Comparative Outcomes Study of Metformin Intervention Versus Conventional Approach

The COSMIC Approach Study

DENNIS R. CRYER, MD[1]
SAVIAN P. NICHOLAS, MD[1]
DAVID H. HENRY, PHD[1]
DONNA J. MILLS, BSN[1]
BRUCE V. STADEL, MD, MPH[2]

OBJECTIVE — Metformin was approved by the Food and Drug Administration in 1995 subject to the conduct of a randomized trial to evaluate the risk of lactic acidosis or other serious adverse events (SAEs) with this agent, under usual care conditions.

RESEARCH DESIGN AND METHODS — The Comparative Outcomes Study of Metformin Intervention versus Conventional (COSMIC) Approach Study was a randomized, open-label, active-comparator, parallel-group, 1-year trial in type 2 diabetic patients suboptimally controlled on diet or sulfonylurea. Patients received metformin (n = 7,227) or other usual care treatments (n = 1,505). The primary end point was the incidence of SAEs, death, and hospitalization.

RESULTS — SAEs occurred in 10.3% (95% CI 9.6–11.1%) of the metformin group and in 11.0% (9.5–12.7%) of the usual care group (P = 0.431). Lactic acidosis did not occur. All-cause mortality (1.1% [0.9–1.4%] vs. 1.3% [0.8–2.0%], P = 0.596) and hospitalization (9.4% [8.8–10.1%] vs. 10.4% [8.9–12.1%], P = 0.229) were similar between groups.

CONCLUSIONS — The incidence of SAEs was similar between groups. Lactic acidosis was not observed. Metformin may be safely prescribed for type 2 diabetes if contraindications and warnings are respected. This study demonstrates the utility of large, simple trials for risk evaluation of treatments for common diseases.

Diabetes Care **28:539–543, 2005**

Lactic acidosis is rare, but serious, with up to 50% mortality (1,2). The risk of lactic acidosis is high when tissue underperfusion and hypoxia coincide (e.g., in renal, cardiac, or hepatic failure; coronary disease; hemorrhage; respiratory distress; or septic shock) (3,4). Biguanide oral antidiabetic agents have been associated with an increased risk of lactic acidosis (5–8). Phenformin was withdrawn from use in the U.S. in 1977 for this reason, with an associated incidence of lactic acidosis subsequently estimated at 40–64/100,000 patient-years (7,8).

Although phenformin and metformin influence lactate metabolism in different ways (9), and even though the risk of lactic acidosis is lower with metformin (10–12), this serious adverse event (SAE) has been described as a biguanide class effect (6), and concerns over this issue delayed the introduction of metformin in the U.S. until 1995. The incidence of lactic acidosis with metformin was uncertain at that time. However, metformin had not been withdrawn elsewhere during decades of therapeutic use, and reviews published before 1995 supported a low or "negligible" risk of lactic acidosis with metformin in patients without lactic acidosis risk factors (1,12). The mean frequency of adverse drug experience (ADE) reporting for lactic acidosis in metformin-treated patients in these areas was <10% of that for phenformin (~3/100,000 person-years). However, ADE reports of a drug-disease association probably seriously underrepresent the actual frequency.

Contraindications for metformin in the U.S. originally included renal dysfunction, metabolic acidosis, and dehydration. Congestive heart failure requiring pharmacologic treatment was added, with instructions to withhold metformin from patients with sepsis and all patients >80 years of age with reduced creatinine clearance, following a review of 47 spontaneous ADE reports of lactic acidosis to the Food and Drug Administration (FDA), during the first year of use of metformin (2).

At the time of approval, the FDA requested a postmarketing safety surveillance study of the safety of metformin in a patient population representative of the U.S. type 2 diabetic population. The results of this study, the Comparative Outcomes Study of Metformin Intervention versus Conventional (COSMIC) Approach Study, are reported here.

From [1]Bristol-Myers Squibb, Princeton, New Jersey; and the [2]Food and Drug Administration, Rockville, Maryland.

Address correspondence and reprint requests to Dennis R. Cryer, MD, Bristol-Myers Squibb Company, 777 Scudders Mill Rd., Plainsboro, NJ 08536. E-mail: dennis.cryer@bms.com.

Received for publication 3 August 2004 and accepted in revised form 14 December 2004.

The views expressed in this article are the authors' and do not constitute an official position of the Food and Drug Administration.

Abbreviations: ADE, adverse drug experience; AE, adverse event; AST, aspartate aminotransferase; COSMIC, Comparative Outcomes Study of Metformin Intervention versus Conventional; FDA, Food and Drug Administration; SAE, serious AE.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

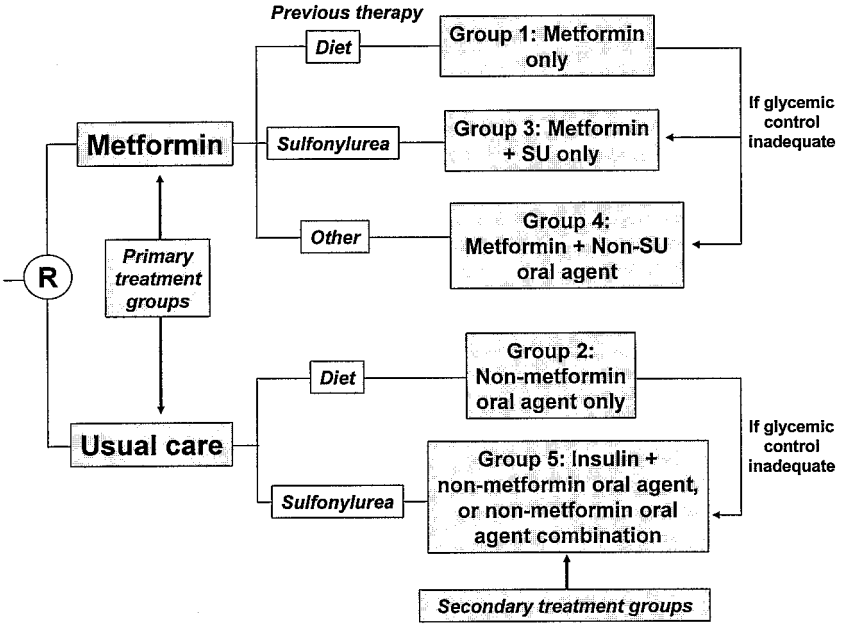

Figure 1—*Treatment allocation and primary and secondary treatment groups. SU, sulfonylurea.*

RESEARCH DESIGN AND METHODS

— Eligible patients were men or women aged ≥18 years with a diagnosis of type 2 diabetes, with glycemia suboptimally controlled (at the discretion of the investigators) on diet or sulfonylurea monotherapy. Women of child-bearing potential had to be practicing an effective method of contraception. Principal inclusion criteria included normal renal function (serum creatinine <1.5 mg/dl [men] and <1.4 mg/dl [women] or normal creatinine clearance), acceptable health (based on interview, medical history, physical examination, and laboratory tests), normal hepatic function (AST <2 × upper limit of normal), no history of metabolic acidosis, and no known hypersensitivity to oral antidiabetic agents or insulin.

Study design

This was a 1-year, randomized, open-label, parallel-group, multicenter, clinical trial. Its simple design met an FDA requirement for relevance to usual care, and it impacted minimally on usual patient management. No special safety instructions were provided, other than the U.S. package insert for metformin and information on the diagnosis and management of lactic acidosis.

Randomization, stratified by site, was in a 4:1 ratio to two primary treatment groups: metformin or usual care (treatment with a sulfonylurea, thiazolidinedione, insulin, or any other nonmetformin monotherapy or combination therapy). All patients received diet counseling. Within the primary treatment groups, patients received monotherapy or combination therapy according to prior treatment. This generated five secondary treatment groups (Fig. 1). Patients previously treated with diet were randomized to additional metformin (group 1) or to oral antidiabetic monotherapy, usually a sulfonylurea or thiazolidinedione (group 2). In groups 3 and 4, metformin was added to existing sulfonylurea or other oral therapy. At the investigator's discretion, previously sulfonylurea-treated patients in the usual care group could receive insulin, with or without an oral agent, or oral combination therapy, provided that metformin was not included (group 5). Patients who became uncontrolled on oral monotherapy could cross to the relevant secondary treatment group (Fig. 1).

Initial metformin treatment was 500 mg b.i.d., with meals, increased weekly in 500 mg steps if required (maximum 2,500 mg/day in three divided doses, with meals).

End points

The primary objective was to compare the long-term (1-year) SAE profile of metformin with that of other usual care regimens in patients with type 2 diabetes. Key outcome measures were the incidence of SAEs, hospitalization, and death. A secondary objective was to compare plasma lactate levels after 1 year of treatment in a substudy.

SAEs comprised any experience that was fatal, life-threatening, permanently or substantially disabling, resulted in permanent or significant disability or incapacity, required or prolonged hospitalization, an important medical event that jeopardized the patient or required intervention to prevent a serious outcome, a congenital abnormality, a cancer, an overdose of medication, or a condition that resulted in the development of drug dependency or drug abuse. Information on SAEs was collected by face-to-face or telephone interviews. Most patients were asked to attend their study clinic at enrollment and after 3 months of treatment. Information on SAEs or severe hypoglycemia requiring medical intervention was obtained by telephone at months 6, 9, and 12. Patients recorded adverse events (AEs) in a diary and were instructed to contact the investigator if a significant AE occurred. SAEs were confirmed by review of hospital records or death certificates. If the patient was unavailable, the interview was conducted with an alternate contact identified by the patient at the beginning of the study or with another relative in the household.

Plasma lactate was measured at selected sites using a standardized blood sampling procedure, without the use of tourniquets, after patients had been at rest for 2 h. Samples were analyzed at a central laboratory.

Statistics

Sample sizes of 7,200 and 1,800 patients in the metformin and usual care primary treatment groups, respectively, would provide 95% confidence of detecting events occurring at a rate of 5/10,000 patient-years in the metformin group, and 17/10,000 patient-years in the usual care group, with ~80% power to detect a 2.4-fold difference in event rates between groups, based on an event rate of ≥5/10,000 patient-years in either group. For the lactate substudy, 456 and 114 patients in the metformin and usual care primary treatment groups would provide 80% power to detect a 0.5 mmol/l difference in mean lactate levels between groups.

SAE incidences were compared using

Table 1—*Characteristics of patients at baseline*

Initial	Metformin	Usual care
n	7,227	1,505
Mean age (years)	58.3 ± 12.9	58.8 ± 13.1
Age <65 years/≥65 years (%/%)	35/65	38/62
Male/female (%/%)	49.3/50.7	49.5/50.5
Race (%)		
White/Caucasian	78.0	76.2
African American	16.2	17.5
Asian	2.9	2.7
Other	2.8	3.6
Mean body weight (lbs)	204.0 ± 48.5	203.2 ± 48.2
Mean body weight (kg)	92.5 ± 22.0	92.2 ± 21.9
Mean diabetes duration (years)	4.9 ± 5.9	4.7 ± 6.0
Previous therapy (%)		
Diet	41.0	35.1
Diet + sulfonylurea	58.5	64.3
Not reported	0.5	0.5

Data are means ± SD. Information on age was not captured for three patients (two in the metformin group and one in the usual care group); these patients are not included in the percentages of patients stratified by age.

Fisher's exact test. All patients who received study treatment were included. Plasma lactate concentrations were compared using a two-sample *t* test.

Ethics

The study was performed in a manner consistent with the Declaration of Helsinki and FDA regulations. The study protocol, the document to be used to elicit patients' informed consent, and material used to recruit patients were approved in advance by institutional review boards (IRBs). Patients provided written informed consent before enrollment, and they consented to study procedures in advance.

RESULTS

Patients

Of 9,000 patients randomized, 7,227 received metformin and 1,505 received usual care. Demographic and other baseline characteristics were similar between groups (Table 1). Patients initially recorded their racial background according to the choices given in Table 1. In response to a further question, 10.0% of the metformin group and 9.5% of the usual care group identified themselves as "Hispanic."

By study end, 89.7% of the metformin group and 76.9% of the usual care group were still receiving their initial study treatment, while 5.4 and 18.9%, respectively, had switched to the alternative treatment arm. The most common reasons for switching from initial treatment (≥1% of patients) were lack of efficacy (1.5 vs. 14.4% in the metformin and usual care groups, respectively), SAEs (0.4 vs. 0.2%), or other AEs (5.6 vs. 2.7%); 3.2% of the metformin group and 1.9% of the usual care group discontinued prematurely.

SAEs

SAEs were reported by 10.3% (95% CI 9.6–11.1%) of the metformin group and by 11.0% (9.5–12.7%) of the usual care group ($P = 0.43$), with a similar pattern of SAEs between groups according to body system (Table 2). Cardiovascular SAEs were the most common (Table 2), including coronary artery disease (1.0 vs. 1.1% for metformin versus usual care, respectively), chest pain (0.7 vs. 1.0%), congestive cardiac failure (0.7 vs. 0.6%), myocardial infarction (0.7 vs. 0.7%), and cerebrovascular accident (0.4 vs. 0.7%). No excess of SAE was observed in the metformin group in elderly (≥65 years) or younger patients (Table 2).

Hospitalizations and mortality

The incidence of all-cause hospitalization, hospitalization for metabolic causes other than lactic acidosis, and all-cause

Table 2—*Overall incidence of SAEs and summary of SAEs by system organ class* (Medical Dictionary for Regulatory Affairs; *SAEs in individual organ classes ≥1.0% in either group before stratification for age) in the metformin or usual care treatment groups: number and percent of patients*

	All patients		Age <65 years		Age ≥65 years	
	Metformin	Usual care	Metformin	Usual care	Metformin	Usual care
n	7,227	1,505	4,710	935	2,515	569
Any SAE	747 (10.3)	166 (11.0)	375 (8.0)	73 (7.8)	371 (14.8)	93 (16.3)
Cardiac disorders	237 (3.3)	49 (3.3)	96 (2.0)	17 (1.8)	141 (5.6)	32 (5.6)
Gastrointestinal disorders	88 (1.2)	18 (1.2)	44 (0.9)	4 (0.4)	44 (1.7)	14 (2.5)
General disorders*	158 (2.2)	39 (2.6)	60 (1.3)	19 (2.0)	98 (3.9)	20 (3.5)
Infections and infestations	121 (1.7)	32 (2.1)	49 (1.0)	10 (1.1)	72 (2.9)	22 (3.9)
Metabolism and nutritional disorders	70 (1.0)	11 (0.7)	35 (0.7)	6 (0.6)	34 (1.4)	5 (0.9)
Neoplasms†	92 (1.3)	20 (1.3)	41 (0.9)	6 (0.6)	51 (2.0)	14 (2.5)
Vascular disorders	92 (1.3)	36 (2.4)	40 (0.8)	16 (1.7)	52 (2.1)	20 (3.5)

Data are *n* (%). *Includes administration site conditions; †benign, malignant, and unspecified (including cysts and polyps). Information on age was not captured for three patients (two in the metformin group and one in the usual care group); data for these patients are included in the 'All patients' section but not in the sections stratified for age at baseline.

Table 3—*Mortality and hospitalizations*

	Metformin (n = 7,227)	Usual care (n = 1,505)	P
All-cause mortality			
All patients (n = 7,227)	1.1 (0.9–1.4)	1.3 (0.8–2.0)	0.596
Patients <65 years (n = 5,645)	0.4 (0.3–0.7)	0.7 (0.3–1.5)	0.21
Patients ≥65 years (n = 3,084)	2.4 (1.8–3.1)	2.1 (1.1–3.7)	0.878
Mortality from lactic acidosis*			
All patients (n = 7,227)	0 (0.00–0.05)	0 (0.00–0.24)	—
All-cause hospitalizations			
All patients (n = 7,227)	9.4 (8.8–10.1)	10.4 (8.9–12.1)	0.229
Patients <65 years (n = 5,645)	7.3 (6.6–8.1)	7.4 (5.8–9.3)	0.945
Patients ≥65 years (n = 3,084)	13.3 (12.0–14.7)	15.5 (12.6–18.7)	0.178
Hospitalizations for lactic acidosis*			
All patients (n = 7,227)	0 (0.00–0.05)	0 (0.00–0.24)	—
Hospitalizations for other metabolic causes			
All patients (n = 7,227)	0.9 (0.7–1.2)	0.9 (0.5–1.6)	1.000
Patients <65 years (n = 5,645)	0.7 (0.5–1.0)	0.7 (0.3–1.5)	0.835
Patients ≥65 years (n = 3,084)	1.3 (0.9–1.8)	1.2 (0.5–2.5)	1.000

Data are percent of patients (95% CI). *Data on mortality or hospitalizations due to lactic acidosis are given for all patients only, as no events due to lactic acidosis were reported. Information on age was not captured for three patients (two in the metformin group and one in the usual care group); data for these patients are included in the 'All patients' section but not in the sections stratified for age at baseline. For numbers of patients aged <65 years or ≥65 years, see Table 2.

mortality did not differ between metformin and usual care in the overall population or in elderly (≥65 years) or younger patients (Table 3). No patient was hospitalized for, or died as a result of, lactic acidosis.

Cardiovascular events were the most common cause of death (0.7% for metformin and 0.9% for usual care). Of these, cardiac deaths occurred in 0.6 and 0.8%, respectively, and vascular deaths in 0.1 and 0.3%, respectively. Principal individual cardiovascular causes of death (metformin versus usual care) were myocardial infarction (0.3 vs. 0.3%), cardiorespiratory arrest (0.1 vs. 0.0%), and congestive heart failure (0.1 vs. 0.3%). There was no difference between primary treatment groups in the pattern of causes of death in patients aged ≥65 years or in younger patients (data not shown).

Mortality rates (% patients, 95% CI) by secondary treatment group were as follows: group 1 (diet-failed, metformin only), 1.0 (0.8–1.4), n = 4,699; group 2 (diet-failed, usual care), 0.4 (0.05–1.4), n = 529; group 3 (metformin added to previous sulfonylurea), 1.3 (0.9–1.8), n = 2,458; group 4 (metformin added to a previous nonsulfonylurea oral agent), 1.4 (0.04–7.7), n = 70; and group 5 (usual care, insulin ± oral antidiabetic therapy, or a nonmetformin oral agent combination), 1.7 (0.95–2.7), n = 68. Within patients previously receiving sulfonylurea monotherapy, slightly lower mortality was observed with metformin-sulfonylurea combination therapy (group 3) than in the corresponding usual care group (group 5). The small number of patients in group 2 precluded a comparison of mortality in diet-failed patients.

Plasma lactate

Mean ± SD plasma lactate was 1.7 ± 0.6 mmol/l in the metformin group and 1.6 ± 0.6 mmol/l in the usual care group after 12 months of treatment (P = 0.137). Plasma lactate >3.0 mmol/l occurred in 4% of the metformin group and 1% of the usual care group (not significant between groups). No patient had plasma lactate >5 mmol/l.

CONCLUSIONS — The COSMIC Approach Study identified no cases of lactic acidosis and no meaningful differences in the incidence of SAEs, the rate of hospitalization for SAEs, or mortality from SAEs, for patients randomized to treatment with metformin or to other antidiabetic regimens in the usual care setting. Secondary analyses demonstrated no meaningful differences for patients randomized to metformin monotherapy versus other monotherapy or to metformin-based combinations versus insulin and/or nonmetformin oral combinations.

The inclusion criteria for the study were broad in order to facilitate recruitment of patients representative of the general U.S. type 2 diabetic population. A comparison of clinical outcomes data from the present study with data provided by the U.S. Centers for Disease Control and Prevention (CDC) suggests that this goal was achieved. The unadjusted mortality rate from "major cardiovascular disease" in 1996 for the overall U.S. diabetic population was 9.7/1,000 (13). In the COSMIC Approach Study, 9.3/1,000 subjects in the usual care group died from a cardiovascular cause. While this is not a quantitative comparison, these data suggest that cardiovascular death rates in the type 2 diabetic population of the COSMIC study were broadly consistent with those receiving usual care elsewhere.

No difference in mean plasma lactate levels was observed between groups in the metformin and usual care groups, consistent with the Cochrane meta-analysis (7), and no patient had a lactate level above the 5.0 mmol/l value included in the definition of lactic acidosis (19,20). The lack of lactic acidosis cases in the COSMIC Approach Study is consistent with the relatively low rates reported before and after the approval of metformin in the U.S. The background rate of lactic acidosis in type 2 diabetic patients not receiving metformin has been estimated as 9.7 cases/100,000 (95% CI 0.2–19.1) person-years (14), which is compatible with the reported rate of about 3 cases/100,000 patient-years for patients treated with metformin, considering the available data on the frequency of reporting of

ADEs. Furthermore, lactic acidosis was not reported in the metformin groups of the U.K. Prospective Diabetes Study (n = 342, average follow-up 10 years) (15) or the Diabetes Prevention Program (n = 1,073, average follow-up 2.8 years) (16). Finally, a Cochrane review of 176 comparative trials and cohort studies revealed no cases of lactic acidosis during 35,619 patient-years of metformin treatment or 30,002 patient-years of other treatments (7,8). Risk factors other than metformin are clearly important in precipitating lactic acidosis (17,18).

The COSMIC Approach Study addressed a specific safety issue relating to the use of metformin in usual medical care. It may serve as a useful model for future post-approval, market place–safety surveillance trials concerning the use of new drugs in the treatment of common diseases.

In conclusion, the long-term (1-year) safety profiles of metformin and other usual care regimens for type 2 diabetes were similar. No cases of lactic acidosis were observed, and plasma lactate did not differ between these therapies. The results of the COSMIC Approach Study suggest that metformin may be safely prescribed for the management of type 2 diabetes if physicians adhere to the contraindications and warnings relating to its use.

Acknowledgments— The COSMIC Approach Study was funded by the Bristol-Myers Squibb Company, Princeton, New Jersey.

References

1. Sirtori CR, Pasik C: Re-evaluation of a biguanide, metformin: mechanism of action and tolerability. *Pharmacol Res* 30:197–228, 1994
2. Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming A: Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 338:265–266, 1998
3. Stacpoole PW, Wright EC, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, Duncan C, Harman EM, Henderson GN, Jenkinson S, Lachin JM, Lorenz A, Schneider SH, Siegel JH, Summer WR, Thompson D, Wolfe CL, Zorovich B: Natural history and course of acquired lactic acidosis in adults: DCA-Lactic Acidosis Study Group. *Am J Med* 97:47–54, 1994
4. Blow O, Magliore L, Claridge JA, Butler K, Young JS: The golden hour and the silver day: detection and correction of occult hypoperfusion within 24 hours improves outcome from major trauma. *J Trauma* 47: 964–969, 1999
5. Misbin RI: Phenformin-associated lactic acidosis: pathogenesis and treatment. *Ann Int Med* 87:591–595, 1977
6. Krentz AJ, Ferner RE, Bailey CJ: Comparative tolerability profiles of oral antidiabetic agents. *Drug Saf* 11:223–241, 1994
7. Salpeter S, Greyber E, Pasternak G, Salpeter E: Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2:CD002967, 2003
8. SalpeterSR, GreyberE, PasternakGA, Salpeter EE: Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. *Arch Intern Med* 163: 2594–2602, 2003
9. Cavallo-Perin P, Aluffi E, Estivi P, Bruno A, Carta Q, Pagano G, Lenti G: The hyperlactemic effect of biguanides: a comparison between phenformin and metformin during 6-month treatment. *Rivista Europe per le Scienze Mediche e Farmacologische* 11:45–49, 1989
10. Kwong SC, Brubacher J: Phenformin and lactic acidosis: a case report and review. *J Emerg Med* 16:881–886, 1998
11. Bailey CJ: Biguanides and NIDDM. *Diabetes Care* 15:755–772, 1992
12. McGuinness ME, Talbert RL: Phenformin-induced lactic acidosis: a forgotten adverse drug reaction. *Ann Pharmacother* 27: 1183–1187, 1993
13. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Diabetes Translation. Diabetes Surveillance 1999 [article online]. Available at http://www.cdc.gov/diabetes/statistics/survl99/chap5/table1.htm. Accessed 6 September 2003
14. Brown JB, Pedula K, Barzilay J, Herson MK, Latare P: Lactic acidosis rates in type 2 diabetes. *Diabetes Care* 21:1659–1663, 1998
15. UK Prospective Diabetes Study Group: Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
16. Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
17. Aguilar C, Reza A, Garcia JE, Rull JA: Biguanide related lactic acidosis: incidence and risk factors. *Arch Med Res* 23:19–24, 1992
18. Lalau J-D, Race J-M: Lactic acidosis in metformin-treated patients: prognostic value of arterial lactate levels and plasma metformin concentrations. *Drug Saf* 20: 377–384, 1999
19. Huckabee WE: Hyperlactatemia. *Helv Med Acta* 35:363–376, 1970
20. Stacpoole PW, Harman EM, Curry SH, Baumgartner TG, Misbin RI: Treatment of lactic acidosis with dichloroacetate. *N Engl J Med* 309:390–396, 1983