Early initiation of eptifibatide in the emergency department before primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: Results of the Time to Integrilin Therapy in Acute Myocardial Infarction (TITAN)-TIMI 34 trial

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Background Early restoration of epicardial flow before primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) has been associated with improved clinical outcomes.

Methods We hypothesized that early administration of the glycoprotein IIb/IIIa inhibitor eptifibatide in the emergency department (ED) would yield superior epicardial flow and myocardial perfusion before primary PCI compared with initiating eptifibatide after diagnostic angiography in the cardiac catheterization laboratory (CCL). Three hundred forty-three patients with STEMI were randomized to either early ED eptifibatide (n = 180) or CCL eptifibatide (n = 163).

Results The primary end point (pre-PCI corrected TIMI frame count) was significantly lower (faster flow) with early eptifibatide (77.5 $\pm$ 32.2 vs 84.3 $\pm$ 30.7, P = .049). The incidence of normal pre-PCI TIMI myocardial perfusion was increased among patients treated in the ED versus CCL (24% vs 14%, P = .026). There was no excess of TIMI major or minor bleeding among patients treated in the ED versus CCL (6.9% [12/174] vs 7.8% [11/142], P = NS).

Conclusion A strategy of early initiation of eptifibatide in the ED before primary PCI for STEMI yields superior pre-PCI TIMI frame counts, reflecting epicardial flow, and superior TIMI myocardial perfusion compared with a strategy of initiating eptifibatide in the CCL without an increase in bleeding risk. (Am Heart J 2006;152:668-75.)

Early, full, and sustained restoration of infarct-related artery patency remains the criterion standard for the treatment of ST-segment elevation myocardial infarction (STEMI). Although fibrinolytic therapy has been shown to reduce mortality in patients with STEMI when administered promptly after the onset of symptoms,[1] the limitations remain: the fibrinolytic therapy achieves normal (TIMI 3) flow in only approximately 60% of cases and carries an inherent risk of major bleeding and hemorrhagic stroke.[2] Primary percutaneous coronary intervention (PCI), on the other hand, achieves higher rates of TIMI 3 flow and is associated with a lower incidence of bleeding and stroke.[2] In order for primary PCI to be effective, however, it must be implemented quickly. Unfortunately, primary PCI is often not performed within 90 minutes of patient arrival as recommended in the American College of Cardiology/American Heart Association guidelines.[3]

Although primary PCI frequently restores TIMI 3 flow, restoration of patency before primary PCI is associated with improved survival.[4] Given the inherent delays in the performance of primary PCI, there remains an unmet need for a safe and effective pharmacologic strategy to

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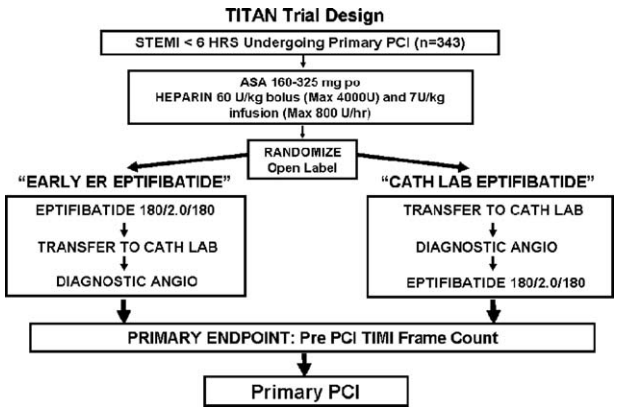
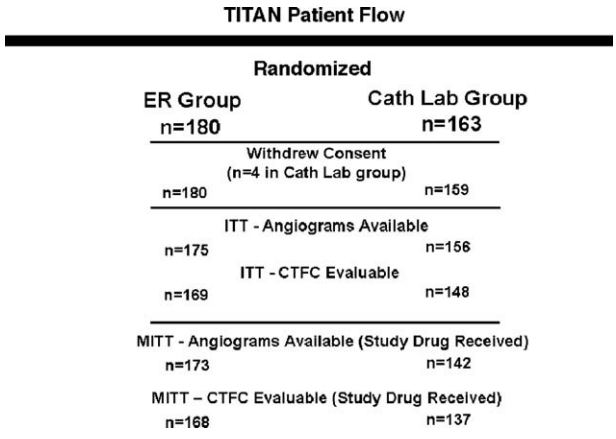
Figure 1



TITAN-TIMI 34 study design.

Figure 2



TITAN-TIMI 34 patient flow.

Table I. Demographic baseline characteristics, ED versus CCL administration of eptifibatide

	ED, n = 174	Catheterization laboratory, n = 142	P
Demographics			
Age (y)	59.1±13.1	60.1 ± 12.6	NS
Male	74.7	73.2	NS
Weight (kg)	85.8±19.2	87.0±17.9	NS
Time from symptoms to randomization			
Median, 25, 75 (h)	2.2 (1.4, 3.8)	2.4 (1.5, 3.8)	NS
Medical history			
Preinfarction unstable angina in preceding week	29.9	32.4	NS
Prior congestive heart failure	2.3	3.5	NS
Prior MI	14.9	10.6	NS
Prior angina	25.3	20.4	NS
Prior PCI	16.1	10.6	NS
Hypertension	42.2	40.9	NS
Smoker within the past year	49.4	40.1	NS
Family history of coronary artery disease	39.6	31.6	NS
Hyperlipidemia	32.2	31.2	NS
Diabetes	15.5	18.3	NS
Prior aspirin use	34.5	28.9	NS
Presenting characteristics			
Heart rate (beat/min)	75.3 ± 15.2	75.6 ± 18.1	NS
Systolic blood pressure (mm Hg)	146.6 ± 26.4	145.3 ± 24.9	NS
Diastolic blood pressure (mm Hg)	82.8 ± 17.5	82.4 ± 16.7	NS
Killip class			
Class I	85.2	83.5	NS
Class II	5.9	5.8	NS
Class III	3.6	5.0	NS
Class IV	5.3	5.8	NS
Infarct location			
Anterior	35.2	39.6	NS

improve coronary flow before primary PCI. Adjunctive antiplatelet therapy administered before primary PCI may improve epicardial and tissue perfusion both before and after the PCI, and may reduce PCI complications in the setting of STEMI.[5-18] The purpose of the TITAN-TIMI 34 study was to evaluate the benefit of a strategy of early initiation of eptifibatide in the emergency department (ED) before primary PCI for STEMI, compared with a strategy of delayed eptifibatide initiation in the cardiac catheterization laboratory (CCL).

Methods

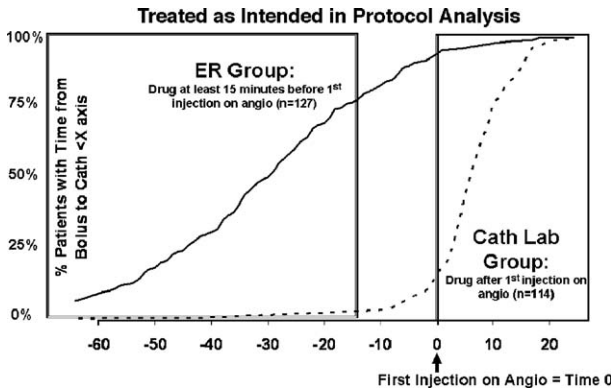
Study protocol

TITAN-TIMI 34 was a phase IV, randomized, open-label multicenter trial used to evaluate the angiographic and clinical efficacy of early initiation of eptifibatide in patients intended to undergo primary PCI for acute ST-segment elevation acute myocardial infarction (MI). Patients were randomized 1:1 in blocks of 10 at each site to receive eptifibatide (180 μg/kg bolus, immediately followed by a continuous infusion of 2.0 μg/kg per minute with a second bolus of 180 μg/kg administered 10 minutes after the first bolus) to be started either immediately in the ED or other triage unit (early ED administration) versus initiation in the CCL after diagnostic catheterization (late CCL administration) (Figures 1 and 2).

Patient population

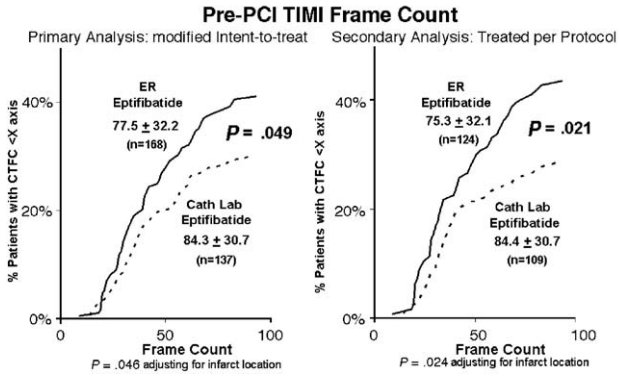
Patients who were 18 years or older were eligible for enrollment if they (1) exhibited symptoms of ischemic chest pain for at least 20 minutes and ≤6 hours suggestive of acute MI; (2) exhibited ST elevation of at least 0.1 mV in 2 contiguous limb leads or ST elevation of at least 0.2 mV in 2 contiguous

Figure 3



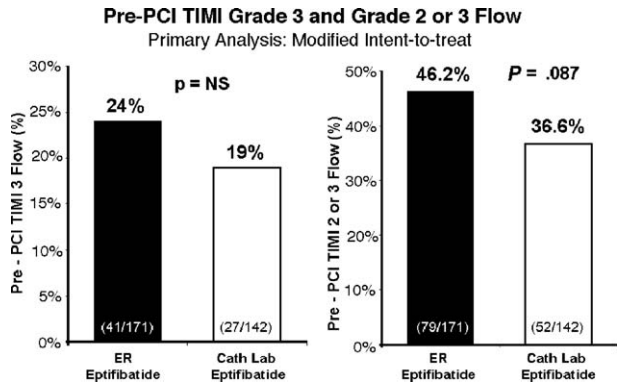
Treatment as intended PP.

Figure 4



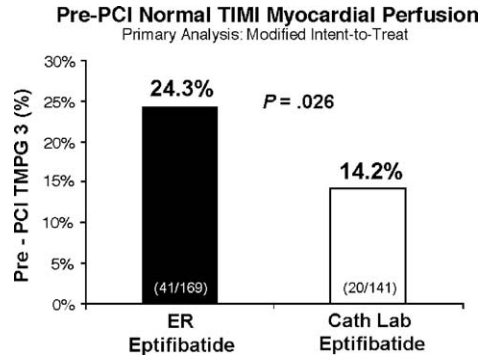
Primary end point: pre-PCI TIMI frame count by treatment group.

Figure 5



Secondary end point: pre-PCI TIMI grade 3 and TIMI grade 2 or 3 flow by treatment group.

Figure 6



Pre-PCI normal TIMI myocardial perfusion by treatment group.

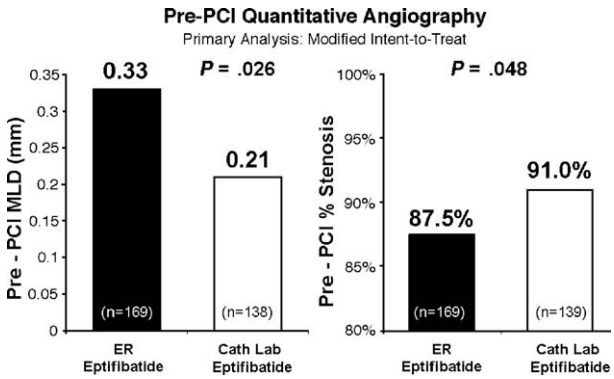
precordial leads; and (3) were scheduled to undergo early PCI within 2 hours of hospital presentation, in which they had not received fibrinolytic therapy.

Exclusion criteria included the following: maximal systolic blood pressure <80 mm Hg after initial fluid and/or pressor resuscitation, uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg) at time of enrollment, ventricular fibrillation or ventricular tachycardia requiring cardioversion, sinus bradycardia (heart rate <50/min), third-degree or advanced second-degree heart block; known pregnancy; new or suspected new left bundle branch block; known thrombocytopenia (platelet count <100 000); known severe renal insufficiency (creatinine >4.0 mg/dL); active or recent gastrointestinal hemorrhage; major surgery less than 1 month prior; known coagulopathy, platelet disorder, thrombocytopenia, or neoplasm; previous hemorrhagic cerebrovascular disorder or active intracranial pathology; and current or recent pharmacotherapy (heparin, warfarin, glycoprotein IIb/IIIa antagonists, antiplatelet agents) or known allergy or contraindication to eptifibatide, aspirin, or heparin.

End point assessment

The primary end point of the trial was the corrected TIMI frame count (CTFC)[19] on diagnostic angiography before primary PCI. The secondary end point was TIMI flow grade (TFG) 3.[20] Other angiographic end points included the pre-PCI TFG 2 or 3, TIMI myocardial perfusion grade (TMPG) 3,[21] minimum lumen diameter (MLD), percent diameter stenosis on diagnostic angiography, and angiographic perfusion score (APS), which is the sum of the epicardial (TFG) and myocardial perfusion grades (TMPG) before and after PCI. The optimal single-plane projection was selected, which identified the stenosis in its greatest severity with minimal foreshortening or overlapping of branches, and end-diastolic frames were chosen

Figure 7



Pre-PCI quantitative angiography by treatment group.

Table II. Post-PCI angiographic characteristics, ED versus CCL administration of eptifibatide

	ED, n = 158	Catheterization laboratory, n = 137	P
CTFC (frames)—all patients	20 (16, 30)	22 (16, 33.5)	.30
CTFC (frames)—open arteries only	20 (16, 28)	22 (16, 33.5)	.14
TFG 3 (%)	86.7	89.1	NS
TMPG 3 (%)	37.0	36.7	NS
Coronary flow reserve	1.44 ± 0.44	1.35 ± 0.42	.10
MLD (mm)	2.5 ± 0.63	2.3 ± 0.52	.031
Percent stenosis	6.7 ± 18.4	7.8 ± 13.6	NS
Full APS of 10-12 (%)	21.1	12.5	.059

Post-PCI CTFC ÷ postadenosine CTFC.

for quantitative angiographic analysis using a previously described and validated automated edge detection algorithm.[22] All angiographic data were evaluated by an angiographic laboratory blinded to randomization and clinical outcomes. Other end points included percent ST-segment resolution at 90 and 180 minutes after randomization and inhospital and 30-day rates of major cardiovascular events.

Safety end points included bleeding, transfusions, stroke, intracranial hemorrhage (ICH), and thrombocytopenia. Bleeding was assessed using the TIMI criteria.[20,21] Specifically, TIMI major bleeding was defined in the protocol either as intracranial bleeding or if there were clinically overt signs of hemorrhage (including imaging) associated with a drop in hemoglobin of >5 g/dL (or when hemoglobin was not available, an absolute drop in hematocrit of >15%). TIMI minor bleeding was defined in the protocol as any clinically significant overt sign of hemorrhage (including imaging) that was associated with a fall in hemoglobin of 3 to ≤5 g/dL (or when hemoglobin was not available, a fall in hematocrit of 9 to ≤15%). TIMI minimal bleeding was defined as any clinically significant overt sign of hemorrhage (including imaging) that was associated with a fall in hemoglobin <3 g/dL (or when hemoglobin was not available, a fall in hematocrit of <9%).

Statistical analysis

The primary efficacy and safety analysis was conducted on the modified intent-to-treat population, which included patients who were randomized and who received at least some eptifibatide irrespective of amount or whether the eptifibatide was given per protocol (PP). Angiographic efficacy data are also reported in the treated-as-randomized PP population, which included patients who were randomized and were administered eptifibatide in the time frame specified by the randomization. Specifically, the PP analysis included those ED patients who were administered eptifibatide at least 15 minutes before diagnostic angiography, and those CCL patients who were administered drug after the first shot on the diagnostic angiogram.

The primary end point CTFC data were analyzed using a Wilcoxon rank sum test as described previously.[19] Data are presented as the number and percentage for categorical end points and as mean and SD for continuous end points. For categorical variables, analyses were performed using a χ^2 test. All analyses were performed using 2-sided tests at the .05 level of significance. Analysis was performed using Stata version 9.1 (Stata Corporation, College Station, TX).[23] Data entry, data management, and data analysis were performed by the TIMI Data Coordinating Center.

Results

Baseline characteristics

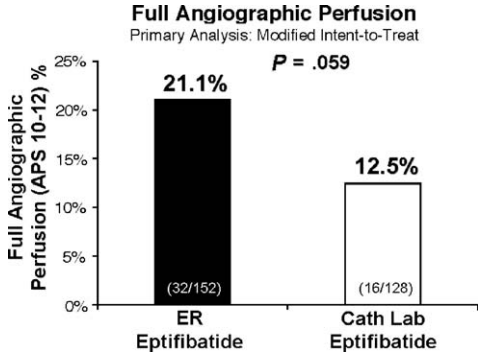
The baseline characteristics of the patients enrolled into the trial were typical of patients with ST-elevation MI. There were no significant differences in baseline characteristics between the 2 arms. However, patients randomized to the ED arm tended to more often have had prior PCI, to have smoked within the past year, and to have a family history of coronary artery disease (Table I).

The median time from bolus to first injection on diagnostic angiogram was 30.5 minutes before the first dye injection in the ED group (n = 164) and 5 minutes after the first dye injection in the CCL group (n = 137) (Figure 3). Study drug was administered at least 15 minutes before first dye injection in 77% of the ED group (127/164) and after first injection in 83% of the CCL group (114/137), and these groups constitute the PP analysis cohort.

Angiographic and electrocardiographic end points

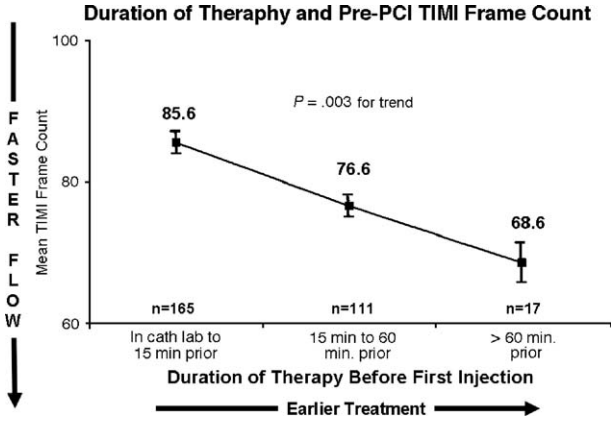
Emergency department administration of eptifibatide was associated with lower (faster) pre-PCI CTFCs, the primary end point of the study (77.5 ± 32.2, n = 168, vs 84.3 ± 30.7, n = 137, P = .049) (Figure 4). Pre-PCI TIMI grade 3 flow was present in 24.0% of the ED group and 19.0% of the CCL group (P = NS), and TIMI grade 2 or 3 flow was present in 46.2% and 36.6%, respectively (P = .087) (Figure 5).

Figure 8



Full angiographic perfusion by treatment group.

Figure 9



Duration of therapy and pre-PCI TIMI frame count in all patients.

Administration of eptifibatide in the ED was associated with a higher rate of normal myocardial perfusion (TMPG 3) pre-PCI (24.3% vs 14.2%, $P = .026$) (Figure 6). In addition, patients in the ED group had a larger MLD (0.33 ± 0.52 mm, n = 169, vs 0.21 ± 0.36 mm, n = 138, $P = .026$) and a smaller percent stenosis pre-PCI (87.5 ± 17.5%, n = 169, vs 91.0 ± 15.1%, n = 139, $P = .048$) before the intervention (Figure 7).

There were no differences between the ED and CCL strategies with respect to post-PCI angiographic outcomes, although a trend was observed for the post-PCI CTFC to be faster in open arteries among those patients treated in the ED (CTFC of 20, n = 138, vs 22, n = 116, $P = .14$) (Table II). A full APS (10 or greater) trended higher in the ED group (21.1% vs 12.5%, $P = .059$) (Figure 8).

Table III. Electrocardiographic characteristics, ED versus CCL administration of eptifibatide

	ED	Catheterization laboratory	P
Resolution from baseline to 90 min	n = 63	n = 50	
Percent resolution	71 (32, 88)	76 (44, 87)	.34
Complete (≥70%) ST resolution (%)	50.8	56.0	.58
Resolution from baseline to 180 min	n = 83	n = 63	
Percent resolution	78 (56, 91)	82 (63, 90)	.33
Complete (≥70%) ST resolution (%)	60.2	66.7	.43

Table IV. Bleeding events (non-CABG related) through discharge or day 5, ED versus CCL administration of eptifibatide.

	ED, n = 174	Catheterization laboratory, n = 142	P
TIMI major bleeds	1.7	3.5	NS
TIMI minor bleeds	5.2	4.2	NS
TIMI minimal bleeds	6.3	4.9	NS
TIMI major or minor bleeds	6.9	7.8	NS
Blood transfusion	9.2	7.0	NS
Thrombocytopenia (platelet count <100 000/mm^3)	2.3	1.4	NS
Stroke	0.6	0	NS
ICH	0	0	–

The results were similar in the PP analysis, with pre-PCI CTFC faster in the ED group (75.3 ± 32.1, n = 124, vs 84.4 ± 30.7, n = 109, $P = .021$) (Figure 4) and higher rates of patency in the ED group (46.8% vs 34.2%, $P = .047$), TMPG 3 (25.8% vs 15.0%, $P = .041$), and full APS (23.9% vs 13.2%, $P = .041$).

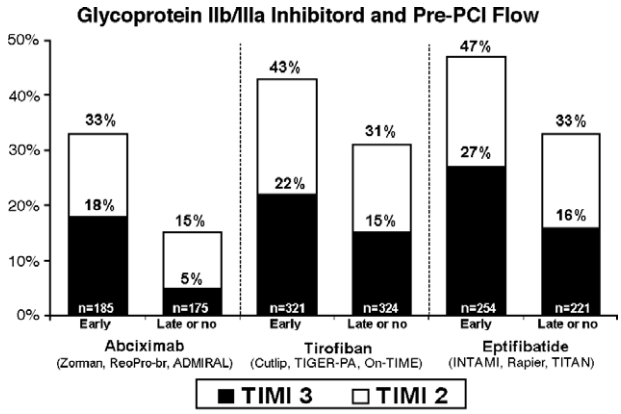
In a pooled analysis, a longer duration of therapy with eptifibatide before angiography was associated with lower (faster) frame counts ($P = .003$ for trend) (Figure 9).

There was no difference between treatment groups in mean percent ST resolution or complete ST resolution from baseline to 90 minutes or from baseline to 180 minutes (Table III).

Clinical events

The incidence of death by 30 days was low and did not differ between the 2 strategies (4.0% in the ED group vs 2.8% in the CCL group, $P = .76$). No cases of reinfarction occurred in either of the 2 treatment arms by discharge or day 5, and each group had 2 reinfarctions by 30 days (1.2% in the ED group and 1.4% in the CCL group, P = NS). Abrupt closure by discharge or

Figure 10



Epicardial flow associated with early versus delayed glycoprotein IIb/IIIa inhibitor administration.

day 5 occurred in 2 patients in the ED group (1.2%) and no patients in the CCL group (0%, P = NS). New or worsening congestive heart failure by discharge or day 5 trended lower in the ED group (2.9% vs 7.1%, P = .082), but did not differ at 30 days (4.6% vs 7.8%, P = .24). Rehospitalization for an acute coronary syndrome by day 30 occurred in 3.7% of the ED group and 0.7% of the CCL group (P = .13). Stroke by 30 days did not differ by treatment group (1.2% in the ED group and 0.7% in the CCL group, P = NS). There were no cases of ICH during the index hospitalization; 1 patient in the ED group had an ICH after discharge (Table IV).

Safety

The rate of non–coronary artery bypass graft (CABG)–related TIMI major bleed did not differ between the ED group and the CCL group (1.7% vs 3.5%, P = NS), nor did the rate of non–CABG-related TIMI minor bleed (5.2% vs 4.2%, P = NS) or the composite of TIMI major or minor bleed (6.9% vs 7.8%, P = NS) (Table IV). Non-CABG transfusion by discharge or day 5 occurred in 9.2% of the patients in the ED group and in 7.0% of the patients in the CCL group (P = NS) (Table IV).

Discussion

This randomized trial demonstrated that a strategy of early initiation of eptifibatide in the ED before primary PCI for STEMI yielded superior pre-PCI TIMI frame counts (epicardial flow) and superior TMPG compared with a strategy of initiating eptifibatide in the CCL, without an increase in bleeding risk. This trial adds to the body of literature demonstrating that early initiation of eptifibatide in the ED improves pre-PCI epicardial flow among patients undergoing primary PCI.[17,18] The improvements in epicardial flow associated with early eptifibatide administration in the present study are also consistent with the epicardial flow data that have been reported previously for both abciximab and tirofiban (Figure 10). In addition to the improvements in epicardial flow, there was also an improvement in myocardial perfusion associated with early eptifibatide administration. Eptifibatide administration has previously been associated with improvements in myocardial perfusion.[24] The ability of eptifibatide to improve parameters of perfusion is consistent with in vitro data demonstrating increasing disaggregation of thrombus with increasing concentrations of eptifibatide.[25]

The improvement in epicardial flow (TIMI frame counts) was time dependent: the earlier the initiation of eptifibatide therapy, the faster the pre-PCI flow (lower CTFCs) (Figure 9). In addition to the potential to improve clinical outcomes, early restoration of flow before primary PCI above and beyond the background rate of spontaneous reperfusion, which was observed in placebo-treated patients, may facilitate the technical performance of the procedure as well. Not only does visualization of the distal artery simplify instrumentation of the artery, but it is also possible (although not tested in the present trial) that pre-PCI visualization of the distal culprit artery may improve the safety of the procedure by defining the lumen and reducing the risk of subintimal wire placement and dissection. Side-branch anatomy can be visualized, which may theoretically assist in formulating the optimal strategy for intervention. Visualization of the distal vessel aids in the assessment of vessel diameter and lesion length and may inform device selection and size. Finally, direct stenting without balloon predilation has been associated with improved myocardial perfusion after the procedure.[26] The ability to visualize side branches and estimate distal vessel diameter and lesion length may theoretically facilitate the performance of direct stenting.[26]

Arterial and venous access were obtained after the onset of drug administration among patients treated with early administration of eptifibatide, and this strategy was not associated with any increased risk of TIMI major or TIMI minor bleeding. The rates of TIMI major bleeding are consistent with those in other primary PCI trials, reported at 7% for PCI in the pooled analysis by Keeley et al.[27]

This mechanistic study was not adequately powered to evaluate the association of early eptifibatide administration with clinical outcomes. Although these angiographic data are consistent with other studies,[5-18] larger studies are needed to determine the true clinical impact of improvements in pre-PCI flow upon clinical outcomes. These clinical studies in turn could further inform the appropriate consideration of an optimal strategy for reperfusion for patients at risk for prolonged

delays in reperfusion, such as those at hospitals without PCI facilities. Although a recent pooled analysis of randomized trials concluded that there was no clinical benefit to treatment with a "facilitated" approach, the subgroup of patients treated with glycoprotein IIb/IIIa inhibitors was not sufficient to assess the primary end point of mortality in the analysis, and the findings of the analysis were largely driven by the use of fibrinolytic therapy to facilitate PCI, rather than the use of glycoprotein IIb/IIIa inhibitors.[27] It is important to note that this pooled analysis did not include data regarding very early treatment from the ADMIRAL study, nor did it include data from the present TITAN study.

Conclusions

A strategy of early initiation of eptifibatide in the ED before primary PCI for ST-segment elevation MI yields superior pre-PCI TIMI frame counts, reflecting epicardial flow, and superior TIMI myocardial perfusion compared with a strategy of initiating eptifibatide in the CCL.

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Appendix A

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