

# Association Between Duration of Tirofiban Therapy Before Percutaneous Intervention and Tissue Level Perfusion (A TACTICS-TIMI 18 Substudy)

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In the setting of acute coronary syndromes, thrombotic embolization and activation of platelets with release of vasoconstrictors into the downstream microvasculature may occur before cardiac catheterization. In the Treat Angina with tirofiban and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18 (TACTICS-TIMI 18) trial angiographic substudy, a shorter duration of tirofiban infusion before percutaneous coronary intervention was associated with impaired myocardial perfusion before and after intervention. ©2004 by Excerpta Medica, Inc.

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**T**irofiban is a novel nonpeptide glycoprotein IIb/IIIa antagonist that has been demonstrated to improve several angiographic characteristics and clinical outcomes in large trials of acute coronary syndromes (ACSs).<sup>1–4</sup> Tirofiban administration before diagnostic cardiac catheterization has been associated with reduced intracoronary thrombus burden and improved epicardial coronary blood flow in an angiographic substudy of The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial.<sup>5</sup> Recently, we demonstrated that impaired tissue perfusion on the diagnostic coronary angiogram before and after percutaneous coronary intervention (PCI) is associated with elevated troponin levels and poorer clinical outcomes.<sup>6</sup> We sought to extend these observations to evaluate the relation of tissue level perfusion to the duration of tirofiban therapy before diagnostic cardiac catheterization. We hypothesized that patients who were treated with shorter infusions of tirofiban would have poorer tissue-level perfusion and other angiographic outcomes on diagnostic cardiac catheterization compared with patients who were treated with longer infusions in the Treat Angina with tirofiban and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18 (TACTICS-TIMI 18) trial.

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TABLE 1 Baseline Characteristics

Characteristic	Duration of Tirofiban Infusion	
	<21 Hours (n = 157)	>21 Hours (n = 159)
Age (yrs)	61 (11)	61 (12)
Men	101 (64%)	103 (65%)
History of hypertension	97 (62%)	104 (65%)
History of hypercholesterolemia	96 (61%)	98 (62%)
Diabetes mellitus*	30 (19%)	49 (31%)
Current smoker	48 (31%)	47 (30%)
Aspirin use	101 (64%)	112 (70%)
Prior coronary bypass surgery	21 (13%)	26 (16%)
Prior myocardial infarction	60 (38%)	55 (35%)
Prior congestive heart failure	5 (3%)	9 (6%)
S-T deviation on enrollment electrocardiogram	55 (35%)	64 (40%)
Troponin T >0.1 ng/ml	77 (59%)	90 (67%)
Index event non-Q-wave myocardial infarction	65 (41%)	78 (49%)

\*The p value for all characteristics was nonsignificant, with the exception of the incidence of diabetes, where the p value is 0.016.

The TACTICS-TIMI 18 study has been previously reported.<sup>4,7</sup> Briefly, 2,220 patients with unstable angina and myocardial infarction without ST elevation were treated with aspirin, heparin, and tirofiban, and were randomized to either an early invasive or early conservative strategy of management. Patients randomized to invasive strategy underwent protocol-mandated angiography within 4 to 48 hours of randomization, and if indicated, subsequent PCI. Patients randomized to the conservative arm received maximum medical therapy. Patients underwent coronary angiography only after meeting clinical or biochemical criteria for recurrent ischemia. One thousand one hundred fourteen patients were randomized to the invasive arm. Of these, 459 (41%) underwent PCI after diagnostic catheterization. Three hundred sixteen of these patients had TIMI myocardial perfusion grade (TMPG) scorable angiograms before PCI, were not believed to require urgent catheterization by the treating clinician, and were enrolled in the present study. Patients who underwent urgent catheterization were excluded because of inherent confounding (they would be more likely to have poorer angiographic characteristics and shorter infusion times). Patients were divided into those who received tirofiban for less than (n = 157) or more than (n = 159) the median duration (21 hours). Exclusion criteria included cur-

**TABLE 2** Angiographic Characteristics

Characteristic	Tirofiban <21 Hours (n = 157)	Tirofiban >21 Hours (n = 159)	p Value
Prepercutaneous coronary intervention			
TIMI flow grade 3	114 (64.4%)	125 (71.4%)	0.158
TIMI myocardial perfusion grade 3	47 (29.9%)	69 (43.4%)	0.013
TIMI flow grade 3 and TIMI myocardial perfusion grade 3	34 (21.8%)	59 (37.6%)	0.002
Minimum lumen diameter (mm) (mean ± SD)	1.70 ± 0.96	1.91 ± 1.36	0.0935
Postpercutaneous coronary intervention			
TIMI myocardial perfusion grade 2/3 (%)	68 (49.3%)	76 (55.9%)	0.273

**TABLE 3** Angiographic Characteristics Controlled for Baseline Troponin T

Characteristic	Odds Ratio	95% Confidence Interval	p Value
TIMI flow grade 3	0.61*	0.37–1.01	0.054
TIMI myocardial perfusion grade 3	0.52†	0.31–0.87	0.012

rent use of warfarin or thienopyridines. Of the 316 patients who underwent angiography, 222 (70%) underwent PCI and had TMPG-scorable post-PCI angiograms.

The TIMI flow grade was assessed as previously defined at the TIMI Angiographic Core Laboratory.<sup>8</sup> To evaluate coronary flow objectively as a continuous quantitative variable, the number of cine frames required for contrast to first reach standardized distal coronary landmarks in the infarct-related artery (the TIMI frame count) was measured using a frame counter on a cine viewer.<sup>9</sup> Data presented here have been converted to 30 frames/s, the most common cine filming speed in the United States. All flow data were assessed by a single-blinded observer (CMG). A pulsatile flow pattern was defined as intermittent cessation of anterograde flow or frank flow reversal during systole. The optimal single-plane projection was selected that identified the stenosis in its greatest severity, with minimal foreshortening or overlapping of branches, and end-diastolic frames were chosen for quantitative angiographic analysis using a previously described and validated automated edge-detection algorithm.<sup>10</sup> Myocardial perfusion was assessed using the previously described TMPG score.<sup>11</sup> TMPG 0 is assigned when dye fails to enter the microvasculature in the territory of the culprit artery, indicating a lack of tissue perfusion. TMPG 1 denotes the presence of myocardial blush but no clearance from the microvasculature, indicating poor tissue perfusion. In TMPG 2, blush clears slowly, indicating moderate tissue perfusion, whereas in TMPG 3, or normal microvascular flow, blush begins to clear with washout.

All analyses were performed using Stata version 7.0 (Stata Corp., College Station, Texas). All continuous variable values are reported as mean ± SD. The

Student's *t* test was used for analysis of continuous variables. The non-parametric Wilcoxon rank-sum test was used when data were not normally distributed or when data were imputed for an occluded vessel. The chi-square test was used for analysis of categorical variables.

The 2 groups were well-matched with respect to all baseline characteristics, with the exception of diabetes (Table 1).

Patients treated with shorter infusions of tirofiban had a lower incidence of pre-PCI TMPG 3 flow (Table 2). The pre-PCI TIMI flow grade trended toward favoring longer infusions, as did minimum culprit artery lumen diameters, although these trends did not achieve statistical significance. Optimal epicardial and myocardial perfusion (both TIMI flow grade 3 and TMPG 3) occurred more frequently in patients who received longer infusions (37.6% vs 21.8%, *p* = 0.002). After PCI, patients treated with longer infusions of tirofiban had a greater incidence of TMPG 2 or 3 than patients treated with shorter infusions.

In a multivariate model controlling for baseline troponin T value, patients treated with shorter infusions of tirofiban had a lower incidence of TMPG 3 and TIMI flow grade 3 (Table 3). In a linear regression analysis controlling for baseline troponin T, patients treated with shorter infusions of tirofiban had tighter minimum diameters on quantitative coronary angiography than patients treated with longer infusions (*p* = 0.032, *n* = 300).

There was no increase in protocol-defined minor or major bleeding events<sup>4</sup> associated with longer infusions of tirofiban.

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In the setting of ACS, tirofiban acts in a time-dependent fashion to improve angiographic outcomes. Previous work by Zhao et al<sup>5</sup> demonstrated that TIMI flow grade was improved and coronary thrombus burden was decreased by the addition of tirofiban to a comprehensive medical regimen for ACS. The present study evaluated the association between the duration of therapy with tirofiban and angiographic outcomes. In the present study, patients who received longer infusions of tirofiban had improved pre- and post-PCI myocardial perfusion, an angiographic finding that has been associated with improved clinical outcomes independently of normal TIMI grade 3 epicardial flow. There was also a trend toward an improvement in TIMI flow grade in a dose time-dependent fashion. This finding achieved statistical significance when baseline troponin T was controlled in the multivariate model. There was no increased incidence of bleeding to offset the observed benefit in the group that was treated with longer infusions.

Among patients with unstable coronary syndromes, deferral of intervention for prolonged anti-thrombotic pretreatment for 3 to 5 days does not improve the outcome compared with immediate inter-

vention accompanied by intense antiplatelet treatment.<sup>12</sup> The present study should not be interpreted to imply that delays in performance of PCI are warranted. Rather, these findings coupled with the clinical findings from the TACTICS-TIMI 18 trial suggest that the earlier initiation of tirofiban in addition to aspirin and heparin therapy for patients with ACS, followed by routine angiography within 48 hours, may yield more favorable angiographic outcomes.

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## Comparison of Quality of Life After Repeat Versus Initial Coronary Artery Bypass Grafting

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**One-year health status improvements in 62 patients with previous coronary artery bypass grafting (CABG) were compared with those of 628 patients undergoing initial CABG using the Seattle Angina Questionnaire (SAQ). Adjusted analyses revealed that repeat CABG conferred similar 1-year improvements in health status compared with patients undergoing a first CABG (changes in SAQ Physical Limitation score [SAQ-PL: repeat CABG 25 ± 27 vs first CABG 20 ± 27; p = 0.30], Quality of Life score [SAQ-QoL: 34 ± 24 vs 35 ± 5; p = 0.87], and Angina Frequency score [SAQ-AF: 35 ± 40 vs 25 ± 24; p = 0.03]). ©2004 by Excerpta Medica, Inc. (Am J Cardiol 2004;94:494–497)**

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**R**epeat coronary artery bypass grafting (CABG) in the United States has more than quadrupled from 1.9% in 1980 to 8.4% of CABG operations in 1999.<sup>1</sup> Despite the growing prevalence of repeat procedures, there is limited evidence about their efficacy.<sup>2–5</sup> The present study was conducted to define the health status outcomes of patients undergoing repeat CABG and to compare them with those receiving their first CABG.

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In all, 907 patients underwent isolated CABG at the Mid America Heart Institute from February 8, 1999 to August 8, 2000, and were screened to participate in an observational study of health status recovery. Of these, 19 (2%) underwent emergent CABG and could not be interviewed, 37 (4%) were inadvertently missed, 18 (2%) were non-English speaking, and 143 (16%) refused. Of the remaining 690 patients, 62 (9%) had undergone previous CABG and form the repeat CABG population for this study. Consenting patients were administered questionnaires at baseline and 1 year after CABG, along with a 1-year inquiry about interval events. Before contact, patients' survival status was confirmed by a query of the Social Security Administration Death Master File and hospital records. Approval from the local institutional review board was obtained before the study.