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Relation of *Metformin* Treatment to Clinical Events in Diabetic Patients Undergoing Percutaneous Intervention

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Diabetic patients undergoing coronary interventions have worse clinical and angiographic outcomes than do patients without diabetes. Metformin, an insulin sensitizer, may decrease the occurrence of these outcomes. Diabetic patients in the Prevention of Restenosis with Tranilast and its Outcomes Trial were identified through their medical records (n = 2,772). In this trial, 1,110 diabetic patients received nonsensitizer therapy (insulin and/or sulfonylureas) and 887 received sensitizer therapy (metformin with or without additional therapy). Logistic regression was used to obtain odds ratios (ORs) (sensitizer vs nonsensitizer therapy) of any clinical event (death, myocardial infarction, or ischemia-driven target vessel revascularization) and adjusted for multiple risk factors. Multivariate analysis showed no effect of lesion characteristics on clinical outcomes. Compared with patients on nonsensitizer therapy, those on sensitizer therapy showed an adjusted OR of 0.72 (95% confidence interval [CI] 0.57 to 0.91, p = 0.005) for any clinical event. The differences between the nonsensitizer therapy group and the sensitizer group were attributable mainly to decreased rates of death (OR 0.39, 95% CI 0.19 to 0.77, p = 0.007) and myocardial infarction (OR 0.31, 95% CI 0.15 to 0.66, p = 0.002). In our retrospective analysis, use of metformin in diabetics undergoing coronary interventions appeared to decrease adverse clinical events, especially death and myocardial infarction, compared with diabetic patients treated with nonsensitizer therapy.
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Metformin may have beneficial effects on cardiovascular outcomes because of its actions as an insulin sensitizer.[1–4] Insulin sensitizers act by decreasing endogenous and exogenous insulin requirements and have other potentially beneficial effects on the cardiovascular system.[5–16] We hypothesized that diabetic patients enrolled in the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) Trial and treated with metformin would demonstrate a lower adverse event rate than diabetic patients treated with non–insulin-sensitizing medications.

METHODS

The PRESTO Trial was the largest randomized interventional trial performed, with extensive patient follow-up. A retrospective review of the 11,484 patients in the PRESTO study was performed to identify all patients with diabetes. A diabetic patient was defined as any patient with diabetes listed as a concurrent medical illness or who was currently receiving medical therapy for diabetes at the time of study enrollment. Medical therapy for diabetes included treatment with any combination of sulfonylureas, biguanides, thiazolidinediones, or insulin. The database was unable to differentiate patients with type 1 diabetes from those with type 2 diabetes. A total of 2,772 patients (25%) with diabetes were identified. Patients were stratified according to the diabetes-treatment regimen: (1) non–insulin-sensitizing therapy (1,110 patients), which included any combination of sulfonylureas and insulin; (2) metformin therapy (887 patients), which consisted of metformin with or without adjunctive medical therapy at any time during the study period; and (3) no medical therapy for diabetes (663 patients) or treatment with thiazolidinediones alone (112 patients). Patients without medical therapy for diabetes were excluded because the aim of the study was to compare the role of medical treatment for diabetes on cardiovascular outcomes. In addition, patients in the PRESTO Trail treated with thiazolidinediones on study entry were required to discontinue this medication for the duration of the study due to potential adverse interactions with tranilast. The residual study population consisted of 1,997 patients.

The primary study end point was the rate of major adverse cardiac events, comprised of the composite incidence of myocardial infarction (MI), death, and ischemia-driven target vessel revascularization (TVR). Secondary end points were incidences of death, MI, and ischemia-driven TVR.

Unadjusted associations between diabetes treatment groups and various demographic variables, medical history variables, and procedural characteristics

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TABLE 1 Baseline Clinical and Angiographic Characteristics

Variable	Nonsensitizer Therapy (n = 1,110)	Metformin Therapy (n = 887)	p Value
Age (yrs)	62.5 ± 10.1	60.7 ± 9.7	<0.001
Gender			0.92
Women	328 (30%)	264 (30%)	
Men	782 (70%)	623 (70%)	
Ethnicity			0.044
Black	51 (5%)	51 (6%)	
White	1,019 (92%)	783 (88%)	
Asian	7 (1%)	11 (1%)	
Other	33 (3%)	42 (5%)	
Weight (lbs)	187.3 ± 37.0	199.7 ± 39.6	<0.001
Treatment			
Statins	752 (68%)	648 (73%)	0.010
β blockers	834 (75%)	694 (78%)	0.10
Angiotensin-converting enzyme inhibitors	635 (57%)	510 (57%)	0.90
Nonsteroidal anti-inflammatory drugs	559 (50%)	517 (58%)	<0.001
Ticlopidine/clopidogrel	1,024 (92%)	833 (94%)	0.15
Glycoprotein IIb/IIIa inhibitors	197 (18%)	182 (21%)	0.12
Angiotensin receptor blockers	899 (81%)	697 (79%)	0.18
Calcium blockers	589 (53%)	451 (51%)	0.32
Thrombolytics	41 (4%)	27 (3%)	0.43
Antiplatelets (excluding aspirin)	1,048 (94%)	843 (95%)	0.54
Medical history			
Current smoker	167 (15%)	146 (16%)	0.39
Systemic hypertension	819 (74%)	687 (77%)	0.06
Dyslipidemia	687 (62%)	578 (65%)	0.13
Prior MI	446 (40%)	353 (40%)	0.86
Prior coronary artery bypass graft	198 (18%)	176 (20%)	0.25
Prior percutaneous coronary intervention	388 (35%)	336 (38%)	0.18
Congestive heart failure	124 (11%)	102 (11%)	0.82
Coronary heart disease	567 (51%)	528 (60%)	<0.001
Unstable angina pectoris	723 (65%)	570 (64%)	0.68
Peripheral vascular disease	114 (10%)	77 (9%)	0.23
Stable angina pectoris	601 (54%)	517 (58%)	0.06
Alcohol consumption	424 (38%)	317 (36%)	0.49
Ejection fraction (%)	60 ± 13.1	58 ± 12.7	0.008

The p values represent interactions between the nonsensitizer and metformin groups. Dyslipidemia is defined as low-density lipoprotein >130 mg/dl and/or treatment for hypercholesterolemia.

were examined. No distinctions were made based on tranilast therapy in the grouping of patients because of the absence of drug effect on the incidence of major adverse cardiac events in the overall trial. A separate analysis was performed to confirm no interaction between metformin and tranilast ($p = 0.16$). To determine whether a categorical variable was related to the diabetes group, chi-square tests of independence were used. For quantitative variables such as age or ejection fraction, 2-sample *t* tests were used. Unadjusted associations between diabetes treatment group and clinical events, including death, MI, ischemia-driven TVR, and the combination of these are also presented, as are p values based on chi-square tests. For patients with multiple lesions treated with percutaneous coronary intervention, the analysis was restricted to the lesion treated that had the most severe stenosis at baseline.

Logistic regression was used to obtain odds ratios (ORs) (metformin vs nonsensitizer therapy) of the primary end point as a function of diabetes treatment group. Unadjusted models and models including age, gender, study center, percent stenosis after percutaneous coronary intervention, and tranilast treatment group are presented. In addition, a stepwise search through baseline characteristics was performed, allowing those significant at the 0.05 level to enter the model.

Similar models were constructed for ischemia-driven TVR only, MI only, and death. A secondary analysis considered time to incident clinical event as a function of diabetes treatment group. Kaplan-Meier curves were used to illustrate the unadjusted relation. In addition, Cox's proportional hazards model was used to adjust for other covariates. For angiographic substudy participants undergoing protocol-driven, 9-month follow-up angiography, we compared the diabetes treatment groups with respect to angiographic restenosis features: minimal lumen diameter (MLD) and late loss (MLD at follow-up vs MLD immediately after percutaneous coronary intervention). Comparisons for MLD and late loss involved a model using analysis of covariance with adjustment for baseline (postprocedure) MLD and diabetes group.

RESULTS

Baseline characteristics (Table 1) show that patients in the sensitizer group tended to be younger and were more likely to receive additional medications, such as statins, nonsteroidal anti-inflammatory drugs, and periprocedural glycoprotein IIb/IIIa inhibitors than were conventionally treated patients. Patients treated with metformin also tended to have a higher incidence of comorbid conditions; they tended to be heavier, have higher incidences of previously documented coronary heart disease, and smaller baseline ejection fractions. Patients receiving metformin therapy tended to have more type A (16% vs 12%) and fewer type B-2 lesions (34% vs 40%) than those treated with nonsensitizer therapy, and the lesions in patients receiving metformin were less frequently calcified (17% vs 21%, $p = 0.05$), tortuous (7% vs 10%, $p = 0.008$), eccentric (45% vs 50%, $p = 0.046$), and had fewer total occlusions (6% vs 9% $p = 0.026$). The number of diseased vessels per patient, before and after Thrombolysis In Myocardial Infarction flow, number of lesions per patient, and vessel type intervened on did not differ between the 2 groups (p = NS, data not shown).

The unadjusted incidence of primary and secondary end points at the 9-month follow-up showed significantly higher incidences of death (3% vs 1%, $p = 0.006$) and MI (3% vs 1%, $p = 0.013$) in the nonsensitizer therapy group than in the metformin group, with a trend toward a higher incidence of the primary end point (24% vs 21%, $p = 0.07$). Ischemia-driven TVR did not differ between groups (22% vs 20%, $p = 0.41$).

TABLE 2 Logistic Regression Models for Metformin Versus Nonsensitizer Therapy

	Unadjusted		Adjusting for Age, Gender, Center, Percent Stenosis After PCI, and Tranilast Treatment		Adjusting for Age, Gender, Center, Percent Stenosis After PCI, Tranilast Treatment, and Other Risk Factors*	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Any clinical event	0.82 (0.67–1.02)	0.069	0.69 (0.56–0.87)	0.001	0.72 (0.57–0.91)	0.005
Ischemia-driven TVR	0.91 (0.74–1.13)	0.412	0.77 (0.61–0.97)	0.024	0.82 (0.65–1.05)	0.110
MI	0.41 (0.20–0.84)	0.016	0.34 (0.17–0.72)	0.004	0.31 (0.15–0.66)	0.002
Death	0.41 (0.21–0.79)	0.008	0.39 (0.20–0.77)	0.007	0.39 (0.19–0.77)	0.007

*Other risk factors after a stepwise search: use of statins, β blockers, nonsteroidal anti-inflammatory drugs, abciximab, angiotensin receptor blockers, or antiplatelets; previous percutaneous transluminal coronary angioplasty; history of acute coronary syndromes; peripheral vascular disease; number of diseased vessels; percent stenosis before PCI; ostial in-stent restenosis and vessel treated (left anterior descending artery vs other); smoking status; weight (lbs): P450 2C9 inhibitors; and number of lesions per patient.

PCI = percutaneous coronary intervention.

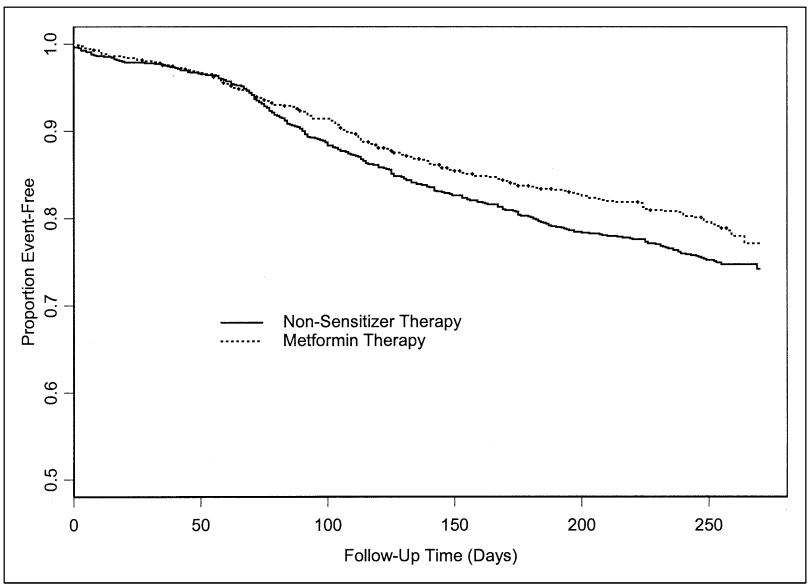

FIGURE 1. Kaplan-Meier survival curve of time to first event. Compared with patients on nonsensitizer therapy, those treated with metformin had a longer time to the first event.

Logistic regression analysis, after adjusting for baseline differences, showed significant differences in the incidence of the primary end point, which was significantly lower in the metformin group than in the nonsensitizer group (OR 0.72, 95% confidence interval [CI] 0.57 to 0.91, p = 0.005; Table 2). A Kaplan-Meier survival curve showed increased survival rate in the metformin group compared with the nonsensitizer group (Figure 1). Analysis of the secondary end points using the same adjusted logistic regression models indicated that most of the benefit seen in the metformin group was derived from decreased rates of death (OR 0.39, 95% CI 0.19 to 0.77, p = 0.007) and MI (OR 0.31, 95% CI 0.15 to 0.66, p = 0.002) and not of ischemia-driven TVR. Ischemia-driven TVR was similar in the nonsensitizer and the metformin groups (22% and 20%, respectively). Because only 703 of the 887 patients in the metformin group continued to receive metformin after coronary intervention, a separate analysis of end points using the smaller number was performed, which showed consistent benefits in the metformin group.

Diabetic patients in the prespecified 9-month angiographic follow-up study were analyzed according to treatment regimen. This analysis demonstrated similar values of MLD (2.67 ± 0.66 vs 2.59 ± 0.63, p = 0.25) and late loss (1.08 ± 0.81 vs 1.01 ± 0.82, p = 0.45) in the metformin group and nonsensitizer groups, respectively. Analysis of glucose measurements during follow-up visits was performed. There were statistically higher ($p < 0.05$) glucose levels in metformin-treated patients at baseline before percutaneous intervention and through weeks 1 to 10, with convergence at week 12 and the 9-month follow-up ($p > 0.05$). Glucose levels were forced into the logistic regression models for any clinical event and each component to determine whether the metformin association was the result of confounding by glucose. Blood glucose levels were not significant in these models and had no effect on the odds ratios and no significance for the metformin effect.

DISCUSSION

The current analysis assessed whether diabetic patients undergoing percutaneous interventions treated with metformin during the study period had fewer adverse events than diabetic patients treated with sulfonylureas and insulin. The PRESTO study was the largest prospective trial of coronary intervention, the results of which have recently been published.[17] In this trial, approximately 25% of the patients (2,772) enrolled had diabetes. Diabetics, as expected, fared worse with regard to the incidence of the combined end point of death, MI, and ischemia-driven TVR than

did the nondiabetic PRESTO population (21% vs 13%, $p < 0.001$). The patient frequencies of MI, death, and ischemia-driven TVR showed similar results. The database was unable to distinguish patients with type 1 diabetes from those with type 2 diabetes. Because the vast majority (>90%) of diabetic patients in the United States have type 2 diabetes, this distinction was unlikely to affect the outcome of our analysis.

When adjusted for differences in baseline characteristics, diabetics treated with metformin had markedly improved outcomes in the primary end point of combined death, MI, and ischemia-driven TVR and in the secondary end points of death alone and MI alone. Analysis of the 2 groups after adjusting for baseline differences and medical treatments showed persistent benefits in the metformin-treated group compared with the nonsensitizer-treated group.

The benefit seen in the metformin group was derived from decreased rates of MI and death and not of ischemia-driven TVR. There was no difference in clinical restenosis, and diabetics in the angiographic subset showed no differences in MLD or late loss between groups. This result suggests the mechanism of action of metformin is not due to an inhibition of intimal hyperplasia but rather to other mechanisms, such as modulation of endothelial function, lipid levels, plasminogen activator inhibitor-1 levels, or platelet reactivity.[5–16] We are unable to comment on the potential effects of thiazolidinediones on clinical outcomes compared with nonsensitizer therapy because this medication was not allowed due to potential drug interactions with tranilast. Analysis of our data, excluding insulin-dependent diabetics, showed preserved benefit with respect to MI and a continued trend toward benefit with respect to death (data not shown) in diabetic patients treated with metformin. Baseline clinical and angiographic characteristics showed some differences between groups; however, modeling our analysis to adjust for these discrepancies did not alter the significance of metformin treatment. The degree of glycemic control, based on random glucose measurements during follow-up before and after the procedure, with respect to random glucose levels was less in the nonsensitizer group than in the sensitizer group at all time points, except at the 12-week and 9-month follow-up, when the 2 values converged, arguing against glycemic control as a factor in the beneficial outcomes seen with metformin treatment. Glycosylated hemoglobin levels were not recorded as part of the PRESTO Trial and thus were not analyzed in this study.

Conclusions and study limitations: Metformin treatment is associated with decreased rates of death and MI in diabetic patients undergoing percutaneous coronary intervention and does not appear to affect ischemia-driven TVR. This is a large but nonrandomized, retrospective subgroup analysis. Although differences in baseline characteristics have been accounted for statistically, confounding effects are possible. Due to the nature of the primary study, we are unable to comment on the duration or type of diabetes, HgA1C levels, or patient cross over. Despite these limitations, this study provides insight into the potential role of metformin therapy in diabetic patients because it is based on a large, well-characterized, and prospectively followed group of patients. To date and to our knowledge, there have been no prospective randomized trials or retrospective subgroup analyses in the English-language literature examining this question.

1. Bailey CJ, Turner RC. Metformin. *N Engl J Med* 1996;334:574–579.
2. Sirtori CR, Pasik C. Re-evaluation of a biguanide, metformin: mechanism of action and tolerability. *Pharmacol Res* 1994;30:187–228.
3. Vialettes B, Silvestre P. Pharmacological approach in the treatment of insulin resistance. *Horm Res* 1992;38:51–56.
4. 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* 1998;352:854–865.
5. Stout RW. Effect of insulin on the proliferation of cultured primate arterial smooth muscle cells. *Circ Res* 1975;36:319–327.
6. Hsueh WA, Law RE. Cardiovascular risk continuum: implications of insulin resistance and diabetes. *Am J Med* 1998;105(suppl 1A):4S–14S.
7. Banskota NK, Tuab R, Zellner K, King GL. Insulin, insulin-like growth factor I and platelet-derived growth factor interact additively in the induction of the protooncogene c-myc and cellular proliferation in cultured bovine aortic smooth muscle cells. *Mol Endocrinol* 1998;3:1183–1190.
8. Sato Y, Shiraishi S, Oshisa Y, Ishiguro T, Sakamoto N. Experimental atherosclerosis-like lesions induced by hyperinsulinemia in Wistar rats. *Diabetes* 1989; 38:91–96.
9. Peuler JD, Phare SM, Iannucci AR, Hodorek MJ. Differential inhibitory effects of antidiabetic drugs on arterial smooth muscle cell proliferation. *Am J Hypertens* 1996;9:188–192.
10. Mather KJ, Verma S, Anderson TJ. Improved endothelial function with metformin in type 2 diabetes mellitus. *J Am Coll Cardiol* 2001;37:1344–1350.
11. Morikang E, Benson SC, Kurtz TW, Pershadsingh HA. Effects of thiazolidinediones on growth and differentiation of human aorta and coronary myocytes. *Am J Hypertens* 1997;10:440–446.
12. Goetze S, Xi XP, Kawano H, Gotlibowski T, Fleck E, Hsueh WA, Law RE. PPAR-gamma ligands inhibit migration mediated by multiple chemoattractants in vascular smooth muscle cell. *J Cardiovasc Pharmacol* 1999;33:798–806.
13. Law RE, Goetze S, Xi XP, Jackson S, Kawano Y, Demer L, Fishbein MC, Meehan WP, Hsueh WA. Expression and function of PPAR-gamma in rat and human vascular smooth muscle cells. *Circulation* 2000;101:1311–1318.
14. Hattori Y, Akimoto K, Kasai K. The effect of thiazolidinediones on vascular smooth muscle cell activation by angiotensin II. *Biochem Biophys Res Commun* 2000;273:1144–1149.
15. Law RE, Meehan WP, Xi XP, Graf K, Wuthrich DA, Coats W, Faxon D, Hsueh WA. Troglitazone inhibits vascular smooth muscle cell growth and intimal hyperplasia. *J Clin Invest* 1996;98:1897–1905.
16. Hsueh WA. PPAR-gamma effects on the vasculature. *J Investig Med* 2001; 49:127S–129S.
17. Holmes DR Jr, Savage M, LaBlanche JM, Grip L, Serruys PW, Fitzgerald P, Fischman D, Goldberg S, Brinker JA, Zeiher AM, et al. Results of Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) Trial. *Circulation* 2002; 106:1243–1250.