

Risk of Fatal and Nonfatal Lactic Acidosis With Metformin Use in Type 2 Diabetes Mellitus

Systematic Review and Meta-analysis

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Background: Metformin therapy for type 2 diabetes mellitus has been shown to reduce total mortality rates compared with other antihyperglycemic treatments but is thought to increase the risk of lactic acidosis. The true incidence of fatal and nonfatal lactic acidosis associated with metformin use is not known.

Methods: A comprehensive search was performed to identify all comparative trials or observational cohort studies published between January 1, 1959, and March 31, 2002, that evaluated metformin therapy, alone or in combination with other treatments, for at least 1 month. The incidence of fatal and nonfatal lactic acidosis was recorded as cases per patient-years for metformin treatment and for placebo or other treatments. In a second analysis, lactate levels were measured as a net change from baseline or as mean treatment values for metformin and comparison groups.

Results: Pooled data from 194 studies revealed no cases of fatal or nonfatal lactic acidosis in 36 893 patient-years in the metformin group or in 30 109 patients-years in the nonmetformin group. Using Poisson statistics with 95% confidence intervals, the probable upper limit for the true incidence of lactic acidosis in the metformin and nonmetformin groups was 8.1 and 9.9 cases per 100 000 patient-years, respectively. There was no difference in lactate levels for metformin compared with placebo or other nonbiguanide therapies.

Conclusion: There is no evidence to date that metformin therapy is associated with an increased risk of lactic acidosis or with increased levels of lactate compared with other antihyperglycemic treatments if the drugs are prescribed under study conditions, taking into account contraindications.

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METFORMIN hydrochloride is a biguanide that has been used to treat type 2 diabetes mellitus for more than 40 years.^{1,2} Aside from its effect on carbohydrate metabolism, metformin treatment is thought to have other positive effects, such as weight loss or stabilization of weight gain.³⁻⁵ In addition, results of the UK Prospective Diabetes Study⁶ indicate that metformin monotherapy leads to reductions in diabetes mellitus-related end points, in the diabetes mellitus-related mortality rate, and in the total mortality rate compared with insulin use, sulfonylurea therapy, or diet alone.

Lactic acidosis is a rare, potentially fatal metabolic condition that can occur whenever substantial tissue hypoperfusion and hypoxia exist.^{7,8} Lactic acidosis is characterized by an elevated blood lactate concentration (>45.0 mg/dL [>5.0 mmol/L]), decreased blood pH (<7.35), and electrolyte disturbances with an increased an-

ion gap. An earlier biguanide, phenformin hydrochloride, was withdrawn from the market because it was associated with a reported rate of lactic acidosis of 40 to 64 cases per 100 000 patient-years.^{2,9} Metformin, however, differs from phenformin in molecular structure and pharmacokinetics and, unlike phenformin, is thought to enhance glucose oxidation without substantially affecting fasting lactate production in peripheral tissues.^{10,11}

The true incidence of metformin-associated lactic acidosis is not known. Population-based studies^{9,12-14} have estimated a rate of 2 to 9 cases of lactic acidosis in metformin users per 100 000 person-years. However, most of the reported cases have occurred in patients with severe acute conditions, such as renal failure, that could in themselves have caused the lactic acidosis.^{14,15} To estimate the risk specifically attributable to metformin use, the background rate of lactic acidosis in patients with type 2 diabetes mellitus who are not treated with metformin was assessed and was found

to be 9 cases per 100000 person-years.¹⁵ This raises the question of whether patients with type 2 diabetes mellitus have an increased risk for developing lactic acidosis with metformin use compared with other glucose-lowering treatments.

Metformin use is now considered to be contraindicated in many chronic conditions that may increase the risk of tissue anoxia and the development of lactic acidosis, such as cardiovascular, renal, pulmonary, and liver disease. These restrictions significantly reduce the number of patients who could benefit from metformin treatment. The objective of this review is to assess the risk of fatal and nonfatal lactic acidosis associated with metformin use in persons with type 2 diabetes mellitus compared with placebo or other glucose-lowering therapies. Another objective is to evaluate levels of blood lactate, measured at baseline and during treatment, for metformin treatment compared with placebo or other hypoglycemic therapies. An earlier version of this analysis was published as a review on The Cochrane Library.¹⁶

METHODS

TRIAL SEARCH AND SELECTION

A comprehensive search through March 31, 2002, was performed of the Cochrane Library (including the Cochrane Controlled Trials Database), MEDLINE, OLDMEDLINE, Database of Abstracts of Reviews of Effectiveness, Reactions, and EMBASE using the terms "diabetes mellitus," "non-insulin-dependent," "NIDDM," "non insulin* dep*," "noninsulin* dep*," "non insulin dep*," "typ* II diabet*," "typ* 2 diabet*," "diabet* typ* 2," "diabet* typ* II," "biguanides," "biguanid*," "metformin," "glucophag*," and "metformin*." Studies published in any language were included. The search was further augmented by scanning references of identified articles and reviews, abstracts at clinical symposia, and the *Cumulated Index Medicus*. In addition, attempts were made to contact authors of identified studies and manufacturers of metformin to obtain additional information.

Two independent reviewers (G.A.P. and S.R.S.) reviewed every record found in the search, and articles on metformin use in patients with diabetes mellitus were retrieved. Two investigators (S.R.S. and E.G.) independently evaluated studies for inclusion, and the observed percentage agreement between raters was measured using the κ statistic.¹⁷

Prospective clinical trials of at least 1 month in duration were included if they evaluated metformin use, alone or in combination with other treatments, compared with placebo or compared with any other glucose-lowering therapy for type 2 diabetes mellitus. In addition, all observational cohort studies evaluating at least 1 month of metformin use were included in the analysis if they provided the number of patients and the duration of treatment. The excluded trials lasting less than 1 month were evaluated separately to see whether there were any cases of lactic acidosis.

Interventions studied included metformin, alone or in combination with other treatments, vs placebo or another antihyperglycemic intervention, such as diet, insulin, or sulfonylureas. Data on participants treated with phenformin were not included in the analysis for lactic acidosis but were included in measurements of lactate levels.

VALIDITY ASSESSMENT

The methodological quality of each study was evaluated based on the quality criteria modified from Schulz,¹⁸ Jadad,¹⁹ and Stroup²⁰

and their colleagues. Studies were divided into 5 categories that characterize the treatment of metformin in the trials. A score of A, B, or C was given to randomized controlled trials using the following factors: (1) Was the study randomized? If so, was the randomization procedure adequate? (2) Were the patients and people administering the treatment masked to the intervention? (3) Were withdrawals and dropouts described? A score of D was given to open-label nonrandomized controlled trials, and a score of E was given to observational cohort studies.

Each trial was assessed independently by 2 reviewers (S.R.S. and E.G.), and consensus was reached in cases of disagreement. Interrater agreement before consensus was calculated using the κ statistic.

DATA EXTRACTION AND DATA SYNTHESIS

Two independent reviewers (S.R.S. and E.G.) extracted data from the selected articles, reconciling differences by consensus. Outcomes measured were (1) death described as due to lactic acidosis; (2) reported cases of nonfatal lactic acidosis, as defined by the investigator; and (3) blood lactate levels for metformin compared with placebo or other nonbiguanide therapies and compared with phenformin.

The treatment effect for fatal and nonfatal lactic acidosis was expressed as a risk difference by taking the incidence of events during metformin, alone or in combination with other treatments, and then subtracting the incidence of events during placebo or alternative treatments. As no cases of lactic acidosis were found, the probable upper limits for the true incidence of lactic acidosis in the metformin and nonmetformin groups were calculated separately using Poisson statistics. Information was obtained on how many patients were older than 65 years or were thought to have concomitant hypoxicemic conditions.

Once pooled results revealed no cases of lactic acidosis, it was decided to report on randomized controlled trials that measured blood lactate levels for metformin use compared with placebo or nonbiguanide treatments and also compared with phenformin use. Three outcomes were analyzed for the metformin group compared with the comparison groups: (1) the change in lactate levels from baseline to treatment, (2) the mean lactate levels recorded during treatment, and (3) the change in treatment lactate levels from a basal state to peak stimulation with either food or exercise. The results were recorded as the weighted mean difference (WMD) and were pooled using the fixed-effects model for continuous data.

RESULTS

SEARCH RESULTS

The electronic database search identified 638 articles, 191 of which were potentially relevant studies on metformin use in patients with type 2 diabetes mellitus. After scanning abstracts from symposia and references from selected articles, an additional 70 studies were identified. Of these 261 studies, 193 met the inclusion criteria.^{6,10,21-211} One additional unpublished trial (2001) was received from Evertine Abbink, MD. The κ score for interrater agreement in trial selection was 0.87 (95% confidence interval [CI], 0.76-0.98), indicating good agreement, and consensus was reached on the remaining trials.

Of the 194 studies included in the analysis, 126 were prospective comparative trials, 56 were prospective cohort studies, and 12 were retrospective cohort studies. A

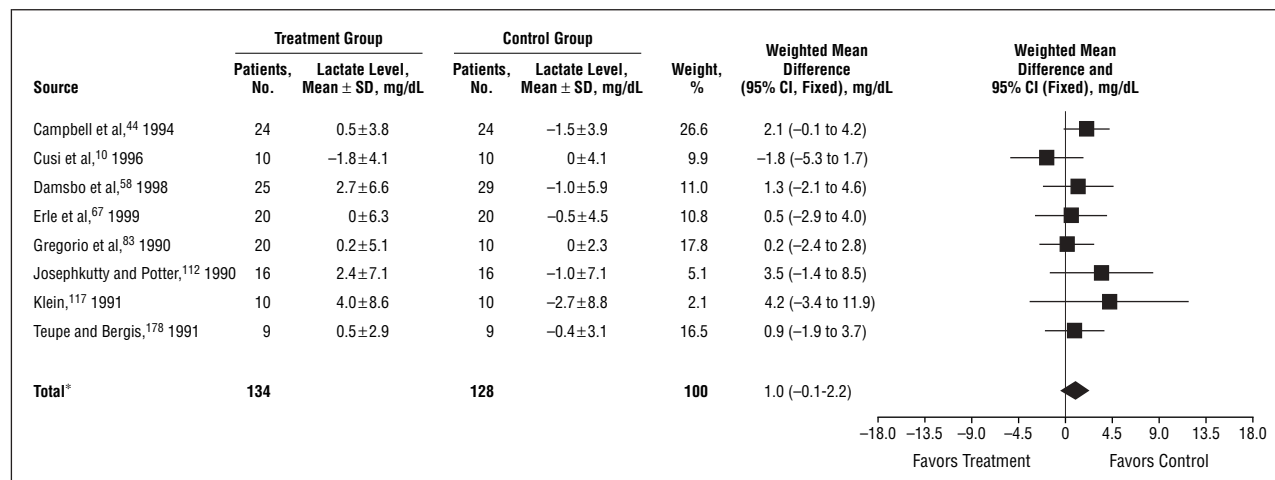


Figure 1. Net treatment effect of lactate levels for metformin treatment compared with nonmetformin treatments. To convert lactate (and weighted mean difference) from milligrams per deciliter to micromoles per liter, multiply milligrams per deciliter by 0.1110. CI indicates confidence interval. *Test for heterogeneity, $\chi^2=5.48$; $P=.60$. Test for overall effect, $z=1.79$; $P=.07$.

total of 56 692 participants were followed for 67 002 patient-years, with 18 689 participants (36 893 patient-years) in the metformin group and 38 003 participants (30 109 patient-years) in the nonmetformin group. The mean \pm SD age of the participants in the metformin group was 57.1 \pm 8.9 years, and 61% were men. In the nonmetformin group, the mean \pm SD age was 57.2 \pm 9.1 years, and 61% were men. The mean trial duration was 2.1 years (range, 0.08-10.7 years). The mean study size in the metformin group was 55 participants (range, 6-683). The mean study size in the nonmetformin group was 76 participants (range, 8-1362). The dropout rate was estimated to be 9.3%.

Metformin was given in daily doses of 1 to 3 g, with the dosage titrated clinically. Comparison treatments included placebo, diet, insulin, glyburide, gliclazide, glipizide, glibenclamide, glimepiride, chlorpropamide, tolbutamide, acarbose, nateglinide, repaglinide, miglitol, troglitazone, rosiglitazone maleate, and guar gum.

No trial was specifically designed to assess the incidence of lactic acidosis, but adverse effects or adverse events were described in almost all of the trials. Attempts were made to reach the authors of the trials, and those who responded confirmed that there were no known cases of fatal or nonfatal acidosis in their trials. Serum bicarbonate or lactate levels were measured in 96 of the included studies (49%). Of the comparative trials, 26 measured lactate levels during metformin and nonmetformin treatment.

Studies were excluded for the following reasons: 2 were retrospective and 13 were prospective cohort studies that did not give information on the number of patients or the length of treatment, 39 prospective comparative trials were less than 1 month in duration, and 13 were retrospective analyses or reviews.

METHODOLOGICAL QUALITY OF INCLUDED STUDIES

Of the trials analyzed, 3 received a score of A; 40, a score of B; 55, a score of C; 28, a score of D; and 68, a score of E. The κ score for interrater agreement was 0.83 (95% CI, 0.75-0.91), indicating good agreement.

QUANTITATIVE DATA SYNTHESIS

Incidence of Lactic Acidosis

When combining the data from cohort studies with the prospective comparative trials (including data from the unpublished data from E. J. Abbink, MD, 2001),^{6,10,21-211} there were no cases of fatal or nonfatal lactic acidosis reported in the metformin group (36 893 patient-years) or in the nonmetformin group (30 109 patient-years). Using Poisson statistics with 95% CIs, the probable upper limit for the true incidence of lactic acidosis in the metformin group is 8.1 cases per 100 000 patient-years and in the nonmetformin group is 9.9 cases per 100 000 patient-years.

Of the 182 prospective studies,* 80 (44%) allowed for the inclusion of renal insufficiency, following 16 233 patient-years of metformin use, and 174 (96%) allowed for the inclusion of at least 1 of the contraindications listed herein. It was estimated from the available data that 16% of the participants in the studies were older than 65 years, and they were followed for approximately 5903 patient-years of metformin use.

Blood Lactate Levels

For randomized controlled trials† that provided the data, the baseline lactate level measured before metformin treatment was 10.2 \pm 2.3 mg/dL (1.1 \pm 0.2 mmol/L). There was no difference in the net change in lactate levels from baseline for metformin treatment compared with placebo or nonbiguanide therapies, with a WMD of 1.0 mg/dL (0.11 mmol/L) (95% CI, -0.1 to 2.2 mg/dL [-0.01 to 0.24 mmol/L]) (**Figure 1**). The mean \pm SD lactate level during metformin treatment was 11.2 \pm 2.8 mg/dL (1.2 \pm 0.3 mmol/L), which was not significantly different from nonbiguanide comparisons (WMD, 0.5 mg/dL [0.06 mmol/L]; 95% CI, 0 to 1.2 mg/dL [0 to 0.1

*References 6, 10, 22-25, 28, 29, 31-39, 41-44, 46-103, 105-108, 110-148, 150-165, 168-171, 173-211.

†References 10, 36, 38, 44, 47, 58, 84, 112, 117, 178.

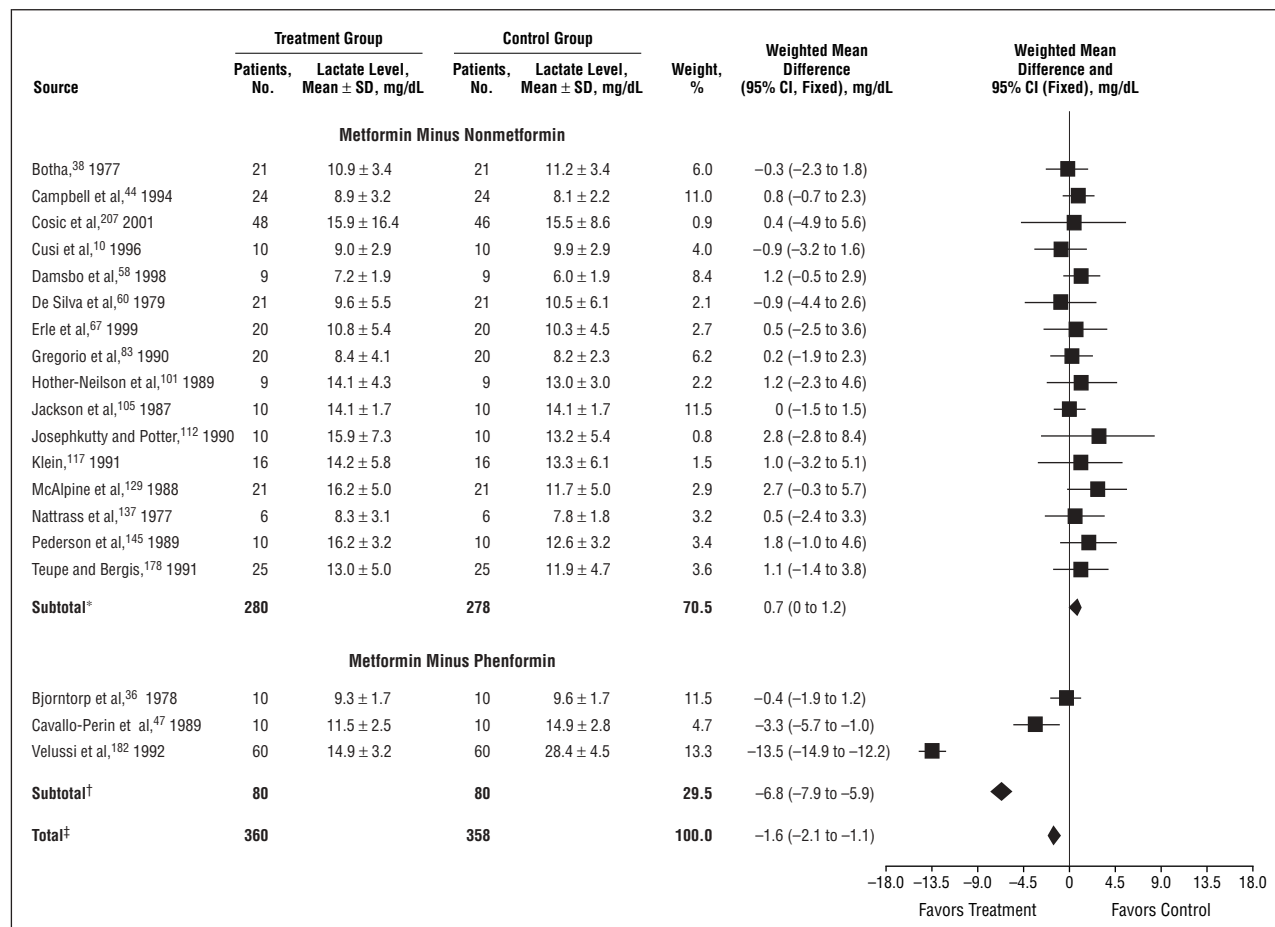


Figure 2. Mean treatment lactate levels for metformin compared with nonmetformin treatments and for metformin compared with phenformin. To convert lactate (and weighted mean difference) from milligrams per deciliter to micromoles per liter, multiply milligrams per deciliter by 0.1110. CI indicates confidence interval.

*Test for heterogeneity, $\chi^2_{15}=7.47$; $P=.94$. Test for overall effect, $z=1.84$; $P=.07$.

†Test for heterogeneity, $\chi^2_{2}=168.7$; $P<.001$. Test for overall effect, $z=14.21$; $P<.001$.

‡Test for heterogeneity, $\chi^2_{18}=343.32$; $P<.001$. Test for overall effect, $z=6.17$; $P<.001$.

mmol/L]), and was 6.8 mg/dL (0.8 mmol/L) lower than with phenformin use (95% CI, -7.9 to -5.9 mg/dL [-0.9 to -0.6 mmol/L]) (Figure 2). The mean \pm SD lactate level during metformin treatment, measured before and after stimulation by a meal or strenuous exercise, was 20.7 \pm 15.3 mg/dL (2.3 \pm 1.7 mmol/L) (Figure 3). This value was not significantly different from that of the metformin group vs the nonbiguanide group (WMD, 0.8 mg/dL [0.1 mmol/L]; 95% CI, -0.3 to 2.0 mg/dL [-0.03 to 0.2 mmol/L]) or the phenformin group (WMD, -3.3 mg/dL [-0.4 mmol/L]; 95% CI, -9.5 to 2.9 mg/dL [-1.1 to 0.3 mmol/L]). Five trials^{62,73,82,152,195} that measured lactate levels did not provide data to be analyzed but reported levels to be normal during metformin and nonmetformin treatment.

Possible heterogeneity was noted in the 3 trials^{38,58,139} that measured lactate levels after stimulation by food or exercise. The results were not significantly different when the random-effects model was used (WMD, 0.4 mg/dL [0.04 mmol/L]; 95% CI, -4.1 to 4.8 mg/dL [-0.4 to 0.5 mmol/L]). In addition, some heterogeneity was noted in the 3 trials measuring mean lactate levels for metformin treatment compared with phenformin treatment. When the random-effects model was used, the difference was no longer sta-

tistically significant (-5.8 mg/dL [-0.6 mmol/L]; 95% CI, -14.7 to 3.2 mg/dL [-1.6 to 0.4 mmol/L]).

Funnel plots of the effect size vs SE were evaluated for the included trials* that measured lactate levels. No evidence of significant small study publication bias was found.

COMMENT

To evaluate the risk of lactic acidosis attributed to metformin use, pooled data from all known prospective comparative trials and observational cohort studies lasting longer than 1 month were analyzed. No cases were found in 194 trials with 36893 patient-years of metformin treatment. In fact, on review of 56 additional trials that were excluded from analysis (those that lasted <1 month or were of unclear duration), no cases of lactic acidosis were found. Using Poisson statistics, the probable upper limit for the true incidence of lactic acidosis associated with metformin use is 8.1 cases per 100 000 patient-years and with other nonbiguanide treatments is 9.9 cases per 100 000 pa-

*References 10, 36, 38, 44, 47, 58, 60, 67, 83, 101, 105, 112, 117, 129, 137, 145, 178, 182, 207.

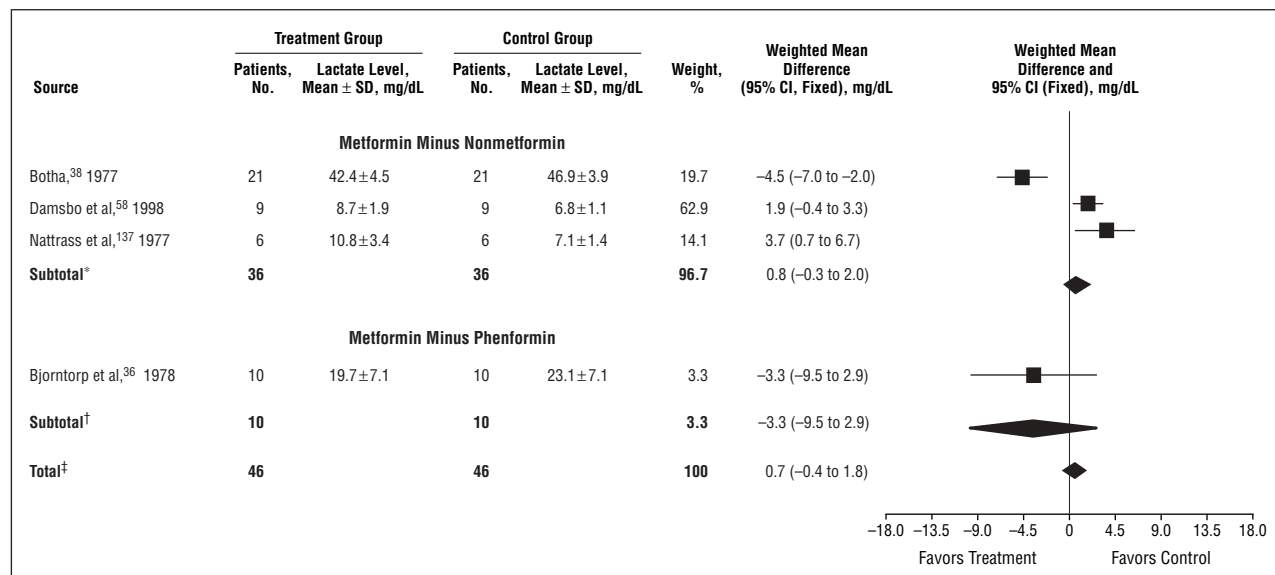


Figure 3. Peak stimulated lactate levels for metformin treatment compared with nonmetformin treatments and for metformin treatment compared with phenformin treatment. To convert lactate (and weighted mean difference) from milligrams per deciliter to micromoles per liter, multiply milligrams per deciliter by 0.1110. CI indicates confidence interval.

*Test for heterogeneity, $\chi^2=22.54$; $P<.001$. Test for overall effect, $z=1.45$; $P=.15$.

†Test for heterogeneity, $\chi^2=0.00$; $P>.99$. Test for overall effect, $z=1.05$; $P=.30$.

‡Test for heterogeneity, $\chi^2=24.21$; $P<.001$. Test for overall effect, $z=1.23$; $P=.20$.

tient-years. Of the trials that measured blood lactate levels, there was no significant difference for metformin treatment compared with placebo or nonbiguanide treatments, and levels were lower for metformin treatment than for phenformin treatment (WMD, -6.8 mg/dL [-0.75 mmol/L]; 95% CI, -7.9 to -5.9 mg/dL [-0.86 to -0.65 mmol/L]).

The mean duration of studies included in this review was 2.1 years (range, 1 month to 10.7 years). In addition, excluded trials of less than 1 month in duration were evaluated to see whether lactic acidosis occurs shortly after initiation of treatment, and no cases were found.

This review has several limitations. Essentially, all the data included in this analysis were from published trials, and this may have produced biased results. A funnel plot of effect size vs SE did not provide evidence for significant publication bias, since no cases were found in any trial. Many of the comparative trials included in the analysis were sponsored by pharmaceutical companies producing antihyperglycemic medications other than metformin, in which case a bias may be to publish adverse effects for metformin.

Another difficulty is that to assess the risk of a rare occurrence such as lactic acidosis, it may be necessary to evaluate more than 36 000 patient-years of metformin treatment. It is especially difficult to assess the risk of lactic acidosis in the presence of standard contraindications such as renal or hepatic insufficiency because it is unclear exactly how many of the participants had these conditions, and it is possible that the number of participants with these conditions may have been too small to detect an effect. For that reason, no conclusions can be made about the safety of metformin use in the presence of these conditions. Despite these limitations, the most important conclusion from this review is that, at present, there is no evidence from prospective comparative trials or observational cohort studies to support the hypothesis that metformin treatment is

associated with an increased risk of lactic acidosis compared with other antihyperglycemic treatments.

Metformin treatment in overweight patients with type 2 diabetes mellitus has been shown to reduce cardiovascular and total mortality rates compared with insulin use, sulfonylurea use, or diet alone.⁶ Concern about the risk of lactic acidosis has led to recommendations that metformin therapy be withheld in persons with chronic conditions that in themselves can cause lactic acidosis. These recommendations, if followed, would reduce the number of patients eligible to receive metformin by approximately half.¹⁵ It has been found that in clinical practice these standard contraindications are largely disregarded, with 54% to 73% of patients taking metformin having at least 1 contraindication to treatment.^{11,212} In a cross-sectional study,²¹² 19% of patients taking metformin who were admitted to a hospital had concurrent renal insufficiency.

Metformin treatment has been implicated as a cause of lactic acidosis because treatment with a related biguanide, phenformin, had been associated with several cases of lactic acidosis, and phenformin was removed from the US market in 1977.²¹³ Despite their similarities, phenformin has a chemical structure substantially different than that of metformin. Unlike metformin, phenformin can impair oxidative phosphorylation in the liver, thereby increasing lactate production by anaerobic pathways.^{47,182,214-216} In contrast, metformin inhibits hepatic gluconeogenesis without altering lactate turnover or lactate oxidation.^{10,217,218} In addition to the trials analyzed in this review, several other trials have confirmed that metformin treatment does not significantly elevate blood lactate levels, even in the presence of renal impairment or advanced age.*

*References 77, 118, 133, 214, 215, 219-222.

Now, the only evidence to indicate that metformin use is associated with lactic acidosis comes from reports of approximately 330 cases that have occurred in patients taking metformin.²²³⁻²²⁶ Lactic acidosis has also been reported in patients with diabetes mellitus not treated with metformin, typically under conditions in which there is significant tissue hypoperfusion or hypoxia.²¹³ One study¹⁵ found that the rate of confirmed lactic acidosis in the United States, measured before the introduction of metformin and after the withdrawal of phenformin, was approximately 10 per 100,000 patient-years, which is equivalent to that thought to be associated with metformin treatment. Another study²¹³ evaluated all cases of nonketotic metabolic acidosis in patients with type 2 diabetes mellitus that occurred during 609 emergency admissions to a university hospital. The rates of nonketotic acidosis per 1000 emergency admissions were 29 for sulfonylurea use, 32 for sulfonylurea plus phenformin use, 48 for insulin use, and 0 for metformin treatment. All cases of nonketotic metabolic acidosis found were associated with severe precipitant disease that could have caused lactic acidosis. The investigators conclude that it is the underlying systemic dysfunction and not the particular treatment that is the main determinant for the appearance of lactic acidosis. In support of that conclusion, the results of this review reveal that there is no evidence of an increased risk of lactic acidosis associated with metformin use if it is prescribed under the study conditions, taking into account contraindications.

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