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The Additive Value of Tirofiban Administered With the High-Dose Bolus in the Prevention of Ischemic Complications During High-Risk Coronary Angioplasty

The ADVANCE Trial

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OBJECTIVES We sought to determine the safety and efficacy of high-dose bolus (HDB) tirofiban in high-risk patients undergoing percutaneous coronary intervention (PCI).

BACKGROUND The use of HDB tirofiban in the catheterization laboratory is controversial. In particular, in patients with acute coronary syndromes undergoing PCI, there is no evidence that tirofiban administered in the catheterization laboratory is superior to heparin alone. This finding probably reflects the suboptimal platelet inhibition when tirofiban is employed at RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis) regimen.

METHODS A total of 202 patients (mean age 69 ± 8 years; 137 males [68%]) undergoing high-risk PCI, pretreated with thienopyridines, were consecutively randomized to HDB tirofiban (25 μg/kg/3 min, and infusion of 0.15 μg/kg/min for 24 to 48 h) or placebo immediately before the procedure and then followed for a median time of 185 days (range 45 to 324 days) for the occurrence of the primary composite end point of death, myocardial infarction, target vessel revascularization (TVR), and bailout use of glycoprotein (GP) IIb/IIIa inhibitors.

RESULTS The cumulative incidence of the primary end point was 35% and 20% in placebo and HDB tirofiban groups, respectively (hazard ratio 0.51, 95% confidence interval 0.29 to 0.88; p = 0.01). This difference was mainly due to the reduction of myocardial infarction and bailout use of GP IIb/IIIa inhibitors, with no significant effect on TVR or death. The safety profile did not differ between tirofiban and placebo.

CONCLUSIONS The use of tirofiban, when administered at HDB, is safe and significantly reduces the incidence of ischemic/thrombotic complications during high-risk PCI. (J Am Coll Cardiol 2004;44:14–9) © 2004 by the American College of Cardiology Foundation

Several randomized, controlled trials have assessed the efficacy of the upstream administration of tirofiban (Platelet Receptor Inhibition for ischemic Syndrome Management in Patients Limited to very Unstable Signs and symptoms [PRISM-PLUS] regimen) in patients with non–ST-segment elevation acute coronary syndromes (ACS) (1,2). Accordingly, this has been endorsed as a class I indication in the most recent American and European guidelines (3,4). At the same time, the use of tirofiban as an adjunctive medication in the catheterization laboratory (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis [RESTORE] regimen) for the prevention of ischemic complications during percutaneous coronary intervention (PCI) gave controversial results.

In the RESTORE trial, the use of tirofiban led to a nonsignificant reduction of the primary end point with respect to unfractioned heparin alone (5), and, when directly compared with abciximab in a broad group of patients submitted to both urgent and elective PCI, the use of tirofiban offered less protection from major ischemic events (6). The reasons for these results are currently speculative and possibly due to an inadequate early platelet inhibition of tirofiban at RESTORE regimen in the trials.

Platelet reactivity is pivotal in the pathogenesis of complications after PCI (7), and the degree of platelet inhibition with the use of glycoprotein (GP) IIb/IIIa inhibitors during PCI is critical for the protection from ischemic events (8).

In the randomized comparison of platelet inhibition with abciximab, tirofiban, and eptifibatide during PCI in the ACS (Comparison Of Measurements of Platelet aggregation with Aggrastat, Reopro, and Eptifibatide [COMPARE] trial), platelet aggregation 15 and 30 min after drug infusion was significantly less inhibited with the tirofiban-RESTORE regimen compared with abciximab and eptifi-

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Abbreviations and Acronyms

ACS = acute coronary syndrome
ACT = activated clotting time
CK = creatine kinase
GP = glycoprotein
HDB = high-dose bolus
MI = myocardial infarction
PCI = percutaneous coronary intervention
TVR = target vessel revascularization

batide and, at 30 min, compared with the tirofiban–PRISM-PLUS regimen (9).

Accordingly, the bolus of tirofiban regimen has been revised and increased from 10 to 25 μg/kg (HDB tirofiban) (10). From preliminary uncontrolled findings, this new regimen appears safe (11), but data on its efficacy are still scanty.

To this end, the aim of the current study was to determine whether the administration of HDB tirofiban is superior to unfractioned heparin alone in patients undergoing high-risk PCI.

METHODS

Patients. This was a single-center, double-blind, placebo-controlled, randomized trial comparing HDB tirofiban with placebo in patients undergoing elective or urgent PCI with clinical or angiographic high-risk features. Our local ethics committee on Human Research approved the protocol, and all participants gave their written, informed consent. From March 2002 to August 2003, 202 patients (of 578 screened) were consecutively enrolled on the basis of the following inclusion criteria: 1) the presence of at least one coronary narrowing ≥70% amenable to coronary stenting (except an unprotected left main stenosis or bypass graft) and the presence of diabetes mellitus; or 2) a planned multivessel intervention (stenting of ≥2 lesions of least 70% coronary stenosis in different coronary vessels); or 3) the presence of non–ST-segment elevation ACS. Exclusion criteria were ST-segment elevation myocardial infarction (MI), administration of any GP IIb/IIIa inhibitors during the previous two weeks, serum creatinine ≥2.5 mg/dl (221 μmol/l), ongoing bleeding or bleeding diathesis, previous stroke in the last six months, major surgery within the previous six weeks, and platelet count <100,000 per mm^3.

Randomization. Patients who met the eligibility criteria were randomly assigned (by the use of computer-based 1:1 randomization scheme) to tirofiban or placebo (0.9% NaCl solution) by an independent study nurse. The study drug bolus was given at least 5 min before the lesion could be crossed with the guide wire. Analyses of the data are based on the intention-to-treat principle.

Medications and procedures. As per the protocol, all patients were pretreated with aspirin (160 to 325 mg orally) and thienopyridine (ticlopidine 500 mg as a loading dose and then 250 mg twice daily or clopidogrel 300 mg orally as a loading dose and then 75 mg/day at least 48 or 6 h before the procedures, respectively). Any stent type approved by a regulatory agency could be implanted. Tirofiban was given as a bolus of 25 μg/kg per 3 min, followed by an infusion of 0.15 μg/kg/min for 24 to 48 h. Heparin was adjusted as follows: patients assigned to tirofiban received 50 to 70 U/kg heparin (maximum 7,000 U), with additional boluses to achieve and maintain an activated clotting time (ACT) of at least 200 s. Patients assigned to placebo received an initial bolus of 100 U/kg (maximum 10,000 U), with additional boluses to achieve and maintain an ACT of at least 300 s. The protocol advised to discontinue heparin after the procedure and remove the arterial sheath when the ACT was <180 s, with an arteriotomy closure device or with external compression for hemostasis. Investigators could modify these guidelines at their discretion to meet the medical needs on a patient-by-patient basis. Patients could be discharged after completion of the study drug, but not <48 h after revascularization.

Study end points. The primary end point was a composite of death, nonfatal MI, urgent TVR, and thrombotic bailout GP IIb/IIIa inhibitor therapy within a median follow-up of 180 days after the index procedure. A new MI was defined as the finding of levels of the MB isoform of creatine kinase (CK-MB) that were above at least three times the upper limit of the normal range in at least one blood sample or by the finding of abnormal Q-wave in two or more contiguous leads. Plasma levels of CK, CK-MB, and troponin I were measured in all patients at baseline, 6 and 18 h after the procedure, and when clinically needed. For patients with a recent MI who had an elevated CK-MB level before the procedure, a value of more than three times the upper limit of normal and at least 50% above the last preprocedural levels was required to meet the definition. Urgent vessel revascularization included any coronary artery bypass graft surgery or a second PCI of the original target vessel(s) performed on a nonelective basis for recurrent myocardial ischemia. Similarly, patients who received bailout GP IIb/IIIa inhibitor therapy were adjudicated as an end point if treatment was given to manage a thrombotic complication, defined as the development of a new filling defect or haziness consistent with thrombosis, abrupt closure, or the development of distal/>2 mm side-branch macroembolization (12). Once bailout treatment was underway, study drug infusion or placebo was discontinued and switched to an infusion of open-label abciximab. Bailout GP IIb/IIIa inhibitor use did not result in unblinding of study drug assignment.

Secondary end points included each component of the composite end point, the effects of study drug on troponin I release after the procedure, and the effects of study medication on prespecified subgroups, defined according to the presence or absence of diabetes and ACS as the indication for PCI.

For an analysis of safety, the end points of major and minor bleeding complications were defined according to the

Table 1. Baseline Characteristics of the Patients

Characteristics	Placebo (n = 101)	HDB Tirofiban (n = 101)	p Value
Age (yrs)	68 ± 7	69 ± 9	NS
Male gender (%)	66	69	NS
Weight (kg)	81.4	80.1	NS
Diabetes (%)	45	53	NS
Hypertension (%)	45	50	NS
Smoker (%)	21	19	NS
Creatinine (mg/dl)	1.1 ± 0.3	1.0 ± 0.2	NS
LV ejection fraction (%)	55	53	NS
Medical history (%)			
CABG	4	3	NS
PCI	38	32	NS
Myocardial infarction	45	52	NS
Heart failure	15	19	NS
Cerebrovascular accident	3	5	NS
Indications to PCI (%)			
Acute coronary syndrome	55	56	NS
Stable angina	37	29	NS
Silent ischemia	7	12	NS
Myocardial viability	1	3	NS
Medications (%)			
Clopidogrel/ticlopidine	65/35	62/38	NS
Statin	87	91	NS
ACE inhibitor	65	71	NS
Beta-blocker	76	65	NS

Data are presented as the mean value ± SD or percentage of patients.
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; HDB = high-dose bolus; LV = left ventricular; NS = not significant; PCI = percutaneous coronary intervention.

criteria of the Thrombolysis In Myocardial Infarction (TIMI) trial (13).

Statistical analysis. A total of 199 patients were required for the study to have 80% power to determine whether HDB tirofiban was superior to placebo, given a 30% rate of events at month 6 in the placebo group and an expected 40% reduction in the tirofiban arm with an alpha error of 5%. The one-tailed Peterson and George method (14), along with the formulas of Schoenfeld (15,16), was employed, considering an accrual time of one year and a follow-up time of six months.

Values are expressed as mean ± SD. Comparisons between the two groups were performed with the Student *t* test. The Fisher exact test was used for categorical variables. The time to first occurrence for the composite end point is displayed with Kaplan-Meier survival curves. The log-rank test has been used to compare survival in tirofiban and placebo groups. The Cox proportional hazards model has been used to calculate adjusted hazard ratios based on the time to event. Probability was significant at a level of <0.05. Statistical analysis was performed using Statistica 6.1 Software (Statsoft Inc., Tulsa, Oklahoma).

RESULTS

The baseline characteristics of the patients are provided in Table 1. Among ACS patients, 45 (82%) in the treatment and 41 (76%) in the placebo arm presented with one or more high-risk features (4), with 41 patients (75%) in the HDB tirofiban and 39 (72%) in the placebo group showing troponin I elevation at entry. Other common high-risk features were ST-segment depression >0.5 mm in two or more electrocardiographic leads and the presence of diabetes, which were present in 28 (51%) and 16 (29%) patients in the HDB tirofiban and 33 (61%) and 10 (19%) patients in the placebo group, respectively. In the remaining 93 elective patients, 36 (39%) and 28 (30%) in the treatment group and 35 (38%) and 32 (34%) in the placebo group presented with diabetes or received multivessel intervention, respectively; the prevalences of type B2 and C coronary lesions were 33% and 12% in the treatment and 29% and 13% in the placebo arms, respectively.

Table 2. Procedural Data

Characteristics	Placebo (n = 101)	HDB Tirofiban (n = 101)	p Value
Primary target vessel (%)			
LAD	42	39	NS
RCA	33	34	NS
LCA	25	27	NS
Multivessel intervention (%)	33	29	NS
Bifurcations (%)	22	28	NS
Delivery of at least 1 stent (%)	98	98	NS
>1 Stent implanted (%)	39	33	NS
Reference diameter (mm)	2.6 ± 0.3	2.7 ± 0.4	NS
Heparin dose (U)	9,500	5,400	<0.01
Activated clotting time (s)	310	243	<0.02
Heparin after sheath removal (%)	7	0	<0.05
ACC/AHA lesion type (%)			
A	13	10	NS
B1	32	30	NS
B2	38	41	NS
C	17	19	NS

Data are presented as the percentage of patients or mean value ± SD.
ACC/AHA = American College of Cardiology/American Heart Association; HDB = high-dose bolus; LAD = left anterior descending coronary artery; LCA = left circumflex artery; RCA = right coronary artery.

All patients assigned to HDB tirofiban received the study drug. Tirofiban was infused for a mean (±SD) of 26.2 ± 2.5 h. One patient in the tirofiban group and seven patients in the placebo group underwent 12-h infusion of heparin after the procedure: the main reasons were distal macroembolization, residual vessel dissection, and reduced TIMI flow in a side branch. Procedural data are shown in Table 2.

In both groups, 98% of patients underwent stenting. The mean heparin dose and mean maximum ACT were significantly higher in the placebo group.

Clinical outcome. The incidences of the primary end point after a median follow-up of 185 days (range 45 to 324) were 35% and 20% in the placebo and HDB tirofiban groups, respectively (Fig. 1), resulting in a difference of 42% (hazard ratio 0.51, 95% confidence interval 0.29 to 0.88; $p = 0.01$ by the log-rank test). The difference in the incidence of events between the two groups emerged soon after the procedure (Fig. 1). The absolute difference was mainly the result of the difference in the incidence of MI (10.8% in the placebo

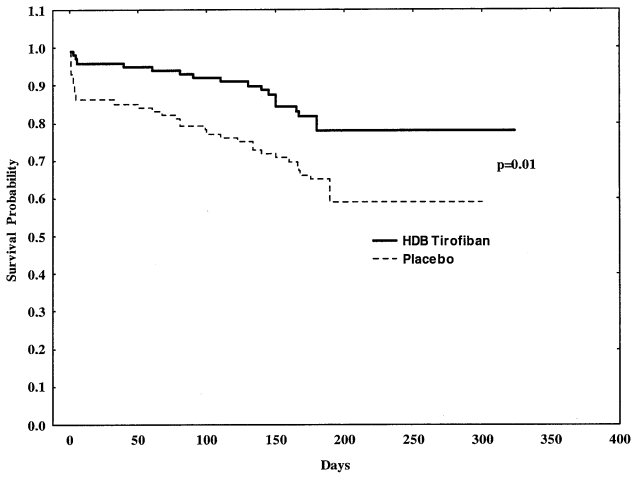

Figure 1. Kaplan-Meier survival analysis: plot of proportion of cumulative survival free from primary end point events in patients treated with high-dose bolus (HDB) tirofiban **(solid line)** and placebo **(dotted line)**. The difference in the incidence of events emerged soon after the procedure. At month 6, the hazard ratio was 0.51 (95% confidence interval 0.29 to 0.88, p = 0.01 by the log-rank test).

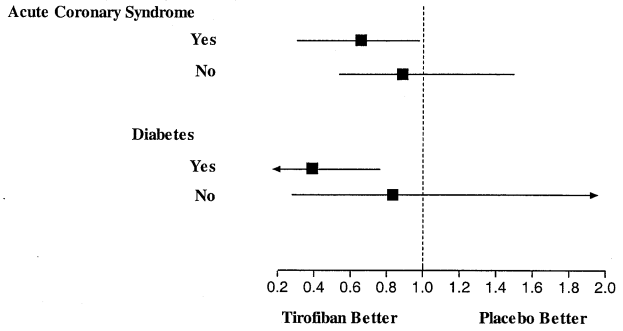

Figure 2. Subgroup analysis. Hazard risk of primary end point according to the presence or absence of acute coronary syndrome as an indication to percutaneous coronary intervention or a history of diabetes. The **horizontal lines** indicate the 95% confidence interval.

group and 3.9% in the tirofiban group, p = 0.052) and of a significant difference in the incidence of MI and bailout GP IIb/IIIa inhibitor administration (14.7% in the placebo group and 3.9% in the tirofiban group, p = 0.02) (Table 3).

Troponin I and CK-MB. At baseline, troponin I and CK-MB levels did not differ between the HDB tirofiban group compared with placebo (0.32 ± 0.2 and 3.3 ± 5.8 ng/ml vs. 0.30 ± 0.22 and 3.8 ± 6.3 ng/ml, respectively), although they peaked significantly higher after PCI in the placebo compared with HDB tirofiban group (5.7 ± 8.3 and 13.2 ± 16.4 ng/ml vs. 1.6 ± 1.1 and 5.3 ± 2.3 ng/ml, p = 0.001 and p < 0.01, respectively). Troponin I levels were significantly higher after PCI in the placebo group also after the exclusion of patients who satisfied the criteria for periprocedural MI (0.05 ± 0.02 vs. 0.07 ± 0.03 ng/ml at baseline and 0.3 ± 0.1 vs. 1.1 ± 2.0 ng/ml, p = 0.001, in the HDB tirofiban and placebo groups, respectively). At entry, patients with troponin I elevation beyond the upper normal limit did not differ between the two groups (as discussed subsequently). After PCI, troponin I was elevated in 55 patients in the HDB tirofiban group versus 83 in the placebo group (p < 0.04). Three patients in the placebo group versus none in the HDB tirofiban group showed major (>5 × normal) CK-MB elevation after PCI.

Subgroup analysis. The hazard risk of the primary end point in patients treated with tirofiban or placebo according to the prespecified subgroups is reported in Figure 2. As shown, a reduction in the incidence of the primary end point was consistent among patients with ACS or diabetes.

Safety data. No major bleedings and no need for red cell transfusion occurred in the study population. Minor bleedings were four in the HDB tirofiban group (two gross hematuria and two groin hematoma) and one in the placebo group (p = 0.19). There was no severe thrombocytopenia. One patient in each group had mild thrombocytopenia.

DISCUSSION

The results of our study show that the administration of HDB tirofiban, when given immediately before PCI procedures, is more effective than heparin alone in the prevention of ischemic complications after high-risk coronary angioplasty. In particular, the comparison of survival curves between placebo and tirofiban groups indicates an early benefit in the latter after PCI that remained almost unchanged at month 6, supporting the hypothesis that it is mainly due to a periprocedural protection. We observed no clear effect when death or TVR were separately analyzed. Rather, there was a borderline reduction in MI incidence and no need for bailout GP IIb/IIIa inhibitor administration to manage thrombotic complications in the tirofiban

Table 3. Clinical Outcome at Six Months

Clinical Events	Placebo (n = 101)	Tirofiban (n = 101)	Hazard Ratio (95% CI)	p Value
Primary end point (%)	35	20	0.51 (0.88–0.29)	0.01
Death/MI/TVR (%)	31	20	0.57 (0.99–0.33)	0.048
Death (%)	1	2	1.7 (19–0.15)	0.6
Myocardial infarction (%)	11	4	0.34 (1.08–0.11)	0.052
Target vessel revascularization (%)	19	14	0.64 (1.28–0.32)	0.29
Bailout GP IIb/IIIa inhibitor use (%)	4	0	0.15 (1.29–0.01)	0.08
MI/bailout GP IIb/IIIa inhibitor (%)	15	4	0.23 (0.75–0.08)	0.01
Death/MI/bailout GP IIb/IIIa inhibitor (%)	16	6	0.34 (0.88–0.13)	0.03

CI = confidence interval; GP = glycoprotein; MI = myocardial infarction; TVR = target vessel revascularization.

arm. On the whole, the use of HDB tirofiban led to a significant reduction of the incidence of both primary end point and major adverse cardiac events (death/TVR/MI). The effect of tirofiban in our study was on top of thienopyridine pretreatment, as, per protocol, all patients included in both arms received clopidogrel or ticlopidine at least 6 and 48 h before PCI, respectively (17,18).

Our study population is not representative of the entire spectrum of patients undergoing PCI in our centre, because we selected patients with clinical (ACS or history of diabetes) or angiographic (multivessel interventions) high-risk features. This explains the high incidence of cardiac events in the placebo group.

In the RESTORE trial, where only patients with ACS were included, the use of tirofiban led to a nonsignificant reduction of the primary end point at 30 days, as compared with heparin alone (5). Similarly, in the Tirofiban And ReoPro Give similar Efficacy outcomes Trial (TARGET), patients with stable coronary syndromes had similar or better outcomes with tirofiban versus abciximab, whereas ACS patients presented a clear opposite response (19). Recently, the Troponin in Planned PTCA/Stent Implantation With or Without Administration of the Glycoprotein IIb/IIIa Receptor Antagonist Tirofiban (TOPSTAR) trial, which included 96 patients submitted to elective PCI, showed a marked benefit of tirofiban compared with heparin alone in terms of major adverse cardiac events and CK/troponin release (20). Because ACS patients display upregulation of platelet IIb/IIIa receptors and higher platelet reactivity, as compared with stable patients, these previous results are in keeping with the hypothesis that ACS patients, who need the strongest antiplatelet activity, are those who are relatively less protected with tirofiban in the RESTORE regimen.

We intentionally included in this trial both elective and urgent PCI in order to assess the differential effect of HDB tirofiban in both groups of patients. Our results indicate that at this revised regimen, tirofiban is apparently more effective in ACS patients than in stable ones, indirectly confirming the validity of the previous hypothesis.

In vitro and ex vivo studies have shown that diabetic patients have increased platelet aggregability (20–23). In particular, diabetes mellitus has been associated with a larger pool of activated circulating platelets (24), a higher density of GP IIb/IIIa receptors per platelet (24), and a greater expression of platelet P-selectin and thrombospondin (25). In the present study, a history of diabetes mellitus was an inclusion criterion among elective patients, so that 45% and 53% of patients in the placebo and tirofiban groups were diabetic, respectively.

Our data show that diabetic patients have a relative higher benefit from HDB tirofiban versus heparin alone, as compared with nondiabetic patients. This observation confirms the previous findings and reinforces the notion that diabetic patients, irrespective of their clinical status, would probably benefit from a tailored drug regimen during PCI (26).

In the current study, the safety profile of HDB tirofiban was remarkable, as no major differences were observed in the treated arm versus placebo. However, this could also reflect the fact that our study was underpowered to detect small differences between groups.

Study limitations. We did not assess the effect of HDB tirofiban on the degree of platelet inhibition, because this was the object of several previous studies (9–11). However, this would have potentially provided additional insights into the relationship between the degree of platelet inhibition and clinical outcome in our trial. Additional studies are needed to better understand the relative role of optimal dosing of the bolus and infusion time on clinical outcome.

Conclusions. Our investigation on the use of HDB tirofiban indicates, for the first time, that the study drug, at the employed regimen, is superior to heparin alone in high-risk patients undergoing PCI. The treatment effect appears to be mainly due to periprocedural protection from ischemic/thrombotic complications, whereas no significant effect was seen on TVR. At present, the effect of study drug on mortality is unclear and out of the scope of our phase II investigation. At the subgroup analysis, the treatment effect appears consistent both in patients presenting with ACS and in those with diabetes. Our current findings, based on a limited and selected sample size, should be viewed as preliminary, thus giving input for further research in this field.

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