Intracoronary Thrombus and Platelet Glycoprotein IIb/IIIa Receptor Blockade With Tirofiban in Unstable Angina or Non–Q-Wave Myocardial Infarction

Angiographic Results From the PRISM-PLUS Trial (Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms)

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Background—The present study describes the effects of tirofiban, a nonpeptide platelet glycoprotein (GP) IIb/IIIa receptor blocker, on the characteristics of culprit lesions in patients with unstable angina (UA) or non–Q-wave myocardial infarction (NQWMI).

Methods and Results—Of 1915 patients enrolled in PRISM-PLUS, 1491 had a readable film obtained a median of 65 hours after randomization. A core laboratory examined the culprit lesions for intracoronary thrombus burden (primary end point) and for TIMI flow grade distribution and severity of the obstruction and of underlying coronary artery disease (secondary end points). The combination of tirofiban plus heparin compared with heparin alone significantly reduced the intracoronary thrombus burden of the culprit lesions (OR=0.77, P=0.022), improved the perfusion grade (OR=0.65, P=0.002), and decreased the severity of the obstruction (P=0.037), but it did not influence the severity of the underlying plaque. Persistence of a thrombus in 45% of patients was associated with a 2.4-fold increase in the odds of death at 30 days (P=0.005) and a 2-fold increase in the odds of myocardial infarction (P=0.002).

Conclusions—The addition of tirofiban to heparin reduced the thrombus burden of the culprit lesion and improved distal perfusion in patients with UA or NQWMI, which supports the clinical benefit observed with the combination treatment.

Key Words: thrombus ■ angiography ■ platelet aggregation inhibitors ■ prognosis

Unstable angina (UA) and non–Q-wave myocardial infarction (NQWMI) are usually associated with intracoronary thrombus superimposed on disruption of atherosclerotic plaque.1 Histologically, plaque hemorrhage, fissure, and intraluminal thrombus are common in patients dying of acute ischemic syndrome.2–6 Culprit lesions often have a complex appearance on angiography and angioscopy4,5 with an intraluminal thrombus.5,6 Blood markers of platelet activity and fibrin generation are usually increased.7,8 Antithrombotic therapy is effective to prevent complications.9–11 Platelet adhesion, activation, and aggregation play a critical role in initiating steps in the pathogenesis of platelet-rich arterial thromboses, and platelet glycoprotein (GP) IIb/IIIa membrane receptor plays a pivotal role in platelet aggregation through fibrinogen binding. A novel class of antiplatelet therapeutics based on GP IIb/IIIa receptor blockade has been developed and has been shown to be effective to prevent complications associated with UA, NQWMI, and percutaneous coronary interventions.12–15 The PRISM-PLUS study investigated tirofiban, a nonpeptide platelet GP IIb/IIIa antagonist, as part of the comprehensive management of UA or NQWMI.15 This report describes the results of a prospectively designed angiographic substudy of PRISM-PLUS to characterize the effects of GP IIb/IIIa receptor blockade on culprit lesions.

Methods

Patients and Randomization

The PRISM-PLUS study was performed in 72 hospitals in 14 countries. A total of 1915 patients with UA or NQWMI were randomized. The entry and exclusion criteria were described in the original study publication.15 The initial study design involved double-blind randomization to 1 of 3 treatment groups: (1) tirofiban alone; (2) tirofiban plus heparin; or (3) tirofiban placebo plus heparin.15 The tirofiban-alone group

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1609
was discontinued prematurely in accordance with a recommendation of the Data Safety Monitoring Board on the basis of an apparent excess mortality at 7 days in this group after enrollment of 345 patients in this arm of the study and of a total of 1031 patients in the trial. This arm had a relatively small sample size and was not strictly comparable with the other groups in the trial cohorts. The present report therefore focused on the comparison between tirofiban plus heparin and heparin alone; the data from the tirofiban-alone arm are provided for descriptive purposes only.

Infusion of study drugs was maintained for a minimum of 48 hours, with any intervention postponed until after this time period unless mandated by a refractory ischemic (RI) condition or by a new myocardial infarction (MI). Angiography was recommended but not required in all patients between 48 and 96 hours after randomization and on study drug infusion.

**Coronary Angiography**

Of 1915 patients, 1719 had an angiography during the initial hospitalization, and 1538 underwent angiography during the first 97 hours. Of these, 1491 (78% of the study population) had a readable angiogram and were included in the angiographic study.

Standard coronary views, with 6- to 7-in image fields, included 5 left and 2 right coronary artery injections suitable for quantitative angiography. Additional views were obtained to clearly visualize the presumed culprit lesion. Sublingual or intracoronary nitroglycerin was used in all patients before the coronary injections.

**Angiographic Analysis**

The angiograms were first reviewed at the clinical sites by the clinical investigators to identify the culprit lesion and then were

![Figure 1. Angiographic examples of culprit lesions containing intracoronary thrombus. A, Very eccentric LCx lesion with large upstream thrombus. B, LAD lesion with medium globular thrombus. C, RCA lesion with large thrombus and ulceration. In this angiographic study, overall angiographically detected thrombi (TIMI thrombus grade 2 to 4) were seen in 28% of patients.](image)

![Figure 2. Totally occluded culprit vessels. A, Example of recent thrombotic occlusion that ended abruptly. Five percent of patients were considered to have fresh total occlusion in this study. B, Chronic occlusion that tapered smoothly and had well-developed collaterals.](image)

![Figure 3. Culprit lesion with appearance of intraplaque hemorrhage. In this example, contrast fills an isolated intramural pocket.](image)
mailed with a copy of the qualifying ECG to the Core Laboratory when the patient was clinically stable and had been released from the study.

All angiograms were analyzed by investigators who were blinded to randomization. Films were projected at high (×37) magnification with an overhead projector. The culprit lesion was identified on the basis of the ECG leads that showed the ischemic ST-T changes and/or the details of the coronary anatomy, particularly the morphology of the lesion(s), such as presence of thrombus, stenosis severity, and other abnormalities of the luminal surface. Concordance between the investigator and Core Laboratory personnel regarding identification of the presumed culprit lesion was present in 92% of patients. The Core Laboratory evaluation prevailed when discordance was present.

The culprit lesions were assessed by techniques developed in the Core Laboratory for characterizing and measuring complex lesions containing thrombus. Each culprit lesion was described qualitatively in terms of anatomic location, perfusion characteristics, morphological features, and intraluminal thrombus.

As illustrated in Figure 1, globular intraluminal masses classified as apparent thrombi had rounded or polypoid shapes and protruded into the lumen. Apparent thrombi were subclassified (on the basis of quantitative measurement of maximum dimension of thrombus relative to normal lumen diameter) as small (<0.5 times normal lumen diameter at greatest dimension, grade 2), medium (0.5 to 1.5 times normal diameter, grade 3), or large (>1.5 times normal diameter, grade 4). Mural opacities that were only suggestive of a thrombus were classified as possible thrombus (grade 1). Totally occluded culprit vessels were subdivided into those with apparently recent thrombotic occlusion (grade 5) if they ended abruptly with a squared-off or an upstream convex termination, creating a stump or arterial cul-de-sac from which dye washout was delayed (Figure 2A), and those with chronic occlusion (grade 6) if they tapered smoothly to supply a terminal side branch with a brisk runoff; such vessels usually had a well-developed distal collateral supply (Figure 2B).

The underlying plaques, when visualized, were classified as very eccentric, ulcerated, or intraplaque hemorrhage (Figure 3). Plaques lacking these distinctive features were simply classified as being eccentric or as having a smooth or an irregular surface.

No significant differences in the above variables were found between tirofiban plus heparin and heparin alone.
TABLE 2. Comparison of Frequency of Patients With Intracoronary Thrombus by TIMI Thrombus Grade

<table>
<thead>
<tr>
<th>TIMI Thrombus Grade</th>
<th>Tirofiban Alone (n=261)</th>
<th>Tirofiban + Heparin (n=608)</th>
<th>Heparin Alone (n=622)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No thrombus</td>
<td>132 (50.6)</td>
<td>338 (55.6)</td>
<td>314 (50.5)</td>
</tr>
<tr>
<td>Possible thrombus</td>
<td>20 (7.7)</td>
<td>71 (11.7)</td>
<td>72 (11.6)</td>
</tr>
<tr>
<td>Small thrombus</td>
<td>33 (12.6)</td>
<td>69 (11.4)</td>
<td>56 (9.0)</td>
</tr>
<tr>
<td>Medium thrombus</td>
<td>43 (16.5)</td>
<td>69 (11.4)</td>
<td>98 (15.8)</td>
</tr>
<tr>
<td>Large thrombus</td>
<td>11 (4.2)</td>
<td>13 (2.1)</td>
<td>19 (3.0)</td>
</tr>
<tr>
<td>Fresh occlusion</td>
<td>14 (5.4)</td>
<td>22 (3.6)</td>
<td>33 (5.3)</td>
</tr>
<tr>
<td>Chronic occlusion</td>
<td>8 (3.1)</td>
<td>26 (4.3)</td>
<td>30 (4.8)</td>
</tr>
</tbody>
</table>

OR=0.774, P=0.022 for trend of the comparison between tirofiban plus heparin and heparin alone by proportional odds model. Values are n (%).

Study Hypothesis and Primary and Secondary Angiographic End Points

On the basis of a high frequency of intracoronary thrombus detected angiographically in patients with UA or NQWMI and of platelet-rich thrombus detected by angioscopy, as opposed to red fibrin-rich thrombus in patients with acute MI, it was hypothesized that profound inhibition of platelet aggregation with tirofiban would reduce the intracoronary thrombus burden and improve coronary flow past the culprit lesion.

The primary angiographic end point was the proportion of patients with each grade of TIMI flow (grades 0 to 5). Grade 6 was not included in the primary end-point analysis because chronic total occlusion (grade 6) was unlikely to be the cause of the current episode of UA or NQWMI. The predefined secondary end points included the proportion of patients with each grade of TIMI flow past the culprit lesion (grades 0 to 3) and the proportion of patients with a culprit lesion in each severity range: (1) 0 to 30% stenosis; (2) 31% to 50%; (3) 51% to 70%; (4) 71% to 99%; and (5) total occlusion.

Statistical Analysis

On the basis of results from TIMI (Thrombolysis In Myocardial Infarction) IIIA, which included patients with similar characteristics, it was estimated that the sample size of the trial would provide 95% power to detect an approximate OR of 0.65. The clinical, ECG, and angiographic characteristics of tirofiban plus heparin and heparin alone were compared by χ² test for dichotomous variables and Wilcoxon rank-sum test for continuous and ordinal variables. A proportional odds model was used to compare the distribution of thrombus grades in the 2 groups. In this model, the odds of thrombus with tirofiban plus heparin relative to heparin alone are assumed to be constant, regardless of the grouping of individual grades. Therefore, the model analyzed general trends toward more severe thrombus grades in 1 treatment group relative to the other. TIMI flow grade and disease severity (secondary end points) were analyzed by the same model. The proportional odds model was also used to identify patient, treatment, and angiographic variables that were independently predictive of thrombus. The results are displayed as OR, 95% confidence limits, and 2-sided P value. A P value <0.05 was considered statistically significant.

Results

Clinical, ECG, and Angiographic Characteristics

The various characteristics studied were similar between patients in the tirofiban-plus-heparin and heparin-alone groups (Table 1). More than 50% of patients had hypertension or hypercholesterolemia; 41% had a previous MI; and 25% had previous PTCA or CABG. The qualifying event was UA in 56% and NQWMI in 44%. Ninety-four percent of patients showed ECG evidence of ischemia, with ST-segment elevation in 15%, ST-segment depression in 57%, and T-wave inversion in 54%.

One-, 2-, and 3-vessel disease was found in 24%, 25%, and 41% of patients, respectively. Ten percent had nonsignificant disease, defined as <50% stenosis in any major coronary artery or branch. Of 1387 culprit lesions located in native coronary arteries, 49% were in the left anterior descending artery (LAD) or its diagonal branches, 34% in the left circumflex (LCx) or its branches, and 17% in the right coronary artery (RCA) or its branches. Culprit lesions were located in a saphenous vein or internal mammary graft or at a graft anastomosis in 7% of patients.

Patients were enrolled a mean of 7±4 hours after chest pain, and angiography was performed a mean of 65 hours after randomization. The infusion period extended for a mean of 8 hours after catheterization.

TABLE 3. Comparison of Coronary Perfusion Status Past the Culprit Lesion by TIMI Flow Grade

<table>
<thead>
<tr>
<th>TIMI Flow Grade</th>
<th>Tirofiban Alone (n=243)</th>
<th>Tirofiban + Heparin (n=570)</th>
<th>Heparin Alone (n=580)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>21 (8)</td>
<td>44 (8)</td>
<td>61 (11)</td>
</tr>
<tr>
<td>1</td>
<td>2 (1)</td>
<td>5 (1)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>2</td>
<td>24 (10)</td>
<td>54 (9)</td>
<td>76 (13)</td>
</tr>
<tr>
<td>3</td>
<td>196 (81)</td>
<td>467 (82)</td>
<td>432 (74)</td>
</tr>
</tbody>
</table>

OR=0.646, P=0.002 for trend of the comparison between tirofiban plus heparin and heparin alone by proportional odds model. Values are n (%).
TABLE 5. Correlations of Intracoronary Thrombus

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>P</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.008</td>
<td>0.072</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.20</td>
<td>0.072</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>1.58</td>
<td>0.002</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>0.86</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.07</td>
<td>0.48</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.25</td>
<td>0.028</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.07</td>
<td>0.59</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>1.07</td>
<td>0.57</td>
</tr>
<tr>
<td>Duration of pain (per hour)</td>
<td>1.004</td>
<td>0.76</td>
</tr>
<tr>
<td>NQWMI</td>
<td>1.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ST-segment elevation</td>
<td>1.11</td>
<td>0.46</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>1.27</td>
<td>0.019</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>0.84</td>
<td>0.076</td>
</tr>
<tr>
<td>Prior heparin</td>
<td>1.19</td>
<td>0.10</td>
</tr>
<tr>
<td>Prior aspirin</td>
<td>1.02</td>
<td>0.85</td>
</tr>
<tr>
<td>Single-vessel disease (relative to</td>
<td>3.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nonsignificant disease)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-vessel disease (relative to</td>
<td>4.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nonsignificant disease)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple-vessel disease (relative to</td>
<td>5.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nonsignificant disease)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA location (relative to LAD)</td>
<td>2.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LCx location (relative to LAD)</td>
<td>1.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment with tirofiban</td>
<td>0.77</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Treatment Effect on Intracoronary Thrombus (Primary End Point)

A possible or definite (small, medium, or large) intracoronary thrombus or a fresh total occlusion was seen in 643 patients (45%) in the present study. Compared with heparin alone, tirofiban plus heparin significantly reduced both frequency and severity of thrombus. A significant shift to smaller thrombi was observed with the combination treatment (OR=0.77, P=0.022 for trend). The number of patients with a fresh total occlusion was reduced with combination treatment, and the number with no thrombus increased. (See Table 2.)

Perfusion Status (Secondary End Point)

Significantly more patients in the tirofiban-plus-heparin group had TIMI 3 flow and significantly fewer had TIMI 2 flow, TIMI 1 flow, or no perfusion (OR=0.65, P=0.002 for trend) (Table 3).

Culprit Lesion Severity (Secondary End Point)

Consistent with the reduction in thrombus burden and improvement in TIMI flow, treatment with tirofiban plus heparin resulted in a shift to less-severe obstructive stenoses (P=0.037 for trend). When the thrombotic component of the lesion was excluded, the severity of underlying disease was the same in the tirofiban-plus-heparin and heparin-alone groups. (See Table 4.)

Predictors of Thrombus

A set of proportional odds models were fit to identify the patient and therapy variables and angiographic characteristics that were independently predictive of intracoronary thrombus. First, each of the variables was included 1 at a time in a separate model; second, all variables were included together in a multivariable model. In the univariate models, male sex and patients with prior CABG, hypercholesterolemia, NQWMI, or ST-segment depression on the qualifying ECG were predictive of thrombus. Compared with nonsignificant coronary disease, single-, double-, and triple-vessel disease had 3.0-, 4.7-, and 5.4-fold higher odds to develop thrombus, respectively. Culprit lesions located in the RCA or LCx had a significantly higher likelihood of containing thrombus than lesions located in the LAD. In contrast, treatment with tirofiban plus heparin significantly reduced the odds of thrombus by 23% (P=0.02).

In the multivariate model, previous CABG, NQWMI, an increasing number of diseased vessels, and RCA or LCx location were independent predictors of thrombus. Treatment with tirofiban independently reduced the odds of thrombus by 20% (P=0.049).

TABLE 6. Effects of Intracoronary Thrombus (TIMI Thrombus Grade 1–5) and Impaired Coronary Perfusion (TIMI Flow Grade 0–2) on Subsequent Clinical Events at 30 Days

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Thrombus (1–5) (n=643)</th>
<th>Thrombus (0) (n=784)</th>
<th>95% CI (Lower-Upper)</th>
<th>P</th>
<th>TIMI Flow (0≤2) (n=298)</th>
<th>TIMI Flow (3) (n=1095)</th>
<th>Odds Ratio</th>
<th>95% CI (Lower-Upper)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>128 (20%)</td>
<td>82 (10%)</td>
<td>2.13</td>
<td>&lt;0.001</td>
<td>59 (20%)</td>
<td>132 (12%)</td>
<td>1.72</td>
<td>1.27–2.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>32 (5%)</td>
<td>17 (2%)</td>
<td>2.36</td>
<td>0.005</td>
<td>14 (5%)</td>
<td>35 (3%)</td>
<td>1.48</td>
<td>0.80–2.75</td>
<td>0.21</td>
</tr>
<tr>
<td>MI</td>
<td>55 (9%)</td>
<td>35 (4%)</td>
<td>2.00</td>
<td>0.002</td>
<td>19 (6%)</td>
<td>55 (5%)</td>
<td>1.29</td>
<td>0.77–2.18</td>
<td>0.34</td>
</tr>
<tr>
<td>Death/MI</td>
<td>77 (12%)</td>
<td>49 (6%)</td>
<td>2.04</td>
<td>&lt;0.001</td>
<td>31 (10%)</td>
<td>81 (7.4%)</td>
<td>1.44</td>
<td>0.95–2.18</td>
<td>0.08</td>
</tr>
<tr>
<td>RI</td>
<td>60 (9%)</td>
<td>39 (5%)</td>
<td>1.97</td>
<td>1.30–2.98</td>
<td>0.002</td>
<td>27 (9%)</td>
<td>60 (5.5%)</td>
<td>1.68</td>
<td>1.07–2.65</td>
</tr>
<tr>
<td>PTCA</td>
<td>258 (40%)</td>
<td>238 (30%)</td>
<td>1.54</td>
<td>1.24–1.91</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>197 (31%)</td>
<td>167 (21%)</td>
<td>1.63</td>
<td>1.28–2.07</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any coronary revascularization</td>
<td>459 (71%)</td>
<td>414 (53%)</td>
<td>2.23</td>
<td>1.79–2.78</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prognostic Impact of Thrombus and Impaired Perfusion

Patients in all treatment groups were pooled together to examine the prognostic impact of thrombus and of impaired TIMI flow (Table 6). Persistence of thrombus increased the risk of the composite end point of death, MI, or RI at 30 days by 2.1-fold ($P<0.001$). It also increased by 2-fold or more the risk of each individual component of the composite end point: death, MI, or RI (all $P<0.005$). Patients with thrombus also had more interventions in the first 30 days: the OR was 1.54 ($P<0.001$) for PTCA, 1.63 ($P<0.001$) for CABG, and 2.23 ($P<0.001$) for any intervention.

As shown in Table 6, suboptimal TIMI flow (grade 0 to 2) also had an impact on the subsequent event rate: the OR of a composite end point was increased by 1.7-fold ($P<0.001$). In component analysis, the association was statistically significant for RI.

Discussion

This angiographic study in PRISM-PLUS was the first to examine the effects of platelet GP IIb/IIIa receptor blockade on the culprit lesion in patients with UA or NQWMI. It was also the largest prospective study that examined the angiographic characteristics of culprit lesions and their prognostic significance. The study demonstrated that the combination of tirofiban, heparin, and aspirin significantly reduced the thrombus burden of the culprit lesion by 23% beyond the effects of heparin and aspirin, resulting in decreased coronary obstruction and improved distal flow. These data are consistent with the 32% reduction in risk of death, MI, or RI observed at 7 days with the combination therapy and with the 43% reduction in the risk of death or MI. The present study also provided evidence that persistence of an angiographic thrombus after a course of medical therapy is an indicator of worse prognosis, which suggests important pathophysiological concepts and therapeutic implications.

The concordance in clinical and angiographic benefits present in this study was not observed in trials with thrombolytic agents in UA or NQWMI.22,23 Although some angiographic improvement and a reduction in diameter stenosis were observed with thrombolysis, clinical events were more frequent.24,25 Enhanced platelet activation and thrombin generation after clot lysis that could exacerbate thrombus formation and precipitate MI could explain the paradoxical findings.20,26 Unlike fibrinolytic agents, GP IIb/IIIa antagonists act on the process of thrombus formation by preventing platelet aggregation and thrombus growth and allowing effective endogenous thrombolysis to dissolve the clot.

The clinical benefits of tirofiban that were seen in PRISM-PLUS were also observed in patients with UA treated with abciximab in the EPIC (Evaluation of Iib/IIIa platelet recep
tor antagonist 7E3 in Preventing Ischemic Complications)12 and CAPTURE (C7E3 fab AntiPlatelet Therapy in Unstable angina REfractory to standard treatment)13 trials and with eptifibatide in the PURSUIT (Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) trial.14 It has been postulated that the prevention of platelet accumulation at the plaque level could favor plaque passivation, preventing recurrent ischemic events. Our study provides support for this concept by showing that treatment with tirofiban and heparin was associated with a reduction in the thrombus burden of the culprit lesions and that the absence of a residual thrombus was associated with a better outcome. Plaque passivation could be explained by better dissolution of the thrombus, which is by itself a powerful thrombogenic stimulus.13 Additional mechanisms could be prevention of the release of platelet-active products associated with cell proliferation27 and prevention of platelet-leukocyte interaction.28

The impaired outcome associated with persistence of thrombus has important implications for patient management. In patients with MI, more rapid and complete restoration of blood flow, as assessed by TIMI 3 flow, correlated with better left ventricular performance and reduced mortality.29,30 No such value of angiography has been shown in patients with UA or NQWMI; indeed, angiography in these patients is mainly used to evaluate disease severity and explore the possibility of a revascularization procedure. The demonstration in the present study that persistence of thrombus is a strong predictor of death and MI and that impaired TIMI perfusion is associated with RI extends the utility of angiography beyond its diagnostic role and suggests that lesion characteristics can be used as risk stratifiers to help orient treatment. They can possibly also be used as markers of an uncontrolled disease process, identifying high-risk patients who may benefit from more aggressive therapy.

The relatively high rate (45%) of persistence of thrombus after a period of medical stabilization with aspirin, heparin, and a GP IIb/IIIa antagonist in half the patients reinforces the importance of additional research in the acute coronary syndromes. One direction is to identify better antithrombotic therapy or better combinations of drugs and the optimal treatment duration. Another, considering the limitations of angiography to appreciate intracoronary thrombus, is to identify more sensitive and ideally noninvasive markers of an active disease process.

Appendix

A list of the principal investigators and committee members of the PRISM-PLUS Study Group has been published previously.15

Angiographic Core Laboratory

Merck Research Laboratories

References
5. The TIMI IIIA Investigators. Early effects of tissue-type plasminogen activator added to conventional therapy on the culprit coronary lesion in patients presenting with ischemic cardiac pain at rest: results of the
Intracoronary Thrombus and Platelet Glycoprotein IIb/IIIa Receptor Blockade With Tirofiban in Unstable Angina or Non–Q-Wave Myocardial Infarction: Angiographic Results From the PRISM-PLUS Trial (Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms)

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for the PRISM-PLUS Investigators

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