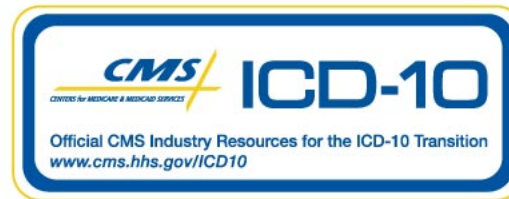


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CLINICAL RESEARCH

Interventional Cardiology

Optimal Glycemic Control Is Associated With a Lower Rate of Target Vessel Revascularization in Treated Type II Diabetic Patients Undergoing Elective Percutaneous Coronary Intervention

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OBJECTIVES	We examined the association between glycemic control determined by preprocedural hemoglobin A1c (A1c) and the incidence of target vessel revascularization (TVR) in diabetic patients undergoing elective percutaneous coronary intervention (PCI).
BACKGROUND	Patients with diabetes mellitus (DM) have increased rates of restenosis and a worse clinical outcome after PCI than patients without DM.
METHODS	A total of 239 patients (60 without DM and 179 with DM) were enrolled in this study. Optimal glycemic control was defined as A1c \leq 7%, and suboptimal control was defined as A1c $>$ 7%. Follow-up was performed at six and 12 months after the index intervention.
RESULTS	Diabetic patients with optimal glycemic control had a rate of 12-month TVR similar to that of nondiabetic patients (15% vs. 18%, $p = \text{NS}$). Diabetic patients with A1c $>$ 7% had a significantly higher rate of TVR than those with A1c $<$ 7% (34% vs. 15%, $p = 0.02$). In a multiple logistic regression analysis, A1c $>$ 7% was a significant independent predictor of TVR (odds ratio 2.87, 95% confidence interval 1.13 to 7.24; $p = 0.03$). Optimal glycemic control was associated with a lower rate of cardiac rehospitalization (15% vs. 31%, $p = 0.03$) and recurrent angina (13% vs. 37%, $p = 0.002$) at 12-month follow-up.
CONCLUSIONS	In diabetic patients undergoing elective PCI, optimal glycemic control (A1c \leq 7%) is associated with a lower rate of TVR, cardiac rehospitalization, and recurrent angina. These data suggest that aggressive treatment of DM to achieve A1c \leq 7% is beneficial in improving the clinical outcome after PCI. (J Am Coll Cardiol 2004;43:8–14) © 2004 by the American College of Cardiology Foundation

There are ~17 million patients with diabetes in the U.S. and an estimated 125 million worldwide. By the year 2025, this number is expected to reach over 300 million. In 1997, the estimated cost for diabetes and its resultant complications was \$98 billion, with \$7.6 billion accounting for cardiovascular complications alone (1). Current statistics

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estimate that of the more than 1.5 million revascularization procedures performed worldwide each year, 25% are for diabetic patients. These figures underscore the enormous health care challenge that diabetic patients with coronary artery disease (CAD) represent.

Diabetes is a potent risk factor for the development and progression of CAD (2–4). With advances in coronary revascularization by use of thrombolytic therapy, percutaneous modalities, and surgical intervention, morbidity and

mortality from CAD have been significantly reduced. However, despite contemporary therapy, cardiovascular disease accounts for ~75% of all hospital admissions and 80% of deaths in diabetic patients (5,6).

The major long-term limitation of percutaneous coronary revascularization is restenosis. Diabetes is a strong predictor of restenosis after coronary intervention. Although the introduction of stents has improved the outcome after intervention in diabetic patients (7), these patients are still at a greater risk for restenosis than nondiabetic patients (8,9). Recent investigations have shown that this is because of exaggerated tissue proliferation and intimal hyperplasia (10,11). This phenomenon appears to be partly due to the diabetic state, which promotes restenosis via intrinsic coagulation and thrombotic abnormalities, endothelial dysfunction, cellular and matrix proliferation, and formation of advanced glycation end products (12,13). Despite this information on the pathogenesis of restenosis in diabetic patients, the importance of glycemic control in the development of restenosis after coronary intervention has not been extensively investigated.

In this study, we examined the association between

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Abbreviations and Acronyms

A1c	= hemoglobin A1c
CABG	= coronary artery bypass graft surgery
CAD	= coronary artery disease
CHF	= congestive heart failure
MI	= myocardial infarction
MLD	= minimum luminal diameter
PCI	= percutaneous coronary intervention
PTCA	= percutaneous transluminal coronary angioplasty
TVR	= target vessel revascularization

glycemic control, as determined by hemoglobin A1c (A1c), and the incidence of target vessel revascularization (TVR) in diabetic patients undergoing elective percutaneous coronary intervention (PCI).

METHODS

Study design. This investigation was approved by the Human Investigation Committee at the William Beaumont Hospital. From January 1998 to December 1999, diabetic patients undergoing planned a percutaneous intervention of de novo coronary artery lesions were identified and screened for participation in this study. Diet-controlled or type I diabetic patients, patients requiring urgent procedures for unstable coronary syndromes, and patients undergoing interventions in multiple vessels, previously instrumented vessels, or vein grafts were excluded. A total of 179 consecutive eligible diabetic patients were prospectively enrolled during this period. Sixty nondiabetic patients who underwent elective PCI during the same period and who met the aforementioned entry criteria were randomly selected as the control group.

Before cardiac catheterization, baseline laboratory studies, including A1c, lipid panel, and fibrinogen, were drawn. Coronary intervention was performed using standard techniques and could include, but was not limited to, percutaneous transluminal coronary angioplasty (PTCA), intracoronary stenting, and mechanical rotational atherectomy. All patients were treated with aspirin. After stent implantation, all patients received either clopidogrel (75 mg/day for four weeks) or ticlopidine (250 mg orally twice a day for two to four weeks). Other adjunctive pharmacotherapy was administered at the discretion of the operator.

Clinical follow-up was performed by telephone interview and by review of the hospital record at 6 and 12 months after the intervention. Repeat cardiac catheterization was performed for recurrent symptoms or objective evidence of ischemia with provocative testing. Routine angiographic follow-up was not undertaken.

Angiographic analysis. The majority of patients had a single lesion treated at the time of PCI. In patients with multiple lesions treated, PCI was performed only on lesions within the same vessel. Quantitative coronary angiography was performed using an automated edge-detection system (Quantcor, Siemens Medical Inc., Malvern, Pennsylvania)

by a single observer blinded to the clinical details and outcomes. Calibration was based on the dimension of a contrast-filled catheter. The following parameters were measured in two orthogonal projections before and after coronary intervention: lesion length, reference vessel diameter, minimum luminal diameter (MLD), and percent diameter stenosis. All lesions were classified in accordance with the American Heart Association/American College of Cardiology (AHA/ACC) classification scheme (14).

End points. The primary end point of the study was the need for TVR (surgical or percutaneous) at 12 months. Secondary end points included post-procedural cardiac death, myocardial infarction (MI), recurrent angina, stroke, congestive heart failure (CHF), renal failure, and cardiac rehospitalization.

Definitions. Diabetic patients were identified as patients undergoing treatment with insulin or oral hypoglycemic medications. Diabetic patients were stratified into two groups based on glycemic control. In accordance with the American Diabetes Association guidelines (15), “optimal glycemic control” was defined as $A1c \leq 7\%$, and “suboptimal control” was defined as $A1c > 7\%$. “Procedural success” was defined as $< 50\%$ residual diameter stenosis and Thrombolysis in Myocardial Infarction flow grade 3 in the absence of major in-hospital complications (death, MI, or urgent coronary artery bypass graft surgery [CABG]). “Acute gain” was defined as the difference between MLD before and after coronary intervention. “Myocardial infarction” was defined by the presence of new Q waves on the follow-up electrocardiogram or elevation of creatine kinase to greater than three times normal. “Cardiovascular mortality” was defined as death attributable to MI, CHF, or arrhythmia. “Target vessel revascularization” was defined as the need for either surgical or percutaneous revascularization of the initial vessel intervened upon and excludes subsequent revascularization of a newly diseased or previously diseased vessel(s).

Statistical analysis. Statistical analysis was performed using the Statistical Analysis Software package (SAS, version 8.2). Continuous variables are expressed as the mean \pm SD and were analyzed for significant differences using one-way analysis of variance, when being compared among all three groups, or the two-tailed Student *t* test, when comparing between diabetic and nondiabetic patients and between diabetic patients with $A1c \leq 7\%$ and those with $A1c > 7\%$. Multiple comparisons were made; thus, adjustments using the Bonferroni correction method were implemented. Categorical variables were analyzed for significant differences, using Pearson’s chi-square test, two-tailed Fischer exact test, or Cochran-Mantel-Haenszel test, as appropriate. In the diabetic cohort, all baseline characteristics, laboratory data, and angiographic parameters were analyzed to determine the independent predictors of TVR. All variables with a *p* value < 0.2 were entered into a forward stepwise multiple logistic regression analysis to determine the most parsimonious subset of variables that best explained the occurrence of TVR among diabetic patients. Similar anal-

Table 1. Clinical Characteristics in Diabetic and Nondiabetic Patients

	DM			Comparisons (p Value)		
	Non-DM (n = 60)	A1c ≤7% (n = 52)	A1c >7% (n = 127)	Across Groups*	Non-DM vs. DM†	DM‡
Oral hypoglycemic medications	—	38 (73%)	59 (46%)	—	—	0.002
Insulin treatment	—	14 (27%)	68 (54%)	—	—	—
Age (yrs)	63 ± 11	65 ± 11	63 ± 11	0.69§	0.60	0.51§
Males	47 (78%)	39 (75%)	75 (59%)	0.01	0.04	0.04
Risk factors						
Current smoker	8 (13%)	9 (17%)	13 (10%)	0.42	0.83	0.19
Hypertension	35 (58%)	35 (67%)	99 (78%)	0.02	0.01	0.14
Hyperlipidemia	36 (60%)	35 (67%)	84 (66%)	0.65	0.36	0.88
Body mass index (kg/m ²)	29 ± 4.4	32 ± 20	32 ± 6.4	0.20§	0.008	0.96
History						
MI	24 (40%)	18 (35%)	34 (27%)	0.20	0.13	0.32
PTCA	24 (40%)	23 (44%)	53 (42%)	0.90	0.74	0.76
CABG	13 (22%)	17 (33%)	30 (24%)	0.35	0.48	0.21
CHF	6 (10%)	10 (19%)	19 (15%)	0.38	0.24	0.48
Arrhythmia	3 (5%)	4 (8%)	6 (5%)	0.72	1.00	0.48
Renal failure	2 (3%)	7 (13%)	10 (8%)	0.14	0.17	0.27

*Pearson's chi-square test (or two-tailed Fisher exact test if <5 events), unless otherwise indicated. †Difference between nondiabetic patients and all diabetic patients (A1c ≤7% and A1c >7%), using Pearson's chi-square test (or two-tailed Fisher exact test if <5 events), unless otherwise indicated. ‡Difference between diabetic patients with A1c ≤7% and diabetic patients with A1c >7%, using Pearson's chi-square test (or two-tailed Fischer exact test), unless otherwise indicated. §Difference among all groups using one-way analysis of variance with contrasts. Contrasts were adjusted using the Bonferroni correction method for multiple comparisons. ||Difference between groups using the two-tailed Student *t* test. Data are presented as the mean value ± SD or number (%) of subjects.

A1c = hemoglobin A1c; CABG = coronary artery bypass grafting; CHF = congestive heart failure; DM = diabetic patients; non-DM = nondiabetic patients; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

yses were performed to determine independent predictors of cardiac rehospitalization and recurrent angina. A p value ≤0.05 was considered statistically significant unless the Bonferroni correction method for multiple comparisons was utilized, in which case a p value ≤0.025 was considered statistically significant.

RESULTS

Demographics. DIABETIC PATIENTS VERSUS NONDIABETIC PATIENTS. Diabetic patients were less likely to be male and had a higher prevalence of hypertension (75% vs. 58%). Compared with nondiabetic patients, diabetic patients had a higher body mass index (mean 32 vs. 29 kg/m²) and higher levels of fibrinogen (324 vs. 295 mg/dl), triglyc-

erides (159 vs. 132 mg/dl), blood urea nitrogen (20 vs. 16 mg/dl), and creatinine (1.2 vs. 1.0 mg/dl) (Tables 1 and 2).

Intracoronary stenting was performed in 67% of diabetic patients and 69% of nondiabetic patients (p = 0.82). The lesion location, AHA/ACC lesion classification, angiographic measurements, and frequency of multi-lesion PCI were similar between patients with and without diabetes (Table 3).

DIABETIC PATIENTS WITH OPTIMAL VERSUS SUBOPTIMAL GLYCEMIC CONTROL. Diabetic patients with suboptimal glycemic control (A1c >7%) were more often treated with insulin (54% vs. 27%) and less often male (59% vs. 75%). Compared with diabetic patients with A1c ≤7%, those with A1c >7% had similar risk factors, historical profile, and

Table 2. Laboratory Data for Diabetic and Nondiabetic Patients

	DM			Comparisons (p Value)		
	Non-DM (n = 60)	A1c ≤7% (n = 52)	A1c >7% (n = 127)	Across Groups*	Non-DM vs. DM†	DM‡
A1c (%)	6.1 ± 0.8	6.5 ± 0.5	8.8 ± 1.6	—	<0.001	—
Fibrinogen (mg/dl)	295 ± 76	311 ± 93	328 ± 94	0.08	0.19	0.69
Cholesterol (mg/dl)	176 ± 42	177 ± 35	176 ± 58	0.99	1.0	1.0
HDL (mg/dl)	42 ± 11	39 ± 12	40 ± 11	0.26	0.27	0.65
LDL (mg/dl)	108 ± 31	106 ± 31	107 ± 65	0.98	1.0	1.0
Total/HDL cholesterol ratio	4.4 ± 1.1	5.0 ± 2.2	4.6 ± 1.7	0.16	0.26	0.30
Triglycerides (mg/dl)	132 ± 77	162 ± 97	158 ± 104	0.19	0.14	1.0
BUN (mg/dl)	16 ± 5.5	22 ± 12	20 ± 9.8	0.001	<0.001	0.28
Creatinine (mg/dl)	1.0 ± 0.2	1.4 ± 1.0	1.1 ± 0.9	0.10	0.018	0.19

*Difference among groups using one-way analysis of variance with contrasts. Contrasts were adjusted using the Bonferroni correction method for multiple comparisons. †Difference between nondiabetic patients and all diabetic patients (A1c ≤7% and >7%), using the two-tailed Student *t* test. ‡Contrast between diabetic patients with A1c ≤7% and diabetic patients with A1c >7%. Comparisons were adjusted using the Bonferroni correction method for multiple comparisons. Data are presented as the mean value ± SD.

BUN = blood urea nitrogen; HDL = high-density lipoprotein; LDL = low-density lipoprotein; other abbreviations as in Table 1.

Table 3. Angiographic Data

	Non-DM	DM		Comparisons (p Value)		
		A1c ≤7%	A1c >7%	Across Groups*	Non-DM vs. DM†	DM‡
Number of lesions	67	53	137			
Multilesion PCI	4 (6.7%)	1 (2.0%)	7 (5.5%)	0.48§	0.50§	0.29§
Lesion location				0.54§		
LMCA	0 (0%)	1 (2%)	3 (2%)		0.48§	0.89§
LAD	23 (34%)	18 (34%)	46 (33%)		0.99§	0.96§
LCx	29 (43%)	14 (26%)	40 (29%)		0.08§	0.70§
RCA	15 (22%)	20 (38%)	48 (35%)		0.12§	0.73§
Lesion type				0.36		
A	8 (12%)	7 (13%)	16 (11%)		0.96§	0.77§
B	46 (69%)	30 (56%)	5 (55%)		0.16§	0.82§
C	13 (19%)	16 (30%)	46 (34%)		0.11§	0.66§
QCA data						
Length (mm)	12 ± 6.5	13 ± 5.9	14 ± 7.9	0.17	0.71	0.31
Pre-intervention						
RVD (mm)	2.8 ± 0.6	2.7 ± 0.5	2.8 ± 0.7	0.53	1.0	0.52
MLD (mm)	0.6 ± 0.4	0.7 ± 0.4	0.7 ± 0.4	0.75	0.97	1.0
DS (%)	78 ± 14	77 ± 13	77 ± 13	0.82	1.0	1.0
Post-intervention						
RVD (mm)	2.8 ± 0.6	2.7 ± 0.5	2.8 ± 0.7	0.53	1.0	0.55
MLD (mm)	2.6 ± 0.7	2.5 ± 0.6	2.6 ± 0.7	0.46	0.77	0.56
DS (%)	9.9 ± 10	10 ± 11	11 ± 12	0.91	1.0	1.0
Short-term gain (mm)	2.0 ± 0.7	1.8 ± 0.6	2.0 ± 0.9	0.56	1.0	0.60

*Difference among groups using one-way analysis of variance with contrasts, unless otherwise indicated. †Difference between nondiabetic patients and all diabetic patients, (A1c ≤7% and A1c >7%), using the two-tailed Student *t* test, unless otherwise indicated. ‡Contrasts between diabetic patients with A1c ≤7% and diabetic patients with A1c >7%. Comparisons were adjusted using the Bonferroni correction method for multiple comparisons, unless otherwise indicated. §Pearson's chi-square test or two-tailed Fisher exact test if <5 events. ||Difference among all groups using the Cochran-Mantel-Haenszel test. Data are presented as the mean ± SD or number (%) of lesions.

DS = diameter stenosis; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; MLD = minimal luminal diameter; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; RCA = right coronary artery; RVD = reference vessel diameter; other abbreviations as in Table 1.

laboratory values (Tables 1 and 2). Angiographic analysis revealed no significant differences in lesion length, reference vessel diameter, MLD, diameter stenosis, or acute gain between diabetic patients with optimal versus suboptimal glycemic control (Table 3).

Target vessel revascularization. The incidence of TVR at 12 months was determined according to diabetic status and glycemic control. Well-controlled diabetic patients had a rate of TVR similar to that of nondiabetic patients (15% vs. 18%, *p* = 0.68). Among diabetic patients, those with A1c ≤7% had a significantly lower rate of TVR than those with A1c >7% (15% vs. 34%, *p* = 0.02) (Fig. 1). Multivariate

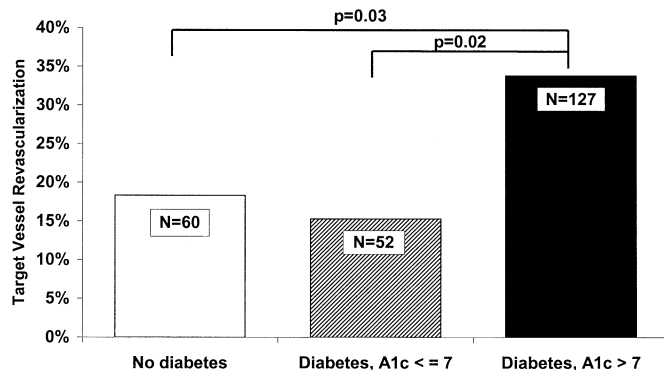


Figure 1. Incidence of target vessel revascularization in diabetic and nondiabetic patients. A1c = hemoglobin A1c.

analysis disclosed that A1c >7% was a significant independent predictor of TVR 12 months following PCI (odds ratio [OR] 2.87, 95% confidence interval [CI] 1.13 to 7.24; *p* = 0.03).

Insulin-requiring diabetic patients had a significantly higher rate of TVR than nondiabetic patients (35% vs. 18%; OR 2.44, 95% CI 1.10 to 5.40; *p* = 0.03). Among diabetic patients, there was a trend toward a higher TVR rate in those treated with insulin compared to those treated with oral hypoglycemics (35% vs. 23%, *p* = 0.06) (Fig. 2). On multivariate analysis, insulin therapy was of borderline

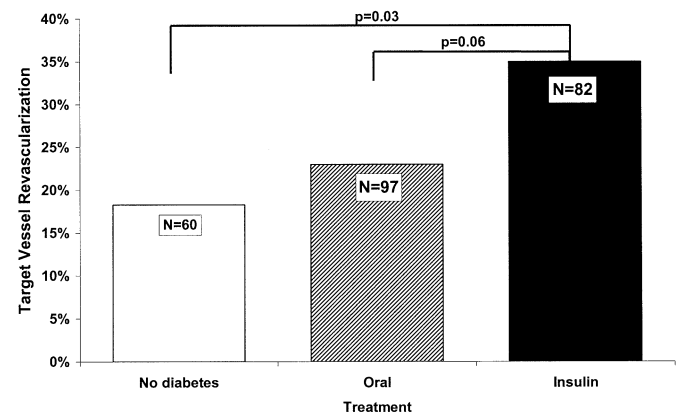


Figure 2. Incidence of target vessel revascularization according to treatment regimen.

Table 4. Follow-Up Data

	Non-DM	DM		Comparisons (p Value)		
		A1c ≤7%	A1c >7%	Across Groups*	Non-DM vs. DM†	DM‡
Cardiovascular mortality	3 (5%)	3 (6%)	2 (2%)	0.24	0.72	0.12
MI	2 (3%)	3 (6%)	7 (5%)	0.87	0.74	0.72
CABG	1 (2%)	2 (4%)	8 (6%)	0.35	0.30	0.73
Recurrent angina	14 (23%)	7 (13%)	47 (37%)	0.004	0.31	0.002
CHF	1 (2%)	1 (2%)	7 (6%)	0.32	0.46	0.44
Arrhythmia	1 (2%)	1 (2%)	2 (1%)	0.99	1.00	1.00
CVA	0 (0%)	1 (2%)	2 (1%)	0.50	0.58	1.00
Renal failure	1 (2%)	1 (2%)	2 (2%)	0.99	1.00	1.00
Cardiac rehospitalization	12 (20%)	8 (15%)	39 (31%)	0.06	0.33	0.03
Noncardiac rehospitalization	5 (8%)	4 (8%)	13 (10%)	0.84	0.79	0.60

*Pearson's chi-square test (or Fisher exact test if <5 events). †Difference between nondiabetic patients and all diabetic patients (A1c ≤7% and A1c >7%), using Pearson's chi-square test (or Fisher exact test if <5 events). ‡Difference between diabetic patients with A1c ≤7% and diabetic patients with A1c >7%, using Pearson's chi-square test (or Fisher exact test if <5 events). Data are presented as the number (%) of subjects. Abbreviations as in Table 1.

significance as an independent correlate of 12-month TVR (OR 1.96, 95% CI 0.94 to 4.10; p = 0.07).

The subgroup of patients undergoing intracoronary stent implantation was analyzed separately. In the stent population, well-controlled diabetic patients had a rate of TVR similar to that of patients without diabetes (16% vs. 13%, p = 0.68). Among diabetic patients undergoing stent placement, those with A1c >7% had a higher rate of TVR than those with A1c ≤7% (33% vs. 16%, p = 0.05).

Follow-up events. Analysis of follow-up data revealed no significant differences in the rate of cardiovascular mortality, MI, subsequent CABG, recurrent angina, CHF, arrhythmias, stroke, renal failure, or cardiac rehospitalization in patients with diabetes compared with patients without diabetes. However, suboptimally controlled diabetic patients had a higher incidence of recurrent angina (37% vs. 13%, p = 0.002) and cardiac rehospitalization (31% vs. 15%, p = 0.03) than well-controlled diabetic patients (Table 4). Multivariate analysis disclosed that A1c >7% was a significant independent predictor of both cardiac rehospitalization (OR 2.44, 95% CI 1.05 to 5.66; p = 0.04) and recurrent angina (OR 4.03, 95% CI 1.66 to 9.78; p = 0.002).

DISCUSSION

Diabetes is associated with a two- to four-fold increase in the risk of developing cardiovascular disease and is a well-recognized risk factor for adverse outcomes after coronary intervention (3,5,9,16). Despite these data, little information exists regarding the effect of glycemic control on outcome in this high-risk patient population. This is one of the first studies to prospectively evaluate the impact of glycemic control on outcome in diabetic patients undergoing PCI. Our findings demonstrate that despite similar baseline clinical and angiographic characteristics, diabetic patients with A1c ≤7% at the time of PCI had a significantly lower rate of TVR than did those with A1c >7%. Furthermore, optimally controlled diabetic patients had rates of TVR similar to those of nondiabetic patients. These

observations demonstrate the importance of glycemic control in reducing restenosis after coronary intervention.

Glycemic control and events after PCI. Findings from the United Kingdom Prospective Diabetes Study (UKPDS) Group (17) showed that intensive glycemic control in patients with type II diabetes resulted in a significant improvement in microvascular events. Despite this, the effect of tight glycemic control on macrovascular end points remained unclear, as only a trend toward improvement in fatal MI, nonfatal MI, and sudden death was observed (16% risk reduction, p = 0.052). Recently, however, a growing body of evidence has shown an association between optimal glycemic control and improvement in macrovascular events. Khaw et al. (18) demonstrated a significant increase in all-cause, cardiac, and ischemic mortality with increasing levels of A1c. In their study, a 1% increase in A1c was associated with a 38% increase in cardiovascular mortality and a 44% increase in risk of ischemic mortality in diabetic patients. In the present study, although the rate of cardiac rehospitalization after PCI was higher in diabetic patients with A1c >7% than in those with A1c ≤7%, an increase in cardiovascular mortality was not observed. There are several potential explanations regarding these discordant findings. The small sample size and short duration of the study limited the ability of this investigation to detect a difference in mortality. Furthermore, diabetic patients often have multiple co-existing cardiovascular risk factors; therefore, the therapeutic efficacy of treatments aimed at reducing overall cardiovascular risk (e.g., lipid-lowering and antiplatelet therapies) must be considered. Nevertheless, although an increase in cardiovascular mortality in poorly controlled diabetics was not observed, these data do indicate that glycemic control may play an important role in the pathophysiology of the restenotic process.

In a small series of diabetic patients undergoing PTCA, Asakura et al. (19) found a significantly higher rate of restenosis in poorly controlled diabetic patients compared with moderately or well-controlled diabetic patients. Multivariate analysis disclosed a significant correlation between

restenosis and the degree of glycemic control. These findings are contrary to those of Hasdai et al. (20), who found no significant relationship between the degree of glycemia, as measured by glycated hemoglobin, and outcome after PCI. These discordant observations may be due to the retrospective nature of the study and potential for significant sampling error, as only 64% of diabetic patients in this study had glycated hemoglobin drawn within 100 days of the index procedure.

This study demonstrates that after vascular injury induced by catheter-based intervention, the rate of TVR is significantly reduced in patients with tight glycemic control. These findings are supported by the fact that chronic hyperglycemia is known to induce vascular endothelial cell damage, with resultant vasomotor dysfunction, excessive extracellular matrix formation, and increased cellular proliferation. Furthermore, increased accumulation of advanced glycation end products in the vessel wall leads to decreased vascular compliance, enhanced smooth muscle proliferation, and augmentation of the inflammatory response after vascular damage from coronary interventions. Many of these abnormalities may be reversible with improved glycemic control (12,13). Our findings imply that strict glycometabolic control may be instrumental in preventing the untoward pathophysiologic mechanisms by which hyperglycemia leads to accelerated restenosis in diabetic patients.

Hyperinsulinemia and restenosis. Hyperinsulinemia has been implicated in a variety of mechanisms that may predispose diabetic patients to increased rates of restenosis after PCI. Insulin may induce endothelial dysfunction, increase smooth muscle cell proliferation, promote extracellular matrix deposition, alter lipid metabolism, and increase plasminogen activator inhibitor-1 levels, resulting in untoward imbalances in the fibrinolytic system (12,13). These findings have led some to theorize that hyperinsulinemia (whether from exogenous therapy or insulin resistance states) could be a major contributing factor in the progression of coronary disease after vascular injury induced by PCI (21). Furthermore, concerns have been raised over the management of diabetes with insulin therapy, as exogenously administered insulin may potentiate progression of CAD via these atherogenic mechanisms (22,23). Clinical data regarding the impact of insulin therapy on restenosis after PCI have been inconclusive. Abizaid et al. (9) found an increased rate of target lesion revascularization in insulin-treated diabetic patients compared with nondiabetic patients. However, there was no difference in target lesion revascularization between non-insulin-treated diabetic patients and nondiabetic patients, implying that insulin treatment may predict an unfavorable clinical outcome in diabetic patients undergoing percutaneous revascularization. Conversely, Schofer et al. (24) demonstrated no significant difference in restenosis rates between insulin-treated and non-insulin-treated diabetic patients.

In this study, we found that compared with patients without diabetes, both insulin-treated and orally treated

diabetic patients had significantly higher rates of clinical restenosis. When the effect of the treatment regimen was examined, there was a trend toward a higher rate of TVR in insulin-treated patients compared with orally treated patients. In a multiple logistic regression analysis, although A1c >7% was shown to be a significant independent predictor of TVR, the use of insulin achieved borderline significance as a correlate of the need for revascularization. Although the use of insulin did not reach statistical significance, perhaps due to the limited sample size, our results suggest that in addition to hyperglycemia, insulin therapy may also be an important potentiating factor in the restenotic process. Given these data, the role of insulin-sensitizing medications, such as metformin and the thiazolidinediones, either alone or in combination therapy, must be prospectively investigated to determine whether such therapies can reduce events after PCI.

Study limitations. This study reports a single-center experience with a relatively small number of patients. Routine angiographic follow-up was not performed, and thus absolute restenosis rates could not be reported. Despite this, we were able to obtain complete clinical follow-up data on all patients enrolled in the study and were thus able to accurately assess rates of cardiovascular mortality, MI, and TVR, which are perhaps more clinically relevant end points. The definition of TVR used in this study is limited solely to the initial vessel intervened upon and, as such, gives no information on the progression of disease in other vessels or the need for revascularization in previously diseased vessels. The effect of other metabolic parameters, such as insulin levels, C-peptide levels, and inflammatory markers, on TVR was not examined in this study and merits further investigation.

Conclusions. In this study, we found a significantly higher rate of ischemia-driven TVR, cardiac rehospitalization, and recurrent angina in diabetic patients with suboptimal glycemic control. Furthermore, well-controlled diabetic patients had rates of adverse clinical events comparable to those of nondiabetic patients. These data suggest that aggressive treatment of diabetes to achieve A1c levels $\leq 7\%$ may be beneficial in reducing the risk of restenosis and may improve the clinical outcome after PCI.

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Optimal glycemic control is associated with a lower rate of target vessel revascularization in treated type II diabetic patients undergoing elective percutaneous coronary intervention

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