>a</sup> Parameters: Sex: men (1) or women (2); HD metformin: prescribed HD metformin at least once (1) or others (0); LD metformin: prescribed LD metformin at least once and no high-dose metformin in the corresponding month (1) or others (0); E86: presence (1) or absence (0) of diagnosis of ICD-10 code E86 (volume depletion); A11E: presence (1) or absence (0) of administration of ACT code A11E (vitamin B complex); seasons (spring: March–May; summer: June–August; autumn: September–November): for the corresponding season (1) or others (0)

prescribed vitamin B complex were highest in the no metformin group (41.88 and 13.96% vs. 6.17 and 2.47% in low-dose group and 18.38 and 2.21% in the high-dose group) (Electronic Supplementary Material Table S1). In the comparison between the groups after adjustment for confounding factors, the order of the incidence rate remained the same, with the low-dose metformin group remaining the highest, followed by the high-dose metformin group and then by the no metformin group (Table 3).

The logistic regression analysis in study 2–2 indicated that lower age, male sex, diagnosis of volume depletion, administration of vitamin B complex and administration of metformin were associated with the incidence of lactic acidosis (Table 4). Seasonal variables showed no

**Table 5** Hazard ratio of each clinical parameter for the incidence of lactic acidosis by the time-dependent proportional hazard analysis

Parameter <sup>a</sup>	Hazard ratio	<i>p</i> value
Age	0.991	0.192
Sex	0.981	0.916
HD metformin	0.78	0.680
LD metformin	0.616	0.410
E86	0.533	0.379
A11E	8.344	< 0.001

<sup>a</sup> Parametersex: men (1) or women (2); HD metformin: prescribed HD metformin at least once (1) or other (0); LD metformin: prescribed LD metformin at least once and no high-dose metformin in the corresponding month (1) or other (0); E86: presence (1) or absence (0) of diagnosis of ICD-10 code E86 (volume depletion) during 3 months before the first prescription of metformin; A11E: presence (1) or absence (0) of administration of ATC code A11E (vitamin B complex) during 3 months before the first prescription of metformin

significant association with the incidence. The regression coefficients for the diagnosis of volume depletion (3.301;  $p < 0.001$ ) and administration of vitamin B complex (2.725;  $p < 0.001$ ) were higher than those for the administration of both low-dose (1.047;  $p < 0.001$ ) and high-dose (0.816;  $p < 0.001$ ) metformin, and the regression coefficient was higher for low-dose than for high-dose metformin administration (Table 4).

### Cumulative Effects of Metformin Administration on Incidence of Lactic Acidosis

There were 118,041 target patients, with a mean age of  $63.97 \pm 12.81$  years; 37.66% were women. The time-dependent proportional hazard analysis indicated that the hazard ratio (HR) of vitamin B complex administration was  $> 1$  and statistically significant (HR 8.344;  $p < 0.001$ ); all other parameters did not show statistical significance (Table 5).



**Table 6** The number of patients receiving high-dose metformin, low-dose metformin and no metformin in the case and control groups

Number of patients	Total	HD metformin	LD metformin	No metformin
Total	2118	222	116	1780
Control group	1059	51	27	981
Case group	1059	171	89	799

### Case–Control Study on Metformin Administration as Related to the Incidence of Lactic Acidosis

In the case–control study there were 1059 patients in each group, with a mean age of  $70.11 \pm 12.30$  years; the percentage of women was 33.52%. The number of patients in each group receiving high-dose metformin, low-dose metformin and no metformin, respectively, is listed in Table 6. The odds ratios between the two groups were 1.02 (95% CI 0.60–1.73) for high-dose metformin versus low-dose metformin; 4.05 (95% CI 2.60–6.29) for low-dose metformin vs no metformin; and 4.12 (95% CI 2.97–5.71) for high-dose metformin versus no metformin.

## DISCUSSION

In this study, we examined the short-term and long-term effects of high-dose metformin administration on the incidence of lactic acidosis. Our results indicate that the administration of metformin in terms of its effect on lactic acidosis can be regarded as a short term effect and that the incidence rate of lactic acidosis is not higher in patients receiving high-dose metformin versus patients receiving low-dose administration. A long-term effect of high-dose metformin administration was not found in the time-dependent proportional hazard analysis in patients who received metformin at least once. Factors other than the administration of biguanide antidiabetics, including metformin, were identified as being associated with the incidence of lactic acidosis in the case–control study, including the administration of vitamin B complex and diagnosis of volume depletion

(i.e. dehydration, hypovolemia, extracellular fluid volume depletion and abnormally decreased volume of circulating fluid [plasma] in the body. Overall, these latter factors were found to be more highly associated with the incidence of lactic acidosis than metformin administration.

With regard to the association of metformin with lactic acidosis, unlike previous studies [11, 12], the present study did not find any difference in the incidence rate of lactic acidosis between patients treated with metformin and those treated with other antidiabetic drugs. Several studies have indicated that complications of T2D, such as renal diseases, increase the risk of lactic acidosis in patients receiving metformin administration [16, 17, 22]. In the package inserts of metformin, the use of metformin is contraindicated for those patients having a high risk of incidence of lactic acidosis, i.e. those with a medical history of lactic acidosis, severe renal dysfunction, severe hepatic dysfunction, severe impairment to the cardiovascular system and pulmonary function and/or dehydration, those at a high risk of dehydration and those with excessive alcohol use [9]. In our study, volume depletion, which includes dehydration, was selected as a confounding factor for the incidence of lactic acidosis in study 1, which was then adjusted for later studies. However, other factors that were not identified as confounding factors as well as those that did not exist in the database, such as excessive alcohol intake, were not adjusted, possibly contributing to the results obtained in this study showing that metformin administration was associated with the incidence of lactic acidosis. It should be noted that a previously conducted propensity score-matched cohort study using the same database as that used in this study (January

2010–August 2014) reported no association of metformin administration with the incidence of lactic acidosis in patients with T2D [17]. This difference with our study may be due to differences in the definition of lactic acidosis used in the earlier study with a diagnosis of lactic acidosis defined as receiving a lactic acid test within 30 days before the diagnosis and receiving either hemodialysis or sodium bicarbonate within 30 days after the diagnosis, as well as the factors adjusted by propensity score matching [17].

Regarding the dose of metformin, we hypothesized that the incidence of lactic acidosis might be higher with high-dose metformin administration than with low-dose administration; however, the incidence with high-dose metformin administration was not higher than that of with low-dose metformin in this study. One possible explanation is that the disease conditions of patients were different between the groups. Therefore, patients who could not be administered high-dose metformin due to their disease conditions might be included in the low-dose metformin group, and some of these conditions might have contributed to the higher incidence of lactic acidosis in patients with low-dose metformin administration. The comparisons were made after adjustment of the confounding factors, and the adjustment might have not been the most appropriate. Another possibility is that if the confounding factors were appropriately adjusted, the administration of metformin, regardless of the dosage, might be a trigger to cause lactic acidosis, but not be the direct cause.

In this study, volume depletion was indicated as one of the factors associated with the incidence of lactic acidosis; this result is consistent with results reported in previous studies. Volume depletion defined as ICD-10 code E86 includes dehydration, which has been reported to be associated with the incidence of lactic acidosis [23]. The association of volume depletion and dehydration with lactic acidosis has also been reported in patients receiving metformin [8]; in the package inserts, metformin administration is contraindicated for those patients subject to dehydration and for those

with a higher risk for dehydration due to the high possibility of developing lactic acidosis [9].

The association of hepatic and renal diseases with lactic acidosis has been previously reported [24], but the authors did not identify hepatic and renal diseases as risk factors. Several studies have indicated that the incidence of lactic acidosis due to metformin administration occurs in patients with hepatic and renal diseases [16, 17, 22]. Hepatic and renal diseases are long-term disease conditions associated with volume depletion. Based on the relation between hepatic and renal diseases and volume depletion, these disease conditions could be positively associated with the incidence of lactic acidosis at levels whose significance cannot be detected in the present study. We do not exclude the possibility that the identification process of the factors influenced our results due to the characteristics of the data source, which does not contain the laboratory test data from the all DPC hospitals, but only from a limited number of hospitals. Thus, we did not include the laboratory test data to secure the sample size. Therefore, there remains a possibility that the absence of estimated glomerular filtration rate and laboratory test data from the candidate factors contributed to the exclusion of hepatic and renal diseases from the risk factors in our study.

Vitamin B complex administration was also indicated as a risk factor of the incidence of lactic acidosis; however, we could not find any existing report of an association between them. Vitamin B complex is often prescribed for patients in malnourished or dehydrated states, or given prophylactically to guard against neurological diseases. It is also possible that vitamin B complex was administered to patients with respiratory failure or to patients in dehydrated conditions. In those cases, vitamin B complex administration alone would not be a risk factor of the incidence of lactic acidosis, but the disease conditions of patients receiving vitamin B complex could be a potential risk factor.

Notably, the average age and percentage of women as well as percentages of volume depletion and vitamin B complex administration were the highest in the no metformin group, indicating that metformin was properly

administered according to the health status of patients. However, considering that in the high-dose metformin group, about 20% of patients who developed lactic acidosis had a diagnosis of volume depletion (in study 2-1), more strict compliance with the description of the package insert might be necessary. As long as the use follows the package insert, increasing the administration dose to a level which is sufficient to gain glycemic control could be considered if the administration dose has been maintained at low levels due to the concern of increased lactic acidosis incidence.

There are a number of limitations to this study which should be considered while interpreting the results. First, because the database we used in this study was comprised of the secondary use of claims data, the accuracy of information on diagnoses and treatments is completely dependent on the records of database; the lack of records and inaccuracy in the records are reflected in the results of the analysis. Regarding the characteristics of this database that consisted of data from DPC hospitals, there is a possibility that more patients in severe state of T2D or with comorbidities are included than general patient groups. Moreover, the database does not have records of treatment conducted in the other medical institutions, which might influence the results of the analysis in the study. Secondly, we defined metformin administration using records of the prescription claims because we could not obtain information on the actual medication use by the patients. Thus, allocated observational months on the basis of the prescription records might be different from the actual timing of drug administration. Thirdly, we comprehensively explored the factors associated with the incidence of lactic acidosis by the logistic regression analysis using a wide range of information obtained from claims data. However, there may be other factors associated with the incidence of lactic acidosis that cannot be obtained from the claims data; consequently, there is always the possibility that confounding factors were not adjusted to a sufficient extent. For example, although smoking habit might be associated with the incidence of lactic acidosis, its association could not be examined because

information about smoking was not included in the database.

## CONCLUSIONS

The effect of high-dose metformin on the incidence of lactic acidosis was investigated in patients with T2D using a Japanese claims database. The results suggest an association between metformin administration and the incidence of lactic acidosis; however, the incidence rate was not higher in patients administered high-dose metformin than in those administered low-dose metformin. Moreover, some factors, including the diagnosis of volume depletion and the administration of vitamin B complex, as well as factors such as a lower age and being a male, were found to be associated with the incidence of lactic acidosis. Overall, these factors were found to have a significant association with the incidence of lactic acidosis in comparison to metformin administration.

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**Compliance with Ethics Guidelines.** The study was approved by the ethics committee of St. Marianna University School of Medicine (4407). As the study only involved analysis of pre-existing data in the databases, written informed consent from the study participants was not required. Clinical trial registration was not required for this study because it was not a prospective study and did not involve any intervention.

**Data Availability.** The data are available from Medical Data Vision Co., Ltd., but restrictions apply to the availability of these data, which were used under license for the current study, and are not publicly available.

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