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Blood Thrombogenicity in Type 2 Diabetes Mellitus Patients Is Associated With Glycemic Control

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OBJECTIVES	This study was designed to determine whether blood thrombogenicity is related to chronic glycemic control in type 2 diabetes mellitus (T2DM).
BACKGROUND	Type 2 diabetes mellitus is associated with accelerated atherosclerosis and a high rate of arterial thrombotic complications. Whether increased blood thrombogenicity is associated with glycemic control has not been properly tested.
METHODS	Forty patients with T2DM with hemoglobin A1c (HbA1c) $\geq 7.5\%$ were selected. Maintaining their current hypoglycemic therapies, patients were randomized into a conservative (diet modification plus placebo) or intensive (diet modification plus troglitazone) hypoglycemic regimen for three months. Blood thrombogenicity was measured at baseline and after three months with the Badimon ex vivo perfusion chamber and assessed as platelet-thrombus formation. The repeated measurements allowed every patient to be his/her own control.
RESULTS	Patients in both groups (48% and 74% of the conservative and intensive groups, respectively) improved glucose control (HbA1c reduction $\geq 0.5\%$), showing a significant decrease in blood thrombogenicity. A significant positive correlation was observed between the reduction in thrombus formation and the reduction in HbA1c ($r = 0.47$, $p < 0.01$). The reduction in HbA1c achieved by both treatments was comparable. Patients without glycemic improvement showed no change in blood thrombogenicity. Improved glycemic control was the only significant predictor of a decrease in blood thrombogenicity.
CONCLUSIONS	In T2DM, there is an association between improved glycemic control and blood thrombogenicity reduction. The effect of glycemic control on the thrombotic complications of T2DM patients deserves further investigation. (J Am Coll Cardiol 2001;38:1307–12) © 2001 by the American College of Cardiology

Type 2 diabetes mellitus (T2DM) is a major independent risk factor for coronary artery disease. These patients show not only accelerated atherosclerosis but increased morbidity and mortality due to thrombotic complications of atherosclerosis (1,2) and following percutaneous coronary interventions (3). As this increased risk is only partially explained by the association of T2DM with other classical risk factors (4), additional contributions to the process of atherosclerosis, such as a hypercoagulable state, are considered likely to play a role (5).

The procoagulant state associated with T2DM (6) is clinically manifested by a high rate of acute arterial thrombotic episodes. Most of the described procoagulant features are more striking in poorly controlled patients. Although there are a number of proposed mechanisms by

which hyperglycemia can induce thrombogenicity (5,7), the evidence for reversibility after glycemic control is not convincing (8–11). One possible explanation for this discrepancy is that the hypercoagulable state is not accurately assessed by measurements such as in vitro platelet aggregation or levels of coagulation or fibrinolytic proteins, which may not reflect the entire process of arterial thrombosis in vivo (12,13). Using an ex vivo model of platelet-dependent thrombus formation under physiologically relevant shear stress, we have previously shown that patients with T2DM have increased blood thrombogenicity when compared with a population of non-diabetic subjects matched for the presence of other cardiovascular risk factors (14).

Our hypothesis was that the observed increase in blood thrombogenicity is partially mediated via chronic glycemic control. To test that hypothesis we compared the effect of a conservative versus an intensive approach of managing diabetes on blood thrombogenicity of patients with T2DM. We therefore designed a protocol in which patients were randomized to continued conventional therapy (conservative approach) or the addition of a thiazolidinedione to their current therapy (intensive approach) for three months.

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Abbreviations and Acronyms

ANOVA	= analysis of variance
CRP	= C-reactive protein
HbA1c	= hemoglobin A1c
MANOVA	= multivariate analysis of variance
PAI-1	= plasminogen activator inhibitor 1
RM-ANOVA	= repeated measures ANOVA
T2DM	= type 2 diabetes mellitus

METHODS

Patient population. The study included 40 patients with T2DM. Inclusion criteria were a history of diabetes of >1 year, age between 20 and 70 years, hemoglobin A1c (HbA1c) levels $\geq 7.5\%$ and current treatment with insulin and/or a sulfonylurea. All subjects were instructed to perform and log finger-stick glucose measurements, and a glucose-monitoring device (One-Touch Profile, Lifescan, Milpitas, California) was supplied to every patient.

Exclusion criteria included a contraindication to the use of thiazolidinediones, baseline transaminase levels >2 times the upper normal limit, uncontrolled hypertension, lactating or pregnant women, fasting C-peptide levels <0.1 ng/ml, treatment with troglitazone or metformin in the prior three months, a history of acute coronary syndrome or revascularization in the past three months, malignant diseases, hematologic disorders and concurrent anticoagulant or antiplatelet therapy (other than aspirin).

Study design. Subjects maintained their current hypoglycemic therapy and were randomized (double blind) to receive placebo or troglitazone 600 mg once a day for three months. Patients returned for monthly visits during the next three months for safety monitoring. Results of home glucose monitoring were reviewed and adjustment of initial antidiabetic therapy (insulin or SU) was made if necessary to avoid hypoglycemia. All other drug therapy remained unchanged during the study period. A reduction in HbA1c ≥ 0.5 was considered to be clinically significant. The Institutional Review Board of Mount Sinai Medical Center approved the protocol and informed consent was obtained from all subjects. Troglitazone and matching placebo tablets were supplied by Parke-Davis (Morris Plains, New Jersey).

The following parameters were determined following an overnight fast at baseline and after three months: lipid profile, fibrinogen, blood cell count, glucose, routine biochemical parameters, creatinine, HbA1c, urine analysis, urine albumin/creatinine, total plasma insulin, C-peptide level and C-reactive protein (CRP). HbA1c was measured by ion-exchange high performance liquid chromatography (Bio-Rad Variant, Hercules, California). C-reactive protein was measured by a high-sensitivity assay (Dade Behring, Germany).

Assessment of blood thrombogenicity. EX-VIVO PERFUSION CHAMBER. The effect of glycemic control on blood thrombogenicity was assessed as the change in the thrombus

area formed in an ex vivo perfusion chamber (15) at baseline and three months after randomization. The description, validity and reliability of the Badimon perfusion chamber to study blood thrombogenicity on defined substrates under stable rheologic conditions have been previously reported (15). Perfusion chamber experiments were performed in the mornings, following an overnight fast.

The perfusion chamber consists of a cylindrical flow channel (1 × 25 mm) that allows the blood to flow over the thrombogenic substrate. Perfusions were performed for 5 min at a flow rate of 10 ml/min (shear rate: 1690/s; Reynolds number 60; average velocity 21.2 cm/s), to mimic the local rheology present in mildly stenotic coronary arteries. In brief, a 19-gauge catheter was carefully inserted into an antecubital vein. After 5 ml of blood was discarded, the catheter was connected to the Badimon perfusion chamber. Constant flow was maintained by a peristaltic pump (Masterflex, Cole-Palmer Instruments, Vernon Hill, Illinois) distal to the chamber. To mimic severe arterial injury, surgically prepared porcine aortic tunica media was used as thrombogenic substrate.

Histologic assessment of thrombus formation was performed by histomorphometry as previously described (15). In brief, the perfused segments were fixed in paraformaldehyde and six 2-mm cross sections (two in the proximal, middle and distal thirds respectively) were removed and paraffin embedded. Sections (5 μm) were cut and stained with Masson's trichrome-elastin to visualize the total thrombus formed on the substrates. Morphometric analysis of the thrombus was conducted at 400 \times magnification and thrombus area on each section was measured by computer-assisted planimetry using ImagePro Plus software. Results are given as the average of the analyzed sections, and the results from the perfusion chamber were averaged to obtain the overall thrombus formation per patient.

HEMATOLOGIC PARAMETERS. Citrated plasma samples, obtained pre- and post-treatment, were kept at -70°C for the analysis of plasminogen activator inhibitor 1 (PAI-1) (American Diagnostics Inc., Greenwich, Connecticut), prothrombin fragment F1+2 (Dade-Behring, Germany) and sP-selectin (Boehringer-Mannheim, Germany). Assays were performed following the manufacturer's instructions.

DATA ANALYSIS. All evaluations were blind to the therapeutic group. Data are given as mean \pm standard error. Baseline differences between the treatment groups were assessed using non-paired Student *t* test or Mann-Whitney *U* test when distribution was not normal. Repeated measures analysis of variance (RM-ANOVA) was used to test the effect of treatment on the HbA1c and thrombus formation-dependent measures. Repeated measures analysis of variance was also used to test treatment and/or glycemic improvement effects, and greenhouse Geisser-adjusted *F*s are reported for these analyses. Post-hoc tests of the hypothesized interaction (time \times glycemic improvement group) were conducted by testing the slopes of each improvement group

Table 1. Baseline Patient Characteristics

	Conservative	Intensive	Total
n	21	19	40
Male	11	13	24
Female	10	6	16
Age	57.0 ± 1.7	57.2 ± 1.8	57.1 ± 1.2
BMI	31.5 ± 2.1	30.4 ± 1.9	31.0 ± 1.4
Smokers	5	5	10
Fasting glucose (mg/dl)	171 ± 11.9	160 ± 12.9	165 ± 8.7
HbA1c (%)	9.2 ± 0.2	9.1 ± 0.3	9.1 ± 0.1
Total cholesterol (mg/dl)	198 ± 8	190 ± 8	194 ± 5
LDL cholesterol (mg/dl)	121 ± 6	122 ± 6	121 ± 4
HDL cholesterol (mg/dl)	45.5 ± 2.6	45.7 ± 2.4	45.6 ± 1.7
ACE inhibitors	8	8	16
Statins	8	4	12
Aspirin	5	8	13
Insulin	7	9	16
Sulfonylurea	15	10	25
Baseline thrombus area	14,389 ± 762	15,347 ± 1,337	14,855 ± 752

Thrombus area is expressed as μm^2 mm. There are no significant differences between groups.

ACE = angiotensin-converting enzyme; BMI = body mass index; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

by an unpaired Student *t* test. Repeated measures multivariate analysis of variance (MANOVA) was conducted for all other exploratory-dependent measures, and Wilk's λ values are reported for these analyses. Subgroup analyses were performed by RM-ANOVAs. Follow-up Pearson correlations between delta scores were conducted. Finally, two-tailed significance level was set at <0.05 . Statistical analyses were performed with SPSS 10.01.

RESULTS

Study population and baseline data. All patients completed the study without adverse events. Baseline thrombus formation in the study population was comparable to previous studies done in patients with a hypercoagulable state (14) and was independent of insulin levels, fasting C-peptide or treatment with insulin and/or sulfonylurea (Table 1).

Comparison between treatment groups. Unpaired *t* tests and non-parametric tests revealed no significant differences in baseline characteristics between treatment groups (Table 2). Although the RM-ANOVA revealed a significant value when the measured biological variables were tested, examination of the interactions for each variable suggested that the significant changes were not slope differences of clinical relevance. Two planned RM-ANOVAs demonstrated that the interaction between treatment group and both HbA1c levels and thrombus formation were not significant ($F [1,38] = 2.1, p = 0.16$; and $F [1,34] = 2.7, p = 0.10$, respectively). These findings are not surprising, as we were testing an intensive treatment against a conservative treatment, and both are active treatments. In fact, 48% of the conservative treated patients and 78% in the intense group showed glycemic improvement (mean change = -0.05% and -0.1% , in the conservative and intensive groups, respectively).

Effect of glycemic improvement on blood thrombogenicity. Twenty-four patients (14 from the intensively treated group and 10 from the conservatively treated group) showed a reduction in baseline HbA1c $\geq 0.5\%$ and a significant reduction in mean HbA1c levels ($9.2\% \pm 0.2\%$ to $7.8\% \pm 0.1\%$ at baseline and three months respectively, $p < 0.01$). Unpaired *t* tests and non-parametric tests revealed no significant differences in baseline characteristics of any of the biological variables between glycemic improvement groups.

A planned RM-ANOVA for thrombus formation with only glycemic improvement as the between-subjects factor demonstrated that the time \times glycemic improvement interaction was highly significant ($F [1,34] = 8.6, p < 0.01$). Including both treatment and glycemic improvement as between-subject factors continued to reveal only a "time by glycemic improvement" interaction ($F [1,32] = 5.8, p < 0.05$). A *t* test of changes in thrombus formation across the study revealed that patients with glycemic improvement had significantly less thrombus formation compared with those without improvement (mean change $-3,373 \mu^2/\text{mm}$ vs. $+1,126 \mu^2/\text{mm}$; for improved versus non-improved respectively, $t [1,34] = 2.9; p < 0.01$).

A repeated-measures MANOVA for the other biologic-dependent measures in the whole study population (sP-selectin, F1+2, CRP, lipid levels, fibrinogen, leukocyte count and PAI-1) revealed that the Wilk's λ for the time by improvement status by type of biological variable was not significant (Wilk's $\lambda = 0.82; F [4,27] = 1.4, p > 0.05$). However, there was one variable (sP-selectin) in which the values of the improved group changed from clinically elevated to not clinically elevated, so we chose to test this one variable singly. We then conducted a RM-ANOVA on this variable, and the time by glycemic improvement interaction ($F [1,37] = 4.8, p < 0.05$) was significant. Glyce-

Table 2. Results in Both Treatment Groups

	Placebo	Troglitazone
Glucose (mg/dl)		
Baseline	171 ± 11.9	160 ± 12.9
Three months	176 ± 11	138 ± 13
HbA1c (%)		
Baseline	9.2 ± 0.2	9.1 ± 0.3
Three months	8.9 ± 0.2	8.0 ± 0.2
Thrombus area		
Baseline	14,389 ± 762	15,347 ± 1,337
Three months	14,123 ± 750	12,292 ± 834
Fibrinogen (mg/dl)		
Baseline	275.9 ± 17	288 ± 18
Three months	264.9 ± 19	252.0 ± 17
Cholesterol (mg/dl)		
Baseline	198 ± 8	190 ± 8
Three months	180 ± 6	188 ± 9
LDL (mg/dl)		
Baseline	121 ± 6	122 ± 6
Three months	108 ± 6	119 ± 7
HDL (mg/dl)		
Baseline	45 ± 2	45 ± 2
Three months	43 ± 2	47 ± 2
C-peptide (ng/ml)		
Baseline	2.6 ± 0.3	1.9 ± 0.2
Three months	3.0 ± 0.3	1.8 ± 0.2
Insulin (mIU/ml)		
Baseline	24.5 ± 4	17.5 ± 3
Three months	21.3 ± 3	12.7 ± 2
PAI-1 (ng/ml)		
Baseline	36.2 ± 2.6	24.1 ± 2.6
Three months	33.4 ± 2.7	20.7 ± 1.6
sP-selectin (ng/ml)		
Baseline	171 ± 14	140 ± 16
Three months	132 ± 10	132 ± 11

HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PAI-1 = plasminogen activator inhibitor 1.

mically improved patients ($X = -45.3$) had a significantly larger decrease in P-selectin levels than did those who did not improve ($X = -4.2$; $t_n [1,37] = 2.2$, $p < 0.05$).

In order to explore clinically significant changes in the measured biological variables, subgroup analysis were performed. RM-ANOVA in the subgroup of patients with glycemic improvement in the conservative treatment group revealed a significant reduction in body mass index and in low-density lipoprotein cholesterol ($p < 0.05$). sP-selectin and CRP levels were also significantly reduced. The same analysis in the subgroup of patients with glycemic improvement in the intensive treatment group revealed significant reductions in sP-selectin, CRP and glucose (Table 3).

A total of 16 patients (five in the intensive group and 11 in the conservative group) showed no improvement in glycemic control and unchanged thrombus formation (Table 3).

Effect of glycemic control improvement on blood thrombogenicity. A significant correlation was observed between thrombus formation changes and HbA1c changes ($r = 0.47$, $p < 0.01$), demonstrating that the more HbA1c was reduced, the more thrombus formation was reduced. The same interaction was not significant for sP-selectin.

DISCUSSION

Our study has demonstrated an association between glycemic control improvement and blood thrombogenicity reduction in patients with poorly controlled T2DM. We found that even placebo-treated patients who achieved a reduction in HbA1c, presumably through better adherence to diet and previously prescribed diabetic medications, demonstrated a significant reduction in thrombogenicity. Subjects without improvement in glucose control (from either treatment group) failed to show improvement in hypercoagulability. Both treatment groups included a significant amount of patients with glycemic improvement (48% and 74% in the conservative and intensive groups, respectively), and there were no differences between treatment groups in glycemic improvement or thrombus reduction. Glycemic improvement was the only independent variable associated with reduction of thrombus formation.

In contrast to our findings, others have failed to show a reduction in the hypercoagulable state of diabetic patients after improving glycemic control (8–11). In these studies, plasma markers of hypercoagulability and *in vitro* platelet aggregometry were used to study the hypercoagulable state. Platelet aggregometry assumes that fibrinogen binding to glycoprotein IIb/IIIa is the only relevant interaction in platelet function. However this may be true only in a stirred platelet suspension used in aggregometry (low shear rate conditions) and cannot be applied to platelet activation in arterioles or arteries (12), where high shear-dependent platelet activation is present. Our goal was to assess platelet-dependent thrombosis in a population with a high incidence of arterial thrombotic episodes. The *ex vivo* Badimon perfusion chamber, using native non-anticoagulated blood, triggers thrombus formation by exposing the blood to collagen under high shear conditions that mimic those present in a mildly stenotic coronary artery. We propose that the effect of metabolic control may be more apparent in this model of arterial thrombosis, which closely simulates *in vivo* conditions following spontaneous or iatrogenic plaque rupture.

Our study design resembles routine clinical practice, in which the addition of an insulin sensitizer and/or dietary modification may be used to treat patients with T2DM who are inadequately controlled on insulin or sulfonylurea treatment (16). The thiazolidinedione troglitazone was selected because of its effect on glucose control in patients with T2DM. The reported *in vitro* antiplatelet effects of troglitazone (17) were not apparent in our model of blood thrombogenicity.

Potential clinical significance. The hypercoagulable state of patients with T2DM appears to be an important factor contributing to the accelerated atherosclerosis and high rate of arterial thrombotic complications described in these patients (5). Although there is no direct evidence linking improved glycemic control to reduction in macrovascular disease in diabetes, several studies have shown a relationship

Table 3. Results

	No Glycemic Improvement						Glycemic Improvement					
	Conservative			Intense			Conservative			Intense		
	Baseline	3-Month	Post	Baseline	3-Month	Post	Baseline	3-Month	Post	Baseline	3-Month	Post
n	11			5			10			14		
BMI, $\mu\text{m}^2/\text{mm}$	29.9 ± 2	30.4 ± 2	31.0 ± 4	30.5 ± 4	31.0 ± 4	31.0 ± 4	33.8 ± 3	30.7 ± 3†	30.5 ± 2	30.5 ± 2	30.6 ± 2	
Thrombus, mg/dl	13,665 ± 847	15,487 ± 1,074	14,265 ± 1,939	14,434 ± 953	14,265 ± 1,939	14,265 ± 1,939	15,188 ± 1,210	12,065 ± 862*	15,607 ± 1,705	11,728 ± 866*	11,728 ± 866*	
Glucose, %	171 ± 20	190 ± 16	195 ± 26	178 ± 22	195 ± 26	195 ± 26	171 ± 9	161 ± 14	153 ± 15	119 ± 13†	119 ± 13†	
HbA1c, mg/dl	9.2 ± 0.4	9.4 ± 0.4	9.4 ± 0.6	9.2 ± 0.6	9.4 ± 0.6	9.4 ± 0.6	9.3 ± 0.2	8. ± 0.2*	9.1 ± 0.4	7.6 ± 0.2*	7.6 ± 0.2*	
Cholesterol, mg/dl	195 ± 11	179 ± 9	188 ± 16	188 ± 16	199 ± 16	199 ± 16	201 ± 12	182 ± 10	191 ± 10	184 ± 11	184 ± 11	
LDL, mg/dl	117 ± 10	105 ± 10	129 ± 10	121 ± 11	129 ± 10	129 ± 10	125 ± 9	111 ± 8†	122 ± 7	116 ± 10	116 ± 10	
HDL, mg/dl	45 ± 3	42 ± 2	48 ± 4	47 ± 3	48 ± 4	48 ± 4	45 ± 4	44 ± 3	45 ± 3	46 ± 3	46 ± 3	
Triglycerides, mg/dl	180 ± 38	172 ± 30	110 ± 23	99 ± 20	110 ± 23	110 ± 23	151 ± 23	132 ± 21	115 ± 13	106 ± 16	106 ± 16	
C-reactive protein, mg/L	3.25 ± 0.91	3.34 ± 0.95	3.49 ± 1.23	4.40 ± 0.78	3.49 ± 1.23	3.49 ± 1.23	7.18 ± 3.06	5.96 ± 3.06†	5.06 ± 1.29	2.97 ± 0.90†	2.97 ± 0.90†	
Fibrinogen, mg/dl	255 ± 25	255 ± 31	268 ± 22	328 ± 36	268 ± 22	268 ± 22	301 ± 19	277 ± 17	308 ± 39	247 ± 20	247 ± 20	
C-peptide, ng/ml	1.81 ± 0.25	2.56 ± 0.35	1.50 ± 0.50	2.38 ± 0.44	1.50 ± 0.50	1.50 ± 0.50	3.48 ± 0.67	3.59 ± 0.46	1.86 ± 0.23	1.96 ± 0.25	1.96 ± 0.25	
Insulin, $\mu\text{IU}/\text{ml}$	17.3 ± 2.4	16.6 ± 2.3	13.78 ± 4.2	16.2 ± 2.2	13.78 ± 4.2	13.78 ± 4.2	30.9 ± 7.8	26.6 ± 6.5	18.1 ± 3.9	12.5 ± 2.4	12.5 ± 2.4	
sP-selectin, ng/ml	134 ± 12	130 ± 10	130 ± 28	135 ± 35	130 ± 28	130 ± 28	215 ± 21	135 ± 19†	142 ± 19	120 ± 11†	120 ± 11†	
F1 + 2, nmol/ml	1.34 ± 0.24	1.36 ± 0.20	4.03 ± 2.66	4.79 ± 3.20	4.03 ± 2.66	4.03 ± 2.66	1.95 ± 0.27	1.53 ± 0.24	1.23 ± 0.15	1.87 ± 0.65	1.87 ± 0.65	
PAI-1, ng/ml	31.2 ± 3.5	33.3 ± 4.3	23.6 ± 2.5	24.9 ± 5.7	23.6 ± 2.5	23.6 ± 2.5	42.3 ± 2.8	33.6 ± 3.7	33.9 ± 3.1	19.6 ± 2.1	19.6 ± 2.1	
Leukocytes, $\times 10^3/\mu\text{l}$	6.05 ± 0.4	6.31 ± 0.4	6.73 ± 0.8	7.47 ± 0.9	6.73 ± 0.8	6.73 ± 0.8	6.96 ± 0.4	6.94 ± 0.4	7.58 ± 0.5	6.34 ± 0.4	6.34 ± 0.4	

*p < 0.05. †p < 0.05 in subgroup analysis. Bold face values indicate statistically significant difference between baseline and post. BMI = body mass index; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PAI-1 = plasminogen activator inhibitor.

between glycemic control and the risk of coronary artery disease (18–21) and cardiovascular mortality (18). Lower blood thrombogenicity in patients with better glycemic control may have contributed to a reduction in cardiovascular events in these patients. Although it was significant only in a subgroup analysis, a reduction in CRP following glycemic improvement supports a potential link between glucose control and the progression of atherosclerosis.

The in-hospital and six-month mortality of diabetic patients following myocardial infarction are twice those of non-diabetic individuals (22). The Swedish Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) (23) study showed a 30% reduction in mortality at 12 months in those diabetic patients who were treated with intensive insulin therapy after myocardial infarction. Lower blood thrombogenicity as a consequence of lower blood glucose levels may have contributed to reduction in coronary reocclusion and re-infarction, which are leading causes of both in hospital death and late mortality excess (24).

Potential mechanisms of blood thrombogenicity reduction after glycemic control. Hyperglycemia accelerates the formation of advanced glycation end products, which are known to cause endothelial dysfunction and thus may be linked to platelet activation in diabetes (25). Advanced glycation end products induce tissue factor production in human monocytes in vitro (7) and may enhance platelet reactivity (25). Hyperglycemia-induced oxidative stress has been reported to promote thrombin formation (26) and platelet activation (27) in patients with diabetes. Our observation that patients showing glycemic improvement also had a significant reduction in sP-selectin levels reflects a decrease in platelet activation in vivo (28) and is consistent with the link between hyperglycemia and persistent platelet activation described by Davi et al. (27). Thus, there are established mechanistic links between hyperglycemia and the prothrombotic state in diabetes.

Levels of fibrinogen, PAI-1 and F1+2 were within or close to the normal range in most of our patients, despite clearly increased thrombogenicity, and may explain why we were unable to observe an association between these variables and thrombus formation.

Study limitations. We cannot rule out the possibility that a non-glucose-mediated effect of troglitazone may have contributed to the improvement in thrombogenicity. However, troglitazone-treated subjects who remained in poor control (n = 5) showed no reduction in thrombogenicity. Furthermore, thrombus reduction among subjects with improved HbA1c was similar in both treatment groups, supporting the critical role of glucose control in reducing blood thrombogenicity.

In conclusion, glycemic control improvement is associated with blood thrombogenicity reduction in patients with poorly controlled T2DM. Adequate glycemic control, especially in the setting of acute coronary syndromes or percutaneous coronary interventions, may have significant clinical

benefit by reducing the increased thrombotic complications that are characteristic of T2DM patients.

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