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Effects of Metformin on Microvascular Function and Exercise Tolerance in Women With Angina and Normal Coronary Arteries

A Randomized, Double-Blind, Placebo-Controlled Study

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OBJECTIVES This study sought to determine whether metformin improves vascular function or myocardial ischemia in nondiabetic subjects.

BACKGROUND Metformin prevents diabetes and may reduce coronary events in patients with diabetes, but effects on microvascular function and angina are not clear.

METHODS We conducted an 8-week double-blind, randomized, placebo-controlled study of metformin 500 mg twice a day in 33 nondiabetic women with a prior history of normal coronary angiography but two consecutive positive (ST-segment depression ≥1 mm) exercise tolerance tests. All parameters were measured at baseline and at 8 weeks, together with an in vivo assessment of forearm (skin) microvascular function using laser Doppler imaging combined with iontophoresis.

RESULTS In comparison with placebo (n = 17), metformin recipients (n = 16) showed significant reductions in weight and in homeostatic model assessment for insulin resistance ($p < 0.05$, intention to treat). Endothelium-dependent microvascular responses improved significantly with metformin (2-way repeated analysis of variance, $p = 0.0003$), but responses with placebo were unchanged ($p = 0.50$). A comparison of change in acetylcholine responses between metformin and placebo recipients was significant, whether analyzed by a 2-way analysis of variance ($p < 0.0001$) or change in area under curves (mean change +392 perfusion units, 95% confidence interval [CI] 20 to 764). Endothelium-independent responses were not altered. Maximal ST-segment depression (−0.84 mm, 95% CI −1.49 to −0.20, $p = 0.013$), Duke score (6.1 U, 95% CI 1.8 to 10.5, $p = 0.008$), and chest pain incidence (−0.11 episodes/day, 95% CI −0.22 to 0.00, $p = 0.056$) improved in metformin relative to placebo recipients.

CONCLUSIONS Metformin may improve vascular function and decrease myocardial ischemia in nondiabetic women with chest pain and angiographically normal coronary arteries. Larger controlled trials of longer duration are warranted. (J Am Coll Cardiol 2006;48:956–63) © 2006 by the American College of Cardiology Foundation

Metformin is an antihyperglycemic agent with a history of successful use in type 2 diabetes. In the UKPDS (United Kingdom Prospective Diabetes Study), metformin was associated with a 39% lower risk of myocardial infarction compared with conventional therapy (1). In a more recent epidemiologic analysis, metformin was associated with a near 40% reduced total and coronary heart disease (CHD) mortality when compared with sulfonylurea monotherapy (2). In a retrospective analysis of the Prevention of Restenosis With Tranilast and Its Outcomes Trial (3), use of metformin in diabetic patients undergoing coronary interventions decreased adverse clinical events, especially death and myocardial infarction (79% risk reduction) when compared with patients treated with either a sulfonylurea or insulin. Consistent with such data, metformin variably improves lipids and hemostatic function in patients with type 2 diabetes (4). One placebo-controlled study in patients with type 2 diabetes suggested that metformin may improve directly measured vascular function (5) independent of any weight change, but such studies are lacking in nondiabetic populations.

Current therapeutic options for a well-recognized group of patients with anginal symptoms—a positive exercise tolerance testing (ETT) but angiographically smooth coronary arteries—are limited (6). The condition, sometimes referred to as cardiac syndrome X, is not as benign as originally reported—patients presenting with unstable angina and nonobstructive atherosclerotic coronary artery disease have a 2% risk of death or myocardial infarction at 30 days of follow-up (6). It is more common in women in whom the first presentation of angina occurs either perimenopausally or postmenopausally (7). Many such patients are insulin resistant (8–10) and have associated metabolic and hemostatic abnormalities (8,9). Aberrant flow-mediated coronary vasomotion is pivotal in the pathogenesis

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Abbreviations and Acronyms

ACh	= acetylcholine
ANOVA	= analysis of variance
CHD	= coronary heart disease
CI	= confidence interval
ETT	= exercise tolerance test
HOMA-IR	= homeostatic model assessment for insulin resistance
LDI	= laser Doppler imaging
PPAR	= peroxisome proliferator-activated receptor
SNP	= sodium nitroprusside
tPA	= tissue plasminogen activator

of this syndrome, and occurs as part of a more generalized (systemic) impairment in endothelial function (11). Indeed, some centers use systemic assessments of vascular function in their diagnostic pathways for this group of women (12). We recently suggested that insulin resistance, acting via endothelial dysfunction, may lead to myocardial ischemia and that insulin sensitization via metformin or other agents may lessen ischemia (13).

In the present study, we tested the hypothesis that metformin offers dual benefits of improving vascular function and lessening ischemia in nondiabetic women with angina, ischemic ETTs, and normal-appearing coronary arteries. The primary end point of the study was the effects of metformin on microvascular function (measured by laser Doppler technology) in women previously categorized after investigation in local hospitals as having cardiac syndrome X (i.e., angina, a positive ETT, and a normal coronary angiogram) and who also had a repeat positive ETT before randomization. The secondary goals of this study were: 1) to assess the effects of metformin on chest pain incidence, maximal ST-segment depression, and Duke score; and 2) to examine whether metformin improved other metabolic parameters linked to insulin resistance in such women.

METHODS

We recruited 33 women with smooth unobstructed epicardial arteries shown on coronary angiography between 1997 and 2001 at Glasgow Royal Infirmary. All of these women had ongoing typical anginal-type chest pain and had previously documented ≥1 mm of flat ST-segment depression on treadmill exercise testing and a repeat positive ETT at the pre-randomization visit (i.e., all had 2 consecutive positive ETTs). Those with even minor coronary plaque disease, insignificant up-sloping ST-segment change during exercise, and coronary artery spasm at angiography were excluded. All women underwent pre-trial screening with blood tests and echocardiography. Other exclusion criteria included age >70 years, diabetes, uncontrolled hypertension, valvular or other structural heart disease, and significant hepatic or renal impairment.

After approval by the Glasgow Royal Infirmary Ethics Committee, eligible patients gave written informed consent to participate. Antianginal therapy was stopped or reduced for a 4-week period before the trial in the majority of patients, in keeping with the procedure in a prior trial of hormonal replacement in cardiac syndrome X in which all cardiac drugs were stopped 3 weeks before active treatment or placebo (14). After this period, a chest pain diary was provided to each woman, and they were each asked to record on a daily basis the number of typical anginal-type chest pains they had suffered. We collated this information separately for 4 weeks before treatment and over the 8 weeks on treatment. All patients were invited to attend in the fasting state for baseline assessments.

Laser Doppler imaging (LDI). Microvascular function was assessed, as detailed previously (15–18), using LDI with the subject relaxed in the supine position in a quiet, temperature- and light-controlled environment. This was carried out before any blood tests were obtained before randomization and repeated in week 8. Briefly, drugs were administered transdermally by iontophoresis, using Perspex chambers (Moor Instruments Ltd., Axminster, United Kingdom) applied to the extensor forearm surface. The cathodal chamber was filled with sodium nitroprusside (SNP), an endothelium-independent vasodilator (1% dissolved in 0.5% sodium chloride), and the anodal chamber with acetylcholine (ACh), an endothelium-dependent vasodilator (1% dissolved in 0.5% sodium chloride). We also used vehicle (0.5% sodium chloride) controls in the opposite forearm. Incremental current (expressed as charge, the integral of the current × time relationship, in milliCoulombs) was applied with concurrent laser Doppler imaging to record the perfusion response. The perfusion response in flux perfusion units is presented as both the area under the curve for the scan and as a plot of the change in perfusion with drug administration (in arbitrary perfusion units) against cumulative charge. The mean (±SD) between-day coefficient of variation in healthy subjects for the ACh response was 6.4%, whereas the within-day, between-site coefficient of variation, measured in both forearms, was 8.9%.

Blood investigations. Fasting blood samples were collected and stored in aliquots at −80°C for batch analysis at the end of the study. Tissue plasminogen activator (tPA), von Willebrand factor (Dako, Copenhagen, Denmark) antigens, intercellular adhesion molecule-1 (R&D Systems Inc., Oxon, United Kingdom) and high-sensitivity C-reactive protein (Dako A/S, DK-2600 Glostrup, Denmark) were determined by enzyme-linked immunosorbent assay techniques. The inter-assay and intra-assay coefficients of variation were <7% across the range of measured results. Insulin was measured by a microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, Illinois) with a coefficient of variation <8% and sensitivity of 0.8 mU/l. Plasma glucose was measured using the glucose oxidase method (glucose reagent kit, Olympus AU5200, Opticals UK Ltd., London, United Kingdom). Finally, the lipid

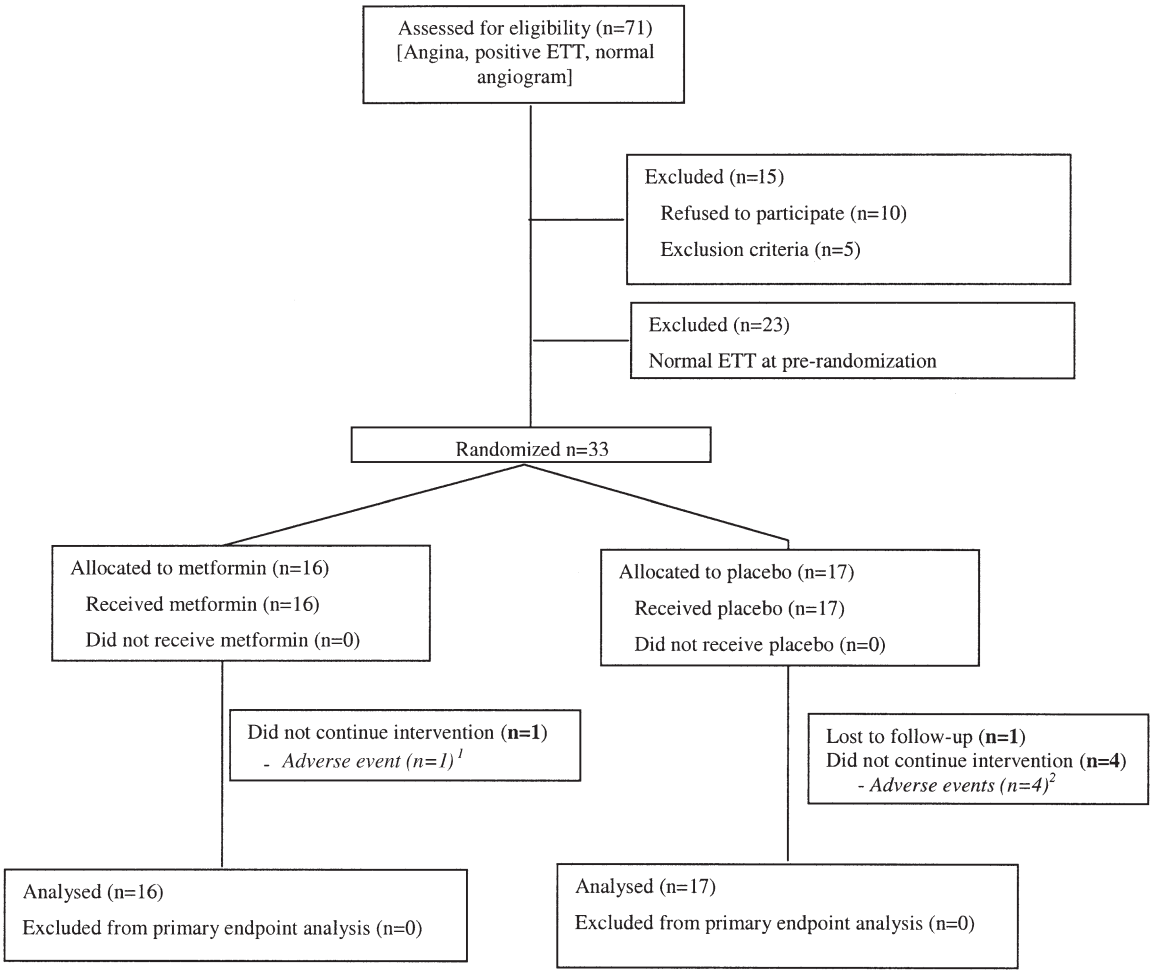

Figure 1. The CONSORT (Consolidated Standards of Reporting Trial) diagram describing outcomes of all women within the study. [1]Gastrointestinal side effects. [2]There was 1 patient admitted with chest pain, 1 patient with gastrointestinal side effects, and 2 patients with nonspecific symptoms. ETT = exercise tolerance test.

profile was measured using established methods (Boehringer reagent kits, East Sussex, United Kingdom). Homeostasis model assessment for insulin resistance (HOMA-IR) (fasting plasma insulin [μU/ml] $\times$ fasting plasma glucose [mmol/l]/22.5) was used to determine insulin resistance.

Other clinical measures. Blood pressure was measured in triplicate following 5 min of rest in the supine position using an Omron 705-CPII (Optical Healthcare UK Ltd., Milton Keynes, United Kingdom), and the average was taken. Height and weight measurements were recorded to calculate body mass index.

ETT. All patients underwent a full Bruce protocol treadmill test at baseline and then again after 8 weeks of metformin or placebo. Exercise time was noted, and maximum ST-segment depression was recorded to the nearest 0.5 mm to avoid artefact contamination. The Duke score (calculated as total exercise time in minutes $-$ [5 $\times$ maximal ST segment deviation] $-$ [4 $\times$ index]) was used to provide an objective measure of treadmill testing performance. A chest pain index of 0 is assigned if no chest pain is experienced, 1 is recorded for nonlimiting pain, and 2 is recorded for limiting chest pain. The Duke score has been shown to indicate prognosis in suspected coronary disease (19).

Table 1. Baseline Characteristics of 33 Women With Repeat Positive Exercise Tolerance Test at Baseline

	Metformin (n = 16)	Placebo* (n = 17)
Age (yrs)	55.8 (8.8)	58.1 (8.4)
Body mass index, kg/m^2	28.2 (3.7)	28.1 (3.6)
Weight (kg)	71.3 (8.7)	72.7 (9.5)
Current smoker, n (%)	3 (19)	3 (18)
Postmenopausal, n (%)	10 (63)	8 (47)
Hormone replacement therapy use, n (%)	6 (38)	3 (18)
Aspirin, n (%)	13 (81)	14 (82)
Statin use, n (%)	8 (50)	5 (29)
Beta-blockers, n (%)	0 (0)	1 (6)
Nitrate, n (%)	2	2
Calcium channel blockers, n (%)	1	0
Nicorandil, n (%)	0	2

*No significant difference ($p > 0.10$) in any baseline characteristics in metformin versus placebo group.

Randomization. Metformin (500-mg tablets) and an identical placebo were administered in a double-blind randomized fashion in a 1:1 ratio. Metformin and placebo were given with instructions to take one tablet daily for 1 week, increasing to twice daily for the remaining 7 weeks of the trial. Randomization was done in blocks of four, with codes being held by the pharmacy until data analysis was completed. Compliance was checked by pill counting. Subjects were asked to record side effects but to persevere with the tablets unless symptoms were severe.

Statistical methods. Data are presented as mean (SD) for all parameters other than chest pain incidence (for which we present median and interquartile range). Comparison of change in parameter concentrations between groups was examined by the two-sample *t* test (or Mann-Whitney *U* test for chest pain incidence) and 2-way analysis of variance (ANOVA) between groups (with group and cumulative charge as main factors) for vascular function measures on an intention-to-treat analysis using the last value carried forward in the case of drop-outs. A p value < 0.05 was considered significant. Change within groups was examined by paired *t* test or Wilcoxon signed rank test (chest pain incidence) or 2-way repeated ANOVA for vascular function (baseline vs. treatment and cumulative charge as main factors). The p values reported for vascular function analyses refer to the vasodilator response to ACh or SNP at baseline compared with the value obtained after treatment with metformin or placebo (i.e., analysis confined within the treatment group), or the difference between baseline and treatment for each vasodilator when comparing metformin with placebo. Whether changes in parameters were associated was assessed using a simple Pearson correlation.

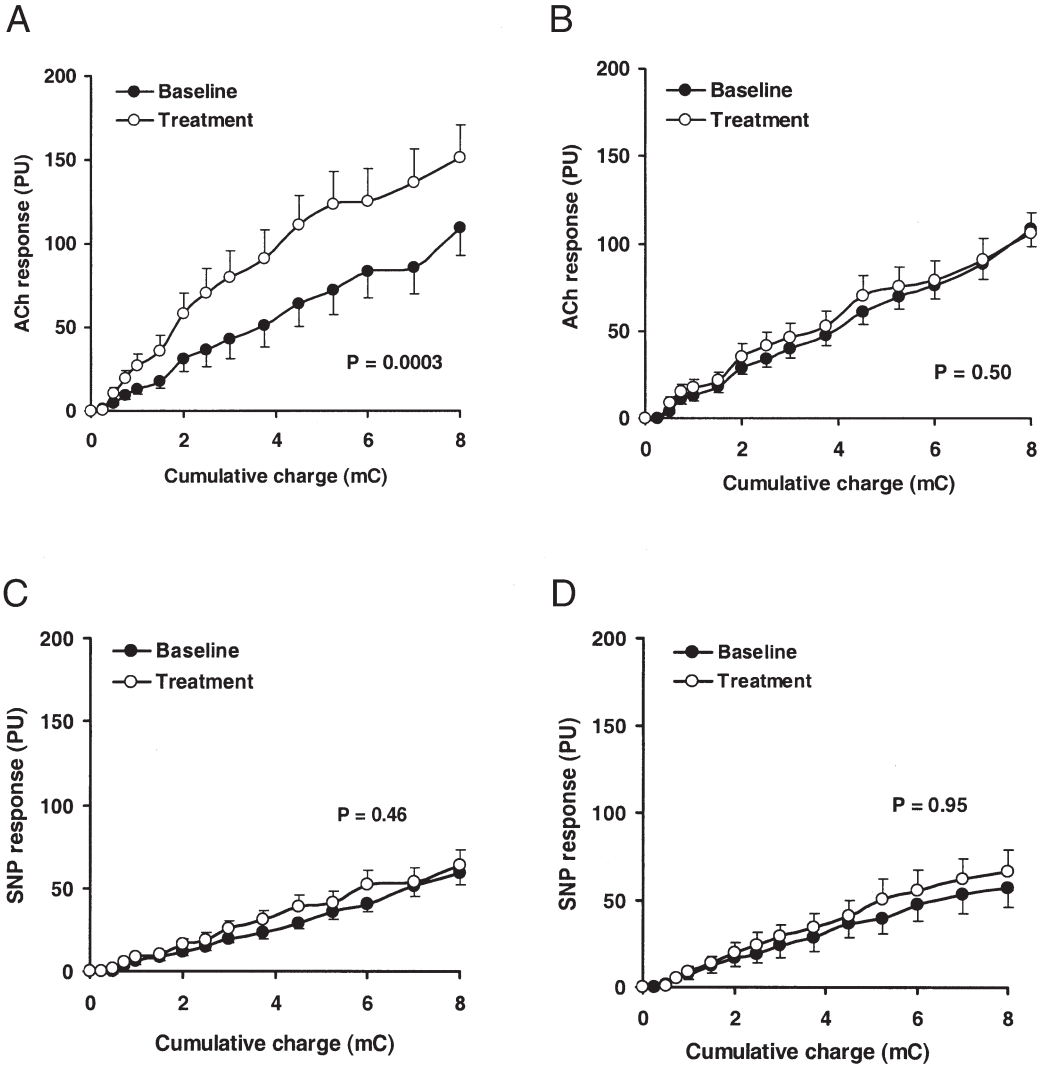

Figure 2. **(A)** Baseline and on-treatment (8 weeks) microvascular responses to acetylcholine (ACh) in the 16 women randomized to metformin (p = 0.0003, 2-way repeated measures analysis of variance [ANOVA]). **(B)** Baseline and on-treatment (8 weeks) microvascular responses to ACh in the 17 women randomized to placebo (p = 0.50, 2-way repeated measures ANOVA). **(C)** Baseline and on-treatment (8 weeks) microvascular responses to sodium nitroprusside (SNP) in the 16 women randomized to metformin (p = 0.46, 2-way repeated measures ANOVA). **(D)** Baseline and on-treatment (8 weeks) microvascular responses to SNP in the 17 women randomized to placebo (p = 0.95, 2-way repeated measures ANOVA).

JACC Vol. 48, No. 5, 2006
September 5, 2006:956–63

Adjustment for change in weight was performed by analysis of covariance.

RESULTS

Seventy-one women were screened for inclusion (Fig. 1). Fifty-six women with a previously documented positive ETT but normal coronary angiograms were seen at a pre-randomization visit. Of these, the 33 who had a repeat positive ETT formed the study cohort. Sixteen women were randomized to receive metformin and 17 were to receive a placebo. Statistical analysis was performed as pre-specified on an intention to treat basis. Compliance, as checked by pill-counting at the end of the trial, was good with 85% of study completers showing >90% compliance, and compliance was not different between groups ($p > 0.50$). Gastrointestinal side effects were more prevalent in the metformin group, affecting 10 of the 16 women, compared with 3 of 17 in the placebo group (chi-square, $p < 0.05$), but were transient in the vast majority. No symptoms of hypoglycemia were reported.

Demographic characteristics. The baseline characteristics are given in Table 1. The women randomized to metformin or placebo were similar for baseline characteristics, including age, body mass index, and smoking history.

Primary end point analyses on vascular function. Blood flow response to ACh improved in women who were randomized to metformin (2-way repeated measures ANOVA $p = 0.0003$) (Fig. 2A), but there was no significant change within placebo recipients (Fig. 2B). Responses to SNP were unchanged for both the metformin and the placebo group (Figs. 2C and 2D). Comparing the change in ACh response (treatment minus baseline) between metformin and placebo recipients revealed a highly significant improvement in the former group relative to the latter (2-way ANOVA $p < 0.0001$), but there was no alteration for SNP (Figs. 3A and 3B). Comparison of the area under the curve in metformin relative to placebo recipients was also significant (change +392 perfusion units, 95% confidence interval [CI] 20 to 764); $p = 0.04$).

Metabolic effects. Analyses of metabolic changes are shown in Table 2. There was a significant reduction in weight and HOMA-IR ($p = 0.026$ and $p = 0.045$, respectively) and a trend toward a reduction in tPA antigen ($p = 0.09$) in metformin relative to placebo recipients.

Exercise tolerance data and chest pain frequency. Baseline and follow-up data for maximal ST-segment depression and chest pain incidence in the women treated with metformin and placebo are shown in Figures 4A and 4B. Baseline values were not significantly different between the two groups for either parameter ($p = 0.23$ and $p = 0.69$, respectively). Significant improvements in both maximal ST-segment depression and chest pain incidence occurred in the metformin recipients (38% reduction, $p = 0.007$, and 30% reduction, $p = 0.039$, respectively), but such parameters were unaltered in placebo recipients ($p > 0.45$).

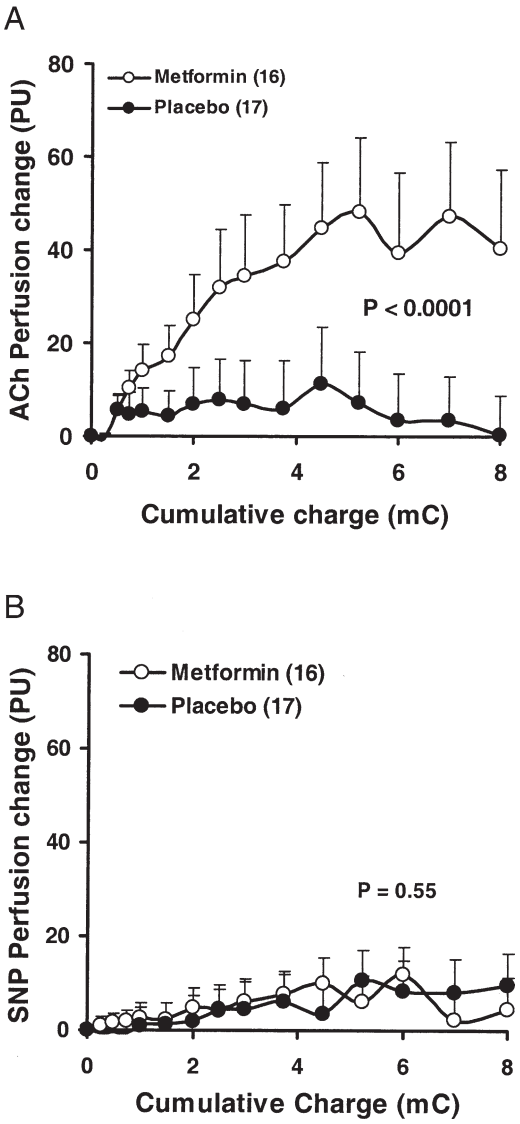

Figure 3. **(A)** Change over 8 weeks in microvascular responses to acetylcholine (ACh) in metformin and placebo groups ($p < 0.0001$, 2-way repeated measures analysis of variance [ANOVA]). **(B)** Change over 8 weeks in microvascular responses to sodium nitroprusside (SNP) in metformin and placebo groups ($p = 0.55$, 2-way repeated measures ANOVA).

Maximal ST-segment improvement was significantly larger for metformin than for placebo ($p = 0.013$). Median reduction in chest pain episodes was larger for metformin than placebo, and this difference approached significance (−0.11 episodes per day, 95% CI −0.22 to 0.00, $p = 0.056$). Duke score improved by a mean of 6.1 U (95% CI 1.8 to 10.5, $p = 0.008$) in metformin versus placebo recipients. Of the 16 women randomized to active therapy, 13 had a reduction in chest pain incidence, in contrast with 6 of the 17 in the placebo group (chi-square $p < 0.01$).

Effect of weight change on primary end point, change in HOMA-IR, and ST-segment depression. In the 16 women randomized to metformin alone, reduction in maximal ST-segment depression correlated significantly only to reduction in tPA antigen concentration ($r = 0.64$, $p = 0.01$)

Table 2. Clinical Characteristics of the Metformin and Placebo Groups at Baseline and Comparison of Change Over 8 Weeks in Metabolic Parameters

	Metformin (n = 16)		Placebo (n = 17)		Mean Difference, 95% Confidence Interval	p Value
	Baseline	Change	Baseline	Change		
Weight (kg)	71.3 (8.7)	−0.64 (1.45)	72.7 (9.5)	0.48 (1.29)	−1.13 (−2.10, −0.15)	0.026
Fasting glucose (mmol/l)	4.89 (0.5)	−0.07 (0.47)	4.87 (0.4)	0.11 (0.28)	−0.18 (−0.46, 0.10)	0.20
HOMA-IR	1.80 (1.02)	−0.51 (0.79)	1.92 (1.32)	0.01 (0.62)	−0.52 (−0.014, −1.025)	0.045
Systolic blood pressure (mm Hg)	130.0 (21.0)	−5.7 (26.0)	136.5 (11.2)	0.12 (8.7)	5.8 (−8.2, 19.8)	0.40
Diastolic blood pressure (mm Hg)	78.3 (8.7)	−2.4 (8.9)	81.3 (26.0)	−3.6 (6.6)	1.2 (−4.4, 6.8)	0.66
Total cholesterol (mmol/l)	4.74 (0.7)	−0.04 (0.71)	5.27 (0.9)	−0.21 (0.68)	0.17 (−0.33, 0.67)	0.49
Triglycerides (mmol/l)	1.31 (0.5)	−0.08 (0.39)	1.40 (0.7)	0.05 (0.36)	−0.13 (−0.40, 0.14)	0.33
Low-density lipoprotein cholesterol (mmol/l)	2.85 (0.5)	0.06 (0.53)	3.26 (0.8)	−0.13 (0.50)	0.07 (−0.29, 0.43)	0.70
High-density lipoprotein cholesterol (mmol/l)	1.49 (0.3)	0.041 (0.15)	1.30 (0.4)	−0.015 (0.11)	0.06 (−0.04, 0.15)	0.23
Tissue plasminogen activator (ng/ml)	7.00 (3.2)	−1.28 (1.93)	8.53 (3.2)	0.06 (2.5)	−1.3 (−2.9, 0.23)	0.09
von Willebrand factor (IU/dl)	122 (41)	7 (14)	134 (36)	8 (16)	−1.0 (−12, 10)	0.86
Intercellular adhesion molecule-1 (ng/ml)	273 (75)	−7 (40)	264 (68)	−5 (12)	−2.3 (−24, 20)	0.83
C-reactive protein (mg/l)	3.45 (2.0)	−0.10 (1.8)	3.3 (2.9)	0.31 (0.67)	−0.4 (−1.5, 0.6)	0.42

Data are mean (SD).
HOMA-IR = homeostatic model assessment for insulin resistance.

and reduction in weight (r = 0.55, p = 0.024), the former association independent of the latter. Changes in ACh responses and ischemic parameters did not correlate. Importantly, metformin-induced changes in ACh-mediated vascular response, HOMA-IR, and to a lesser extent ST-segment depression were minimally attenuated by adjustment for weight change differences by group (Table 3).

DISCUSSION

This is the first placebo-controlled study to show that metformin improves endothelium-dependent vascular function in nondiabetic subjects. Because abnormal systemic/coronary endothelial function may be causally linked both to states of insulin resistance (20,21) and to CHD (22,23), our findings are clinically relevant and consistent with other favorable effects of metformin (1–3) and for its prevention of type 2 diabetes in subjects at elevated risk (24). Our study also suggests that metformin may reduce myocardial ischemia in women with exercise-induced angina and normal coronary arteries. The combined beneficial effects of metformin on vascular function, metabolic parameters, and ischemia suggest its potential to lessen vascular risk. These findings are important because the prognosis of this common condition is not as benign as previously considered (6).

We examined effects of skin microvascular function using LDI combined with iontophoresis of vasoactive agents. Our group has considerable experience with this technique, having shown impaired skin microvascular function in obesity, in diabetes, and in the post-prandial state, whereas others have linked it to insulin resistance (15–18). The metformin-treated subjects showed a clear improvement in ACh response (Figs. 2A and 3A), a finding also consistent in analyses of completers (data not shown).

Why should vascular function improve with metformin? If insulin resistance is a precursor to endothelial dysfunction, ameliorating insulin resistance should improve it. Metformin induced a small but significant reduction in weight (approximately 1 kg or 2% relative to placebo) and a significant change in HOMA-IR relative to placebo (>20%). Although this reduction in HOMA-IR was slightly attenuated (p = 0.045 to p = 0.08) after adjusting for weight change, neither change correlated with improvement in ACh response. However, reduction in tPA antigen (partially endothelial-derived) concentration in the metformin group did correlate with reduction in maximal ST-segment depression; of note, elevated tPA is an independent predictor of both CHD events (25) and type 2 diabetes (26). Of interest, improvements in vascular function occurred despite no significant changes in glucose or inflammation parameters. De Jager et al. (27) reported that beneficial effects of metformin on circulating markers of endothelial function were independent of glycemic changes in patients with type 2 diabetes. Changes in vascular function were also not explained by change in weight (Table 3). It should be noted that metformin has other complex intra-cellular actions, one of which is activation of AMP-activated protein kinase (28,29), and to exert this action by phosphorylation of the endothelial isoform of endothelial nitric oxide synthase at serine 177 in human aortic endothelial cells (30,31). This is a plausible candidate mechanism for the vasoactive effects of metformin, independent of its effects on insulin action, weight, or other parameters.

Our study was designed to detect change in endothelial function, but we were also interested in effects on ischemia given prior, albeit uncontrolled, evidence of such benefits with metformin and troglitazone in patients with diabetes and angina (reviewed in [13]). Our positive results on the effects of metformin (but not placebo) on maximal ST-segment depression, Duke score, and episodes of chest pain suggest a reduction in ischemia. As such, our findings are of potential clinical importance and are in keeping with recent novel approaches to target metabolic processes in the vasculature as a method of reducing myocardial ischemia (32). Similarly, in studies of diabetes patients, thiazo-

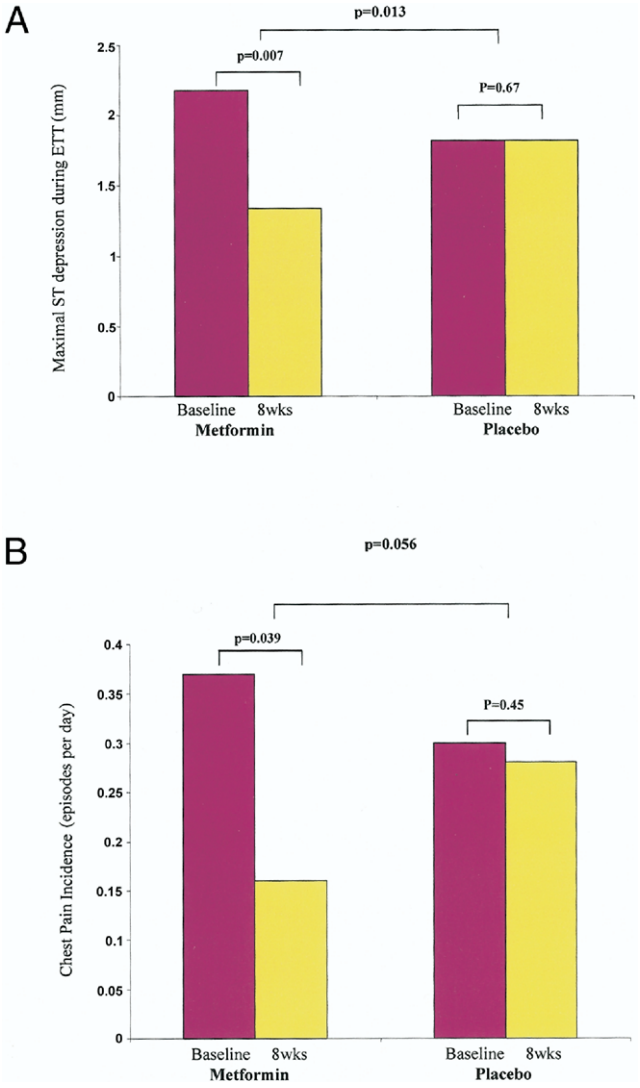

Figure 4. (A) Mean maximal ST-segment depression during exercise tolerance test (ETT) (mm) at baseline and on treatment (8 weeks) in the 33 women randomized to placebo (n = 17) or metformin (n = 16). **(B)** Median chest pain incidence before randomization and on treatment in the 33 women randomized to placebo (n = 17) or metformin (n = 16).

lidinedione insulin sensitizers have been shown to lessen anginal pain (33), improve myocardial blood flow (34), and regulate activity of endothelial nitric oxide synthase, the latter occurring at least in part via a peroxisome proliferator-activated receptor (PPAR)-gamma action (35). Interestingly, a significantly lower incidence of admission for angina was reported for the pioglitazone arm relative to placebo in the recent PRO-ACTIVE (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study (36).

Study limitations. We acknowledge that a more robust measure of myocardial ischemia would have enhanced the study. Nevertheless, the women in our cohort had a good history of exercise angina, two consecutive positive ETTs, and evidence of impaired systemic vascular dysfunction, a collection of findings that, we believe, would be considered satisfactory by many cardiologists to make the diagnosis of cardiac syndrome X. Moreover, the consistency of improvements in vascular, metabolic, and ischemia data by chest pain questionnaire and during the ETT in the metformin group, even at a relatively low dose, is reassuring. We also accept that although the measure of vascular function we used is well validated, it would have been optimal to measure endothelial function in coronary arteries directly. That noted, to repeat coronary angiography in a group with recently documented normal coronary arteriography would have raised ethical issues.

Table 3. Raw and Weight Change-Adjusted Differences in Metformin Versus Placebo Recipients for Change in Vascular Response (AUC for ACh-Mediated Perfusion), HOMA-IR, and ST-Segment Depression

	Beta	SE	p
AUC for ACh response	392	179	0.04
Adjusted for delta weight	395	197	0.05
HOMA-IR (raw difference)	−0.52	0.25	0.045
Adjusted for delta weight	−0.49	0.27	0.08
ST-segment depression (raw difference)	−0.84	0.30	0.013
Adjusted for delta weight	−0.51	0.29	0.095

ACh = acetylcholine; AUC = area under the curve; HOMA-IR = homeostatic model assessment for insulin resistance; SE = standard error.

Conclusions. In summary, using a double-blind placebo-controlled study design, we have shown that metformin improves endothelium-dependent vascular function and ischemia in women with a history of exercise-induced angina, reproducible positive ETTs, but normal coronary arteries on angiography. Such effects suggest that metformin may have the potential not only to improve clinical symptoms in this patient group, possibly via positive effects on microvascular function, but also to reduce vascular risk in the longer term. Larger studies are now required to expand these novel findings.

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