Effects of Aggressive Cholesterol Lowering and Low-Dose Anticoagulation on Clinical and Angiographic Outcomes in Patients With Diabetes

The Post Coronary Artery Bypass Graft Trial

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Diabetic patients have greater risk for coronary heart disease (CHD) events after coronary artery bypass graft (CABG) surgery than nondiabetic patients. The Post CABG trial studied the effects of aggressive cholesterol lowering and low-dose anticoagulation in diabetic patients compared with nondiabetic patients. A double-blind, randomized clinical trial in 1,351 patients (1–11 years after CABG), the Post CABG trial consisted of two interventions (aggressive cholesterol-lowering versus moderate lowering and low-dose warfarin versus placebo) on angiographic end points. Angiographic changes in saphenous vein graft conduits 4.3 years after entry were compared in 116 diabetic and 1,235 nondiabetic patients. Seven clinical centers participated in the trial, as well as the National Institutes of Health project office (National Heart, Lung, and Blood Institute), the coordinating center (Maryland Medical Research Institute), and the Angiogram Reading Center (University of Minnesota). Baseline characteristics of the diabetic patients differed from the nondiabetic patients in the following ways: percentage of women participants, 15 vs. 7%, *P* = 0.002; mean baseline weight, 87.4 vs. 82.8 kg, *P* = 0.006; mean BMI, 29.5 vs. 27.6 kg/m^2, *P* = 0.0002; mean systolic blood pressure, 141.7 vs. 133.6, *P* < 0.0001; mean triglyceride concentrations, 2.09 vs. 1.77 mmol/l, *P* < 0.0001; and mean HDL cholesterol concentrations, 0.93 vs. 1.02 mmol, *P* = 0.0001. The percentage of clinical events was higher in diabetic than nondiabetic patients (20.6 vs. 13.4, *P* = 0.033) and angiographic outcomes were not different. The benefits of aggressive cholesterol lowering were comparable in diabetic and nondiabetic patients for the angiographic end points. Warfarin use was not associated with clinical or angiographic benefit. Diabetic patients in the Post CABG trial had more CHD risk factors at study entry and higher clinical event rates during the study than nondiabetic patients. The benefits of aggressive cholesterol lowering in diabetic patients were comparable to those in nondiabetic patients for both angiographic and clinical end points. The small number of diabetic patients provided limited power to detect significant differences between diabetic and nondiabetic patients or between diabetic patients in the aggressive versus moderate cholesterol treatment strategies. *Diabetes* 48:1289–1294, 1999

Patients with diabetes are known to be at increased risk for coronary heart disease (CHD), atherosclerotic vascular disease, and CHD death (1–7). Part of this increased risk is related to clustering of other CHD risk factors in diabetic patients including dyslipidemia, hypertension, obesity, and alterations in the risk for clotting (8–13). Therefore, diabetic patients often undergo coronary revascularization procedures.

The outcomes of diabetic patients who have undergone coronary artery bypass graft (CABG) procedures are reported to be worse than their nondiabetic counterparts (14–18). These reports indicate increased mortality, increased CHD events including myocardial infarction (MI), higher rates of graft occlusion/narrowing, and an increased need for repeat CABG or percutaneous transluminal coronary angioplasty (PTCA).

Whether cholesterol lowering or anticoagulation will improve the outcomes in diabetic patients who have undergone CABG has not been carefully studied. Results from other cholesterol-lowering trials that included diabetic patients generally support a beneficial effect of cholesterol lowering on CHD events (19–24).

The Post CABG trial involved 1,351 patients 1–11 years after a CABG procedure (25). It was designed to assess the effects of aggressive cholesterol lowering and low-dose anticoagulation on changes in saphenous vein graft conduits as

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4S, Scandinavian Simvastatin Survival Study; CABG, coronary artery bypass graft; CHD, coronary heart disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; RR, risk ratio; SVG, saphenous vein graft; UKPDS, U.K. Prospective Diabetes Study.

determined by quantitative angiography. Data on specified clinical outcomes (death, MI, stroke, repeat CABG, PTCA) were also collected. The study demonstrated a beneficial effect of aggressive cholesterol lowering on angiographic outcomes but no effect of low-dose anticoagulation.

In this report, the clinical and angiographic outcomes are presented for diabetic patients on oral glucose-lowering agents (sulfonylureas) or insulin and for nondiabetic patients. We evaluate the effects of the interventions (cholesterol lowering and low-dose anticoagulation with warfarin) in patients with and without diabetes.

RESEARCH DESIGN AND METHODS

Design. The details of the design of the Post CABG trial have been reported (25). Briefly, patients recruited at seven clinical centers included men and women ages 21 to 74 years who had CABG procedures using saphenous vein grafts (SVG) 1 to 11 years previously. Two interventions (lipid-lowering and anticoagulation) were studied in a double-blinded randomized 2 × 2 factorial design. Patients were assigned to aggressive cholesterol lowering using lovastatin (and cholestyramine as necessary) to achieve an LDL cholesterol goal of 1.55–2.20 mmol/l (60–85 mg/dl) or to moderate cholesterol lowering using the same medications to achieve a goal of 3.36–3.62 mmol/l (130–140 mg/dl). Patients were also randomly assigned to receive 1–4 mg/day of warfarin or a warfarin placebo to achieve a mean International Normalized Ratio (INR) of <2. The selection of patients who were at low CHD disease severity, risk for death, or repeat revascularization; had medication contraindications; and had specified lipid levels and graft patency may have excluded more patients with diabetes than patients who did not have diabetes.

Angiographic end points were determined by comparing angiograms obtained before randomization and at the end of the trial (mean interval 4.3 years). Angiograms were quantitated at a central reading site and analyzed for the following: mean and minimum diameter of each SVG, minimum diameter and percentage of stenosis at the site of any lesion, and diameter of the lumen at the lesion site showing the greatest change (progression or regression) from baseline. The primary end point of the study was the per-patient percentage of initially patent major grafts that had substantial progression of atherosclerosis (decrease of ≥0.6 mm in lumen diameter) at the site of greatest change at follow-up. Our definition of substantial change included new lesions in grafts with no preexisting lesion of more than 15% stenosis, the progression of one or more lesions present at baseline, and new occlusions. Clinical end points were defined before the trial and included death, MI, stroke, and repeat revascularization (CABG or PTCA).

Patients. There were 1,351 enrolled patients including 116 who had type 2 diabetes requiring pharmacologic treatment with sulfonylureas (n = 89) or insulin (n = 27). All other patients were considered to be nondiabetic. Fasting plasma/serum glucose determinations were not obtained with sufficient consistency during the screening process to diagnose diabetes in patients not on pharmacologic therapy.

Statistical analyses. Comparisons between patients with and without diabetes were performed using χ^2 tests for categorical variables and t tests for continuous variables. Four-year cumulative event rates for specified clinical outcomes were estimated using the Kaplan-Meier method (26). Cox proportional hazards models (27) were used to adjust simultaneously for diabetes status and treatment group as well as other baseline variables.

The angiographic outcomes (substantial progression, occlusion, and mean change in minimum lumen diameter) were calculated for all SVGs patent at baseline. The percentage of grafts per patient with specified outcomes and mean changes were compared between treatment groups for diabetic and nondiabetic patients using the general estimating equations (GEE) regression model (28,29). For each diabetic subgroup, the difference in outcome for the two treatment groups is expressed as a risk ratio (RR) and 99% CIs of the RR. For the angiographic outcomes, this risk ratio is more specifically an odds ratio (OR) = $[p_1(1 - p_2)]/[p_2(1 - p_1)]$, and for clinical outcomes it is a hazard ratio (HR) = $[\ln(1 - p_1)]/\ln(1 - p_2)]$, where p_1 and p_2 are the proportions of events for the two treatment groups. Interaction terms were added to each model to test if the treatment effects were different between diabetic and nondiabetic patients. All analyses were performed using SAS programs.

As this is a secondary analysis of the Post CABG trial data, comparisons with P values <0.01 were considered as providing suggestive evidence of differences, and P values <0.001, as providing strong evidence of differences for all of the comparisons in this report. All P values of ≤0.05 are reported.

RESULTS

A higher percentage of diabetic patients were women (15 vs. 7%, P = 0.002). Diabetic patients had higher mean baseline weight (87.4 vs. 82.8 kg, P = 0.006) and BMI (29.5 vs. 27.6 kg/m^2, P = 0.0002) than those without diabetes (Table 1). Diabetic patients had higher mean systolic blood pressure (141.7 vs. 133.6 mmHg, P < 0.0001), higher mean triglyceride concentrations (2.09 vs. 1.77 mmol/l [185.5 vs. 157.5 mg/dl], P < 0.0001), and lower mean HDL cholesterol concentrations (0.93 vs. 1.02 mmol/l [36.0 vs. 39.6 mg/dl], P = 0.0001). Diabetic patients were slightly older (mean age 63.1 vs. 61.4 years, P = 0.02). Reduction in LDL cholesterol was comparable in diabetic and nondiabetic patients for both aggressive and moderate treatment strategies. Cholestyramine use was comparable in diabetic patients (12.9%) and nondiabetic patients (12.1%). When diabetic patients assigned to the aggressive

TABLE 1
Characteristics at study entry of diabetic and nondiabetic patients in the Post CABG trial

	Diabetes	No diabetes	P value
n	116	1,235	
Age at baseline (years)	63.1	61.4	0.02
Time from CABG to entry into trial (years)	4.7	4.9	NS
Weight at baseline (kg)	87.4	82.8	0.006
Baseline BMI (kg/m^2)	29.5	27.6	0.0002
Blood pressure (mmHg)			
Systolic	141.7	133.6	<0.0001
Diastolic	80.4	79.7	NS
Baseline lipid profile (mmol/l)			
Total cholesterol	5.82	5.87	NS
Triglycerides	2.09	1.77	<0.0001
HDL cholesterol	0.93	1.02	0.0001
LDL cholesterol	3.93	4.03	0.05

Data are means.

TABLE 2
Occurrence of specified events in diabetic and nondiabetic patients in the Post CABG trial

	Diabetes	No diabetes	P value
Clinical events			
4-Year event rate (%)			
Composite end point	20.6	13.4	0.033
Death	8.1	4.4	0.081
Myocardial infarction	8.1	4.7	NS
CABG	6.5	3.7	NS
PTCA	6.3	4.6	NS
Angiographic events*			
Substantial progression			
Per patient % of grafts	34.5	33.3	NS
Number of grafts	226	2,452	—
Occlusion			
Per patient % of grafts	15.0	13.2	NS
Number of grafts	226	2,452	—
Change in lumen diameter			
Mean change (mm)	–0.265	–0.288	NS
Number of grafts	180	2,106	—

The composite end point was death attributed to cardiovascular or unknown cause, nonfatal MI, stroke, CABG, or PTCA. *General estimating equations analysis.

TABLE 3
Changes in SVGs patent at entry in diabetic and nondiabetic patients treated with aggressive versus moderate cholesterol-lowering

	Diabetes				No diabetes			
	Cholesterol-lowering treatment		RR (99% CI)	Difference (99% CI)	Cholesterol-lowering treatment		RR (99% CI)	Difference (99% CI)
	Aggressive	Moderate			Aggressive	Moderate		
Substantial progression								
Per patient % of grafts	27.0	43.3	0.49 (0.20–1.19)	—	27.8	39.0	0.60 (0.46–0.79)	—
Number of grafts	122	104			1,238	1,214		
Occlusion								
Per patient % of grafts	11.5	19.2	0.54 (0.15–2.02)	—	10.4	16.0	0.61 (0.41–0.92)	—
Number of grafts	122	104			1,238	1,214		
Mean change in minimum lumen diameter (mm)	–0.227	–0.315	—	0.088 (–0.184 to 0.361)	–0.194	–0.389	—	0.195 (0.105 to 0.285)
Number of grafts	103	77			1,085	1,021		

There were no statistically significant differences for RR or changes in lumen diameter between diabetic and nondiabetic patients.

strategy (n = 63) were compared with those randomized to the moderate strategy, there were no differences in age, sex, time from CABG to entry into the trial, weight, or baseline lipid profiles; mean diastolic blood pressure was higher in the moderate-strategy patients (83 vs. 78, P = 0.007). None of these variables were different in the diabetic patients randomized to warfarin (n = 58) versus placebo (n = 58).

The combined percentage of adverse clinical events (death from cardiovascular or unknown cause, nonfatal MI, stroke, repeat CABG, PTCA) was higher in diabetic than nondiabetic patients (20.6 vs. 13.4, P = 0.033). Each of the individual adverse clinical event rates was higher in diabetic patients, although none of the differences were statistically significant (Table 2).

Three major angiographic outcomes were considered: *1*) substantial progression (primary end point), *2*) occlusion, and *3*) change in minimum lumen diameter of SVGs. The probability of SVG substantial progression or occlusion did not differ in diabetic and nondiabetic patients. This observation was also true for changes in minimum diameter (Tables 3 and 4). These results were not affected by inclusion in the analyses of several baseline risk factors. The adjusting variables included LDL cholesterol–lowering treatment, warfarin treatment, sex, age, systolic and diastolic blood pressure, hypertension, smoking status, hard exercise, diabetes, LDL cholesterol, total cholesterol, triglycerides, current medication usage (aspirin, beta blockers, calcium channel blockers), number of risk factors, graft age, and percent stenosis. No pairwise interactions were significant, and therefore they were not included in the reported models.

The beneficial effect of aggressive cholesterol lowering on changes in SVGs was similar in diabetic and nondiabetic patient groups (Table 3). The effect of cholesterol lowering on the risk of substantial progression in SVGs was comparable in diabetic and nondiabetic patients (RR 0.49 [99% CI 0.20–1.19] and 0.60 [0.46–0.79], respectively). The RR for occlusion with aggressive cholesterol lowering compared with moderate cholesterol lowering for diabetic patients was 0.54 (0.15–2.02), and for nondiabetic patients, 0.61 (0.41–0.92).

There was a general reduction in RR for clinical events associated with aggressive cholesterol lowering (although it did not achieve statistical significance). The relative risk associated with aggressive cholesterol lowering for the composite end point was lower (but not statistically significant)

TABLE 4
Change in SVGs patent at entry in diabetic and nondiabetic patients treated with warfarin or placebo

	Diabetes				No diabetes			
	Warfarin treatment		RR (99% CI)	Difference (99% CI)	Warfarin treatment		RR (99% CI)	Difference (99% CI)
	Warfarin	Placebo			Warfarin	Placebo		
Substantial progression								
Per patient % of grafts	35.4	33.3	1.10 (0.44–2.73)	—	33.8	32.9	1.04 (0.80–1.36)	—
Number of grafts	127	99			1,229	1,223		
Occlusion								
Per patient % of grafts	14.2	16.2	0.86 (0.23–3.18)	—	13.1	13.2	0.99 (0.66–1.47)	—
Number of grafts	127	99			1,229	1,223		
Mean change in minimum lumen diameter (mm)	–0.284	–0.240	—	–0.044 (–0.311 to 0.222)	–0.310	–0.266	—	–0.044 (–0.135 to 0.048)
Number of grafts	100	80			1,068	1,038		

There were no statistically significant differences for RR or changes in lumen diameter between diabetic and nondiabetic patients.

TABLE 5
The 4-year life table clinical event rate in diabetic and nondiabetic patients treated with aggressive versus moderate cholesterol lowering

	Diabetes (n = 116)			No diabetes (n = 1,235)		
	Cholesterol-lowering treatment			Cholesterol-lowering treatment		
	Aggressive	Moderate	RR (99% CI)	Aggressive	Moderate	RR (99% CI)
Number of patients	63	53		613	622	
Composite end point	14.9	26.2	0.53 (0.18–1.60)	12.5	14.3	0.87 (0.58–1.31)
Death	6.5	9.6	0.67 (0.12–3.75)	4.3	4.4	0.98 (0.48–1.98)
MI	4.8	11.6	0.40 (0.07–2.47)	4.9	4.6	1.05 (0.53–2.08)
CABG	6.6	5.8	1.14 (0.16–8.19)	2.7	4.8	0.55 (0.25–1.23)
PTCA	4.9	7.9	0.61 (0.09–4.39)	4.2	5.0	0.84 (0.42–1.69)

The composite end point was death from cardiovascular or unknown cause, nonfatal MI, stroke, CABG, or PTCA. There were no statistically significant differences for RR between diabetic and nondiabetic patients.

in diabetic patients (0.53 [CI 0.18–1.60]) than in nondiabetic patients (RR 0.87 [CI 0.58–1.31]) (Table 5).

Warfarin had no statistically significant effect on angiographic or clinical end points in the Post CABG trial. Also, no differences in warfarin effects were detected for diabetic and nondiabetic patients (Tables 4 and 6).

DISCUSSION

We had hypothesized that the angiographic outcomes would be worse in the diabetic compared with nondiabetic patients based on several observations. Diabetic patients who undergo CABG generally have worse clinical outcomes than nondiabetic patients (14–18). Diabetic patients seem to have a greater risk for arterial vascular disease as a result of greater clustering of CHD risk factors such as dyslipidemia, hypertension, and central/visceral obesity (8–10). Diabetes is associated with a greater risk for thrombogenic events because of abnormalities of platelet aggregability (30) and altered clotting factors such as increased fibrinogen and plasminogen activator inhibitor (PAI)-1 (11–13). There is also the possibility that less well-characterized risk factors such as glycoxidation of lipoproteins may be associated with increased risk in diabetic patients (31–34). In fact, our data show that each of the angiographic measures of the SVG conduits showed comparable changes in diabetic and nondiabetic patients. Furthermore, the beneficial effects of aggressive cholesterol lowering on SVG conduits were the same in diabetic and nondiabetic patients. The Post CABG trial did not have sufficient power to show an effect of aggressive cholesterol lowering on clinical events. Nevertheless, the relative risk of combined clinical events was <1.0 for both nondiabetic (0.87 [0.58–1.31]) and diabetic (0.53 [0.18–1.60]) patients. This similarity suggests that aggressive cholesterol lowering has the same beneficial effects on clinical outcomes in CABG recipients as demonstrated in other trials (19–24).

Although the current study did not measure clotting factors, which may be abnormal in diabetic patients, it is likely that the diabetic patients in our study do have clotting abnormalities similar to those reported in other studies (11–13). Nevertheless, low-dose anticoagulation did not show any benefit in either diabetic or nondiabetic patients.

Other randomized trials of cholesterol lowering that included diabetic subjects have demonstrated reductions in CHD events and all-cause mortality (19–24) (Table 7). In those studies, diabetic subjects have higher risk for events in both placebo and treatment (gemfibrozil or statin) arms. However, the incremental reduction in risk is the same or greater in the diabetic subjects. The Helsinki Heart Study (19) reported on 135 diabetic subjects. Diabetic subjects on placebo had a higher 5-year incidence of CHD death and MI (10.5%) than the other subjects in the placebo group (7.4%). The incidence of CHD and MI in diabetic subjects was 3.4% on gemfibrozil, which was comparable to other subjects on gemfibrozil (3.3%). The net result was a greater reduction in the risk for CHD in the diabetic subjects than in the nondiabetic subjects in that trial. This incremental reduction in risk did not reach statistical significance (P = 0.19). In the Scandinavian Simvastatin Survival Study (4S) (21,22), the diabetic

TABLE 6
The 4-year life table clinical event rate in diabetic and nondiabetic subjects treated with warfarin or placebo

	Diabetes (n = 116)			No diabetes (n = 1,235)		
	Warfarin treatment			Warfarin treatment		
	Warfarin	Placebo	RR (99% CI)	Warfarin	Placebo	RR (99% CI)
Number of patients	58	58		616	619	
Composite end point	21.1	19.3	1.10 (0.38–3.24)	12.4	14.4	0.86 (0.57–1.28)
Death	5.3	10.6	0.49 (0.08–3.01)	3.8	4.9	0.77 (0.38–1.57)
MI	8.6	7.1	1.23 (0.22–6.93)	4.7	4.8	0.97 (0.49–1.92)
CABG	7.1	5.4	1.32 (0.18–9.43)	3.5	4.0	0.88 (0.41–1.89)
PTCA	10.6	1.8	6.07 (0.38–98.1)	4.3	4.8	0.90 (0.45–1.79)

The composite end point was death from cardiovascular or unknown cause, nonfatal MI, stroke, CABG, or PTCA. There were no statistically significant differences for RR between diabetic and nondiabetic patients.

TABLE 7
Effects of cholesterol lowering in diabetic subjects from five randomized clinical trials

Trial and reference	End point	Mean or median duration of follow-up (years)	Number of patients		Reduction in risk (%)	
			Diabetes	No diabetes	Diabetes	No diabetes
Helsinki Heart Study (19,20)	Nonfatal MI or CHD death	5.0	135	3,946	68	30
CARE (23)	Nonfatal MI or CHD death	5.0	586	3,573	25	23
4S (21,22)	Total mortality	5.4	202	4,242	43	29
	Major CHD event				55	32
	Any atherosclerotic event				37	26
AFCAPS/TexCAPS (24)	Acute MI (fatal or nonfatal), unstable angina, CHD death	5.2	155	6,440	43	26
Post CABG trial (25)	Composite ASCVD events	4.3	116	1,235	43*	13

*Based on relative risk (treated group % – control group %/control %).

subjects (n = 202) in the placebo group had a higher incidence of CHD events (CHD-related death or nonfatal MI) than those without diabetes (45 vs. 27%). With lipid-lowering therapy, the incidence of CHD events was still greater in diabetic subjects (24%) than in nondiabetic subjects (19%), but that incidence represented a greater incremental reduction in CHD events for diabetic subjects (54% risk reduction) than nondiabetic subjects (32%). Mortality rates in the 4S trial were also higher in diabetic versus nondiabetic subjects in both placebo (25 vs. 11% mortality) and simvastatin (14 vs. 8%) groups. There was a greater percent reduction in all-cause mortality in diabetic subjects treated with simvastatin than in those without diabetes (43 vs. 28%). In a study looking at the effect of pravastatin on coronary events after myocardial infarction in subjects with average cholesterol levels (CARE study) (23), diabetic subjects treated with pravastatin had a 25% reduction in nonfatal MI or CHD death compared with placebo. The effect was similar in nondiabetic subjects (23% reduction). Finally, in the AFCAPS/TexCAPS primary prevention trial (24), which included 155 type 2 diabetic subjects, results suggested higher event rates for the diabetic patients in both lovastatin and placebo treatment arms compared with nondiabetic patients. Although the numbers were too small to show statistically significant differences in event rates with lovastatin therapy, the incremental difference in event rates between lovastatin and placebo was greater in diabetic than in nondiabetic patients. In summary, several trials (including the Post CABG trial) suggest that aggressive LDL cholesterol lowering has greater incremental benefit in diabetic than nondiabetic patients. With the exception of 4S, the number of subjects in these trials was usually too small to demonstrate statistical significance for this observation.

Although the reduction in the occurrence of angiographic outcomes and clinical events with treatment in Post CABG trial was not statistically significant between diabetic and nondiabetic patients, the consistency in risk reduction (as determined by RR) was the same (or perhaps even greater) in the diabetic patients, suggesting that diabetic patients who undergo CABG should be treated as aggressively as patients without diabetes.

Although a number of studies have shown that diabetic patients have a thrombogenic potential and have earlier closure of bypass conduits, our data do not suggest that this risk was modified by low-dose warfarin. In the current study, diabetic patients were similar to nondiabetic patients on 1–4 mg of warfarin and did not demonstrate any angiographic or clinical benefit from the intervention. All participants were on aspirin, which has been associated with a reduction in risk for CHD events in diabetic patients (35).

The relationship between glycemic control and the risk for CHD events in diabetic patients is still not well established. Epidemiologic data in some cases show a relationship between integrated measures of glycemic control (such as glycated hemoglobin) and CHD risk (36–38), while other data sets do not show such a relationship. Intervention trials in type 2 diabetes have not had sufficient power to show a beneficial effect of glycemic control (39–42). The U.K. Prospective Diabetes Study (UKPDS), the largest trial to address this issue, did not show a clear reduction in CHD events with lower mean glucose concentrations (43–45). Fasting glucose concentrations were not obtained as a part of the Post CABG trial study protocol; hence, there may be some diabetic patients included in the "nondiabetic" group. Since both groups achieved comparable angiographic and clinical benefit, the inclusion of diabetic nonpharmacologically treated (or unrecognized) diabetic patients should not materially affect our conclusions. In the Post CABG trial, no attempt was made via protocol to control blood glucose rigorously. Our data would support the comparable benefits of aggressive cholesterol lowering in diabetic and nondiabetic patients.

In summary, the observations from diabetic patients in the Post CABG trial indicated that they received the same benefit from aggressive cholesterol lowering as nondiabetic patients. This was true for both clinical and angiographic outcomes. Although diabetic patients may have greater thrombogenic potential than nondiabetic patients, this was not evident in our angiographic measures. Furthermore, no benefit of low-dose anticoagulation was seen in the diabetic or nondiabetic patients.

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