Randomised controlled trial evaluating the role of tirofiban in high-risk non-ST elevation acute coronary syndromes: an East Indian perspective

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ABSTRACT

Introduction: Glycoprotein IIb/IIIa inhibitors such as tirofiban inhibit platelet aggregation. We evaluated the immediate and early outcomes in patients with high-risk non-ST elevation acute coronary syndrome (NSTE ACS) who received tirofiban with conventional therapy compared to patients who received only conventional therapy (a combination of aspirin, clopidogrel, low-molecular-weight heparin with or without beta-blockers and angiotensin-converting enzyme inhibitors).

Methods: A total of 165 patients received conventional therapy with a placebo, and 136 patients received conventional therapy with tirofiban after randomisation. The outcomes were measured on Day 7, Day 14, one month and three months after the administration of therapy.

Results: A significant reduction was noted in the occurrence of primary endpoints in patients receiving tirofiban, compared to those who received a placebo at seven days (14 versus 32; p-value is 0.036), 14 days (14 versus 28; p-value is 0.043), one month (19 versus 34; p-value is 0.01) and three months (30 versus 44; p-value is less than 0.001) after administration. There was a significant reduction in the occurrence of fatal myocardial infarction (MI) (1 versus 8; p-value is 0.044) and non-fatal MI at Day 7 (1 versus 8; p-value is 0.044), and refractory ischaemia at the end of one month (14 versus 24; p-value is 0.04) and three months (25 versus 36; p-value is less than 0.01) in patients receiving tirofiban as compared to those receiving a placebo.

Conclusion: It may be concluded that tirofiban has a definite role in improving the outcome of patients with high-risk NSTE ACS.

Keywords: acute coronary syndrome, non-ST elevation myocardial infarction, TIMI score, tirofiban

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INTRODUCTION

The role of anti-platelet drugs in patients with acute coronary syndrome (ACS) arises from the fact that the deposition of a platelet-rich thrombus on an atherosclerotic plaque is a critical step in the pathogenesis of the disease. A combination of aspirin and clopidogrel has been found to be more useful than either drug alone in patients with ACS. However, both aspirin and clopidogrel are relatively weak inhibitors of platelet aggregation. Recently, antagonists to platelet glycoprotein IIb/IIIa (GPIIb/IIIa) have been found to be useful in the treatment of patients with unstable angina (UA) and myocardial infarction (MI). These antagonists are potent inhibitors of platelet aggregation and act by inhibiting GPIIb/IIIa, a platelet surface integrin whose activation and subsequent binding to fibrinogen is the final common step in the formation of platelet aggregates.

Various studies have reported that GPIIb/IIIa receptor antagonist improves outcome in patients with UA/non-ST elevation MI (NSTEMI) with or without any coronary intervention.[1-3] Initial reports have suggested that tirofiban, a novel, specific low-molecular-weight GPIIb/IIIa receptor antagonist, plays a role in improving outcomes in high-risk patients with non-ST-elevation ACS.[4-7]

In developing countries such as India, most patients cannot afford interventional procedures. Hence, GPIIb/IIIa receptor antagonist could be a good option; however, information on its role and outcomes on the Indian population is still lacking. The aim of this study was to assess the immediate and early outcomes in patients with high-risk ACS (UA/NSTEMI) who received tirofiban with conventional therapy compared to those who received only conventional therapy.

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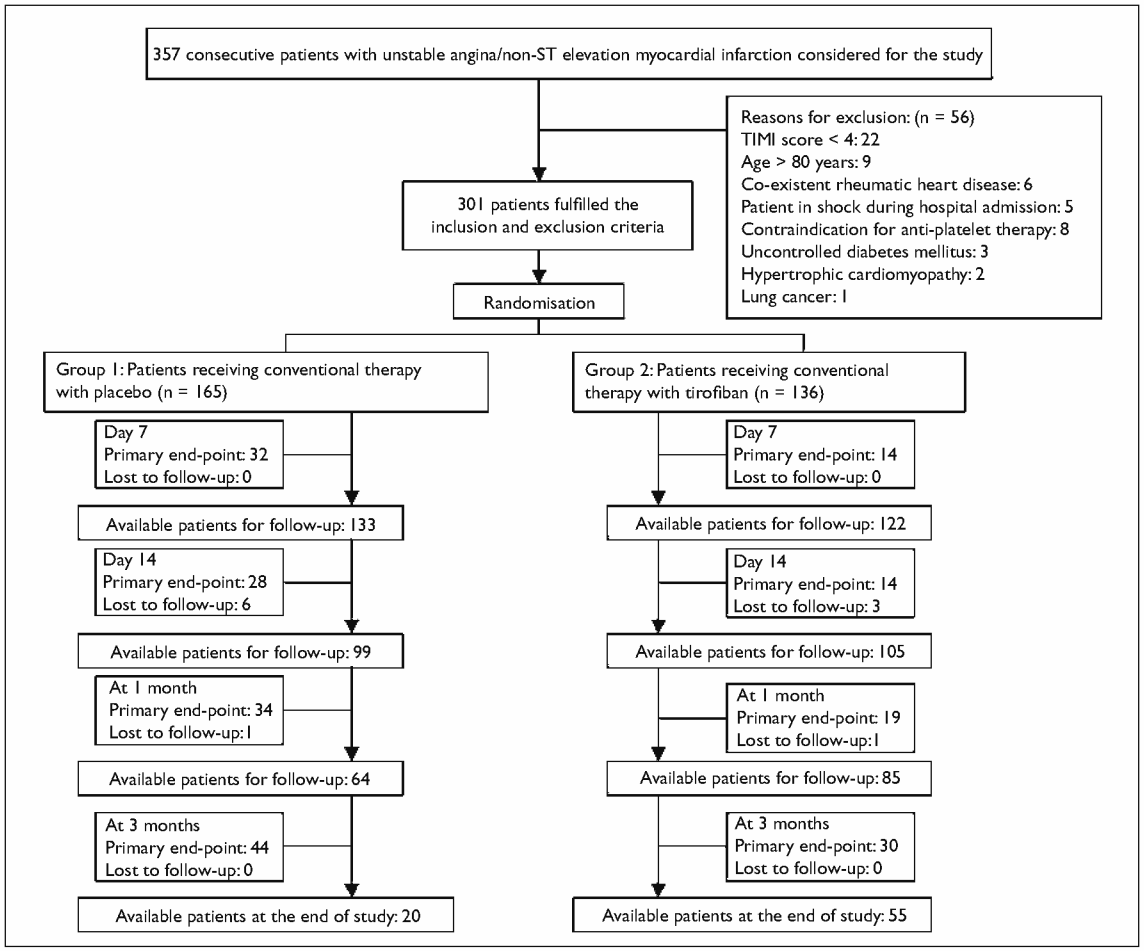

Fig. 1 Flowchart of the study protocol and outcomes.

Conventional therapy was defined as a combination of anti-platelet drugs, aspirin and clopidogrel (aspirin 375 mg stat during admission by chewing 75 mg once daily after food along with clopidogrel 300 mg loading dose, followed by 70 mg daily) with low-molecular-weight heparin (LMWH) (enoxaparin 1 U/kg sc twice daily). The stratification of patients as "high-risk ACS" was done in accordance with their thrombolysis in myocardial infarction (TIMI) score.[8,9]

METHODS

A total of 357 patients who attended the emergency department or outpatient department (OPD) of the Department of Cardiology, Medical College Kolkata and who presented with UA/NSTEMI were initially considered for the study. The study was carried out from June 2007 to May 2009. The patients were examined and evaluated clinically, and subsequently admitted for the duration of the study. The study protocol was approved by the institutional ethics committee.

Initially, only those patients who had angina at rest within the last 48 hours of presentation (classified as Braunwald class 3[10]) and a new ST depression of > 1 mm in at least two electrocardiogram (ECG) leads, or a positive biomarker (cardiac troponin T > 0.04 µg/L or creatine kinase myocardial band (CK-MB) elevation > the upper limit of normal) were considered. The TIMI score of each patient was calculated and the patients were further stratified according to the TIMI criteria. High-risk score was defined as a score ≥ 4. Only patients who had a high-risk TIMI score were subsequently included in the study. Patients were excluded if they were aged > 80 years, had persistent ST segment elevation, were previously treated with tirofiban within the three months of presentation, had percutaneous coronary intervention (PCI) within the last six months, had cardiogenic shock, were contraindicated for the use of anti-platelet drugs such as LMWH, angiotensin-converting enzyme (ACE) inhibitors and beta blockers, or had any valvular congenital heart disease even with a TIMI score ≥ 4. The entire procedure was explained to the patients, and only those patients who gave informed written consent were finally included in the study.

The included patients were randomised into two

Table I. Comparison of the baseline parameters of patients in Group 1 and Group 2.

Parameter	No (%)		p-value
	Group 1 (n = 165)	Group 2 (n = 136)	
Age ± SD	62.73 ± 8.04	62.61 ± 8.33	0.90
Male: female	89:76	74:62	1
Family history of CAD	126 (76%)	95 (70%)	0.23
Past history of MI	45 (27%)	34 (25%)	0.69
Smoker	69 (42%)	52 (38%)	0.55
Hypertension	145 (88%)	113 (83%)	0.25
Diabetes mellitus	69 (42%)	66 (49%)	0.24
Hypercholesterolaemia	61 (37%)	60 (44%)	0.23
Troponin T-positive	73 (44%)	63 (46%)	0.72
ST depression	155 (94%)	130 (95%)	0.14
T inversion	121 (73%)	87 (64%)	0.10
Systolic BP ± SD	149.381 ± 19.597	145.19 ± 20.07	0.07
CPK-MB ± SD (IU/L)	25.47 ± 17.77	27.31 ± 18.35	0.37
Mean TIMI score ± SD	4.39 ± 0.67	4.43 ± 0.70	0.99
Hb ± SD (mg/dl)	12.41 ± 0.92	12.47 ± 1.04	0.60
Platelet ± SD (lakhs/mm^3)	1.96 ± 0.45	1.97 ± 0.46	0.85
Creatinine ± SD (mg/dl)	1.13 ± 0.86	1.17 ± 0.96	0.70
Urea ± SD (mg/dl)	37.66 ± 10.38	37.51 ± 12.47	0.90

NB. p-value < 0.05 was considered statistically significant.
Group 1: Patients receiving conventional therapy with placebo. Group 2: Patients receiving conventional therapy with tirofiban.
CAD: coronary artery disease; SD: standard deviation; BP: blood pressure; CPK-MB: creatine phosphokinase myocardial band; Hb: haemoglobin; TIMI: thrombolysis in myocardial infarction; MI: myocardial infarction

groups by a computer-generated randomised table. Group 1 consisted of patients receiving conventional therapy with a placebo, and Group 2 comprised patients receiving conventional therapy with tirofiban. Tirofiban was initially administered at the rate of 0.4 μg/kg/min for 30 minutes and thereafter, the infusion rate was reduced to 0.1 μg/kg/min. This was continued for the next 47 hours and 30 minutes. The placebo was administered in bottles similar to those of tirofiban and consisted of 0.9% normal saline. The patients, the investigator who administered the drugs and the person who evaluated the patients were blinded to the treatment administered. In addition, patients in both groups received beta blockers, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, statins, nitrates and antidiabetic medications as and when required, as determined by the clinical status of the patient. All patients underwent immediate clinical assessment, investigations like fasting lipid profile, fasting and postprandial blood sugar, complete haemogram with platelet count, and serum urea, creatinine, Na^+ and K^+.

All patients also underwent evaluation for biochemical evidence of myocardial injury by estimating the following: (1) creatine phosphokinase (CPK), as measured by the enzymatic UV kinetic method (Auto analyser XL-600 [ERBA], Transasia, Mannheim, Germany) (Reference range: male 46–171 IU/L, female 34–145 IU/L); (2) CPK (MB), as measured by the immune-inhibition enzymatic UV kinetic method, (Auto analyser XL-600 [ERBA], Transasia, Mannheim, Germany) (Reference range 0–25 IU/L); and (3) cardiac troponin T (cTnT), as measured by electrochemiluminescence immunoassay (Elecsys E170 analyser, Roche Diagnostics Inc, Indianapolis, IN, USA). ECG (Cardiart 108T/MK-VII, BPL Limited, Bangalore, India) was conducted to visualise the ST segment changes and the appearance of a new Q wave at the time of admission and subsequently to examine the change in ST depression. The inverted T wave amplitude was calculated. Echocardiography (Philips SONO 4500, Agilent, Santa Clara, CA, USA) was performed in all patients to evaluate the myocardial contractility and ejection fraction. The subjective complaints of the patients were noted. All patients were specifically evaluated for any evidence of active bleeding before and after the administration of the drugs.

The patients were re-evaluated and all the abovementioned investigations were repeated on Day 7, Day 14, and after one month and three months of randomisation. Patients who were found to be stable after indoor management were discharged with medication and followed up in the cardiology OPD, initially weekly for the first month and thereafter, once every two weeks until three months of follow-up were completed. During this

Table II. Comparison of primary and secondary outcomes of patients in Group 1 vs. Group 2 on follow-up.

Parameter	Day 7			Day 14			1 month			3 months		
	Group 1 (n = 165)	Group 2 (n = 136)	p-value	Group 1 (n = 133)	Group 2 (n = 122)	p-value	Group 1 (n = 99)	Group 2 (n = 105)	p-value	Group 1 (n = 64)	Group 2 (n = 85)	p-value
Primary endpoint												
Fatal MI	8	1	0.04	6	1	0.12	5	2	0.26	2	2	1
Nonfatal MI	8	1	0.04	9	2	0.06	5	3	0.48	5	2	0.14
Refractory ischaemia	13	10	1	12	10	0.82	24	14	0.04	36	25	< 0.01
Death due to unknown causes	3	2	1	1	1	1	-	-	-	1	1	1
Secondary endpoint												
Bleeding	-	-	-	-	-	-	-	-	-	-	-	-
Lost to follow-up	0	0	-	6	3	-	1	1	-	0	0	-

NB. p-value < 0.05 is considered as statistically significant.
Group 1: patients receiving conventional therapy with placebo; Group 2: patients receiving conventional therapy with tirofiban;
MI: myocardial infarction

period, the patients were contacted through telephone for any other relevant information.

The primary endpoint of our study was infarction (fatal and nonfatal), death and refractory ischaemia not amenable to conservative medical therapy (rest angina). Major bleeding was defined as that which created a requirement for at least two units of blood and a fall in haemoglobin > 2 mmol/L. Gastrointestinal or cerebrovascular haemorrhage, or retroperitoneal bleeding was considered as a secondary endpoint. MI was defined as a CK-MB elevation > 6.5% of total CK, whenever CK was > 200 U/L (male) or > 170 U/L (female).

Values were expressed as mean ± standard deviation, or in absolute numbers with percentages. Student's *t*-test was used for comparison of continuous variables and Fisher's exact test, for non-continuous variables. A p-value < 0.05 was considered statistically significant. The primary endpoint for the result analysis was the composite of death from any cause, new instances of MI or refractory ischaemia, and the null hypothesis was that there was no difference in the primary outcome of patients in Group 1 and Group 2. Survival curves were estimated according to the Kaplan-Meier method and compared using the log-rank test. Survival comparisons between groups were performed on an intent-to-treat basis. Statistics were generated by GraphPad InStat Software (GraphPad Software Inc, San Diego, CA, USA) (available at: www.graphpad.com) for Student's *t*-test and Fisher's exact test. XLstat2009 calculator (Addinsoft, New York, NY, USA) (available at: www.xlstat.com) was used for survival analysis.

RESULTS

Out of the 357 patients who were initially considered for the study, 301 patients who fulfilled the inclusion and exclusion criteria and gave informed written consent were finally included in the study. There were 165 patients in Group 1 (patients receiving conventional therapy with a placebo) and 136 patients in Group 2 (patients receiving conventional therapy with tirofiban). The study protocol and outcomes are elaborated in Fig. 1. The baseline clinical and investigational parameters of the patients in the two groups are shown in Table I. All the baseline parameters of the patients in both groups were comparable.

A significantly greater percentage of patients receiving tirofiban showed resolution of ST depression after seven days (70/130, 53.85% vs. 61/155, 39.35%; p = 0.01). A significant reduction in the occurrence of primary endpoints was noted in patients receiving tirofiban (Group 2) compared to those receiving the placebo (Group 1) at the end of seven days (14 vs. 32; p = 0.036, 95% confidence interval [CI] 0.30–0.95), 14 days (14 vs. 28; p = 0.043, 95% CI 0.30–0.99), one month (19 vs. 34; p = 0.01, 95% CI 0.32–0.86) and three months (30 vs. 44; p < 0.001, 95% CI 0.37–0.71) of follow-up. On individually analysing the primary endpoints, a significant reduction was observed in the occurrence of fatal MI among patients receiving tirofiban at the end of seven days (1 vs. 8; p = 0.04, 95% CI 0.02–1.20) of follow-up, as compared to those receiving the placebo. The occurrence of nonfatal MI was also reduced among patients receiving tirofiban at the end of seven days (1 vs. 8; p = 0.04, 95% CI 0.02–1.20) of follow-up. The occurrence of refractory ischaemia was significantly reduced among patients receiving tirofiban at the end of one month (14 vs. 24; p = 0.04, 95% CI 0.30–1.00) and three months (25 vs. 36;

Table III. Risk of an event among Group 1 and Group 2 patients.

Follow-up period	Risk of an event		Absolute risk (%)	Relative risk (%)
	Group 1	Group 2		
Day 7	0.24	0.11	12.6	48
Day 14	0.27	0.13	13.7	48.6
1 month	0.52	0.22	30.3	42
3 months	2.20	0.54	165.5	24.8

NB. An event is defined as an occurrence of fatal/non-fatal myocardial infarction, refractory ischaemia or death.
Group 1: patients receiving conventional therapy with placebo; Group 2: patients receiving conventional therapy with tirofiban

Table IV. Expected vs. actual number of patients facing events among Group 1 and Group 2 patients.

Follow-up period	Group 1		Group 2	
	Expected no. of patients facing events	Observed no. of patients facing events	Expected no. of patients facing events	Observed no. of patients facing events
Day 7	25.21	32	20.78	14
Day 14	21.90	28	20.09	14
1 month	25.84	34	27.41	19
3 months	29.79	44	39.56	30

NB. An event is defined as an occurrence of fatal/non-fatal myocardial infarction, refractory ischaemia or death.
Group 1: patients receiving conventional therapy with placebo; Group 2: patients receiving conventional therapy with tirofiban

$p < 0.01$, 95% CI 0.35–0.77) of follow-up. There was a mild non-significant reduction in platelet count among patients receiving tirofiban at seven days as compared to the baseline (1.97 ± 0.46 vs. 1.87 ± 0.44; $p = 0.075$). However, this did not affect the clinical outcomes. Thrombocytopaenia (platelet count < 80,000) was infrequent and the incidence was almost similar in Group 1 and Group 2 (28/165, 16.97% vs. 32/136, 23.53%; $p = 0.19$, 95% CI 0.88–2.18). Significant bleeding was not observed in any of the patients in Group 1 or Group 2 during the course of the study. The details of the primary and secondary outcomes of follow-up are shown in Table II. A total of seven patients in Group 1 and four patients in Group 2 were lost to follow-up during the course of the study (Table II).

On further analysis, it was observed that the risk of an event among patients receiving tirofiban along with conventional therapy (Group 2) was only 48%, 48.6%, 42% and 24.8% of the risk among patients receiving only conventional therapy (Group 1, with placebo) on Day 7, Day 14, after one month and after three months of follow-up, respectively (Table III). In Group 2, a lower than expected number of patients faced events as compared to Group 1, where a higher than expected number of patients faced events on Day 7, Day 14 and after one and three months of follow-up (Table IV). On calculating the numbers needed to treat, it was observed that on treating eight patients with tirofiban along with conventional therapy, one patient would be protected from facing further events on the seventh day of follow-up. The Kaplan-Meier survival curves in Fig. 2 show a significantly better survival for patients in Group 2 (tirofiban) as compared to those in Group 1 (placebo) ($p = 0.009$; log-rank test).

DISCUSSION

An unstable atherosclerotic plaque with superimposed platelet deposition forms the basis of unstable angina, and such patients are at a significant risk of thrombotic complications, which can further trigger recurrent ischaemia, MI or death. Potent platelet inhibitors such as GPIIb/IIIa receptor antagonists have been shown to prevent thrombotic complications associated with percutaneous revascularisation.[3,4,11-16] Reports have suggested that tirofiban, a tyrosine derivative and a specific, low-molecular-weight GPIIb/IIIa receptor antagonist, plays a role in improving outcomes in high-risk patients with non-ST elevation acute coronary syndrome (NSTE ACS).[6] However, similar data for patients in India is not available.

It has been commonly noted that a majority of patients with ACS in developing countries such as India have a prolonged door to hospital time and/or are unable to afford early invasive therapy. Hence, primary PCI is an option that is not available to a large section of the population. GPIIb/IIIa inhibitors have the potential of being a reasonable alternative and go a long way in improving clinical outcomes and survival among this group of patients. However, randomised controlled

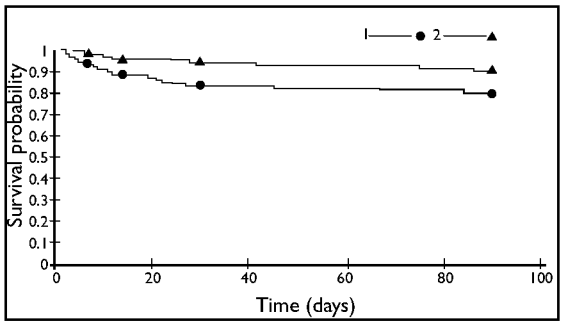

Fig. 2 Kaplan-Meier survival plot of patients in Group 1 and Group 2.

trials evaluating the role of GPIIb/IIIa inhibitor (tirofiban) on the clinical and survival outcomes among patients with NSTE ACS who do not have access to primary PCI are lacking, especially among patients from this part of the country.

In this study, it was observed that tirofiban significantly reduced the occurrence of fatal and non-fatal MI at the end of Day 7 of follow-up. In addition, there was a significant reduction in the occurrence of refractory ischaemia among patients receiving tirofiban at the end of one and three months of follow-up. The incidence of composite primary endpoint (fatal/non-fatal MI, refractory ischaemia or death) was also found to be significantly lower in patients receiving tirofiban at Day 7, Day 14, and after one month and three months of follow-up. The results of our study are comparable to those observed in the PRISM study, in that there was a significantly lower incidence of composite endpoint (death, MI and refractory ischaemia) at 48 hours in patients receiving aspirin with tirofiban in comparison to those receiving aspirin with heparin (3.8% vs. 5.6%; p = 0.01), whereas the incidence was similar in both groups at 30 days (15.9% vs. 17.1%; p = 0.34). However, the mortality in the PRISM study was significantly low (2.3% vs. 3.6%; p = 0.02).[10]

In spite of the initial positive reviews, it was observed in the PRISM-PLUS trial that patients who received tirofiban alone reported higher mortality at Day 7, and hence, the study in this group was discontinued prematurely. However, it was observed that when tirofiban was administered along with heparin, there was a significant reduction in the composite endpoint, compared to the case when only heparin was administered (death, MI and refractory ischaemia) at seven days (12.9% vs. 17.9%; p = 0.004), 30 days (18.5% vs. 22.3%; p = 0.03) and six months (27.7% vs. 32.1%; p = 0.02) of follow-up. Importantly, benefit was observed in both the subgroups of patients who underwent coronary intervention and who were medically treated.[11] In the ELISA-2 trial, which evaluated dual (aspirin and clopidogrel) vs. triple antiplatelet (aspirin, clopidogrel and tirofiban) therapy, patients receiving triple therapy were found to have a significantly improved blood flow in the affected coronary arteries. According to the follow-up conducted at 30 days, MI was reported to have occurred in only 40% of patients in the triple antiplatelet group as compared to 57% in the dual antiplatelet group (p = 0.052), which clearly indicates that an improvement in blood flow resulted in the reduction of MI incidence.[12]

In our study, patients in Group 2 received tirofiban in combination with LMWH (enoxaparin), aspirin and clopidogrel, while patients in Group 1 received LMWH, aspirin and clopidogrel. One of the concerns raised regarding the use of potent GPIIb/IIIa inhibitors is the increased risk of bleeding complications. In the PRISM study, major bleeding occurred in 0.4% of the patients in both groups, and reversible thrombocytopaenia occurred more frequently with tirofiban than with heparin (1.1% vs. 0.4%; p = 0.04).[10] Similarly, in the PRISM-PLUS study, major bleeding episodes were reported in 3% of the patients who received heparin alone and in 4% of the patients who received a combination therapy (p = 0.34), and there was infrequent reversible thrombocytopaenia.[11] In the ELISA-2 trial, there was no significant difference in the bleeding incidence between the two groups; however, in patients who were treated with coronary artery bypass grafting, a slightly higher incidence of bleeding was observed in patients treated with triple antiplatelet therapy as compared to that in patients treated with dual antiplatelet therapy (14/28 vs. 10/24).[12] In our study, a mild reduction in platelet count was observed among patients receiving tirofiban. However, this reduction did not affect the clinical outcome. Tirofiban was well tolerated, and no major bleeding episodes were reported among patients who received tirofiban throughout the study.

In the PRISM-PLUS study, an increased risk for death, MI or recurrent ischaemia at Day 14 was observed among patients who were stratified as high-risk using the TIMI score. Patients with a score > 4 had a greater relative risk reduction with tirofiban (p = 0.025).[8] Our study highlights the role of TIMI score in the risk assessment of patients with ACS at the time of admission, as a simple tool to stratify patients of UA/NSTMI in high, low and intermediate risk groups. The most important observation in our study was the significantly improved survival rates among patients who received tirofiban along with conventional therapy (Fig. 2), which suggests that the improvement

in clinical outcomes actually translated into survival benefit.

In conclusion, tirofiban has a definite role in improving outcomes in patients with high-risk NSTE ACS and provides a reasonable alternative to patients who cannot afford invasive therapy. Although most of the observations in this study are not new, its importance lies in the fact that this is the first set of data from patients in the Indian subcontinent, especially the eastern region of India, and it reinforces the observations already made in other multicentric trials.

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