Safety and Efficacy of Peri-Angioplasty Tirofiban in Patients with ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: Experience in a Single Medical Center

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Abstract

Background: Data on peri-angioplasty glycoprotein IIb/IIIa inhibitor use, especially tirofiban, in ST-elevation myocardial infarction (STEMI) are lacking.

Methods and Results: A prospective database of 1659 consecutive cases undergoing primary percutaneous coronary intervention for STEMI, including 1006 with- and 653 without tirofiban, was retrospectively analyzed. Mortality and TIMI bleeding events were registered during the hospital course and 3 month follow-up. Patients receiving tirofiban were slightly younger (56 ± 8 years vs. control 59 ± 12 years, p=0.047), more predominantly male (90.2% vs. 84.7%, p=0.001), with higher body mass index (BMI) (25.4 ± 2.8 vs. 24.6 ± 3.2, p=0.035) and a lower proportion of Killip class IV (11.5% vs. 23.5%, p=0.021). The TIMI major bleeding rate and peak serum creatine kinase-MB (CKMB) level were similar in both groups. Peri-angioplasty use of tirofiban was associated with lower 30-day all-cause mortality (4.1% vs. 6.6%, p=0.023), especially in the Killip class IV group (11.5% vs 23.5%, p=0.021). There was more diabetes, more renal insufficiency, more extracorporeal membrane oxygenation (ECMO) use in Killip IV patients, and tirofiban use was an independent beneficial prognostic factor of 30-day all-cause mortality (hazard ratio: 0.73, 95% CI: 0.059-0.824; P = 0.039) in Killip class IV patients.

Conclusions: The bleeding events were similar. Survival benefit from peri-angioplasty tirofiban therapy for STEMI was not statistically higher in low Killip classes, but notably so in Killip class IV patients.

Keywords: Tirofiban; glycoprotein IIb/IIIa inhibitor; ST-segment elevation myocardial infarction; percutaneous coronary intervention; Killip class

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Introduction

Patients with acute ST- elevation myocardial infarction (STEMI) have been shown to benefit from timely primary percutaneous coronary intervention (PCI), which is highly recommended under current guidelines_ENREF_1.[1-3] Besides intervention, adequate anti-platelet agent use is also a beneficial prognostic factor for mortality in STEMI. Glycoprotein IIb/IIIa inhibitors (GPIs) can inhibit platelet aggregation, enhance microvascular flow, increase reperfusion efficacy and reduce thrombotic events in primary PCI[4-7]_ENREF_3_ENREF_2. Data from previous meta-analyses has shown that adjunctive GPI use in primary PCI for STEMI patients brings a significant reduction in 30-day and long-term mortality, as well as 30-day re-infarction rates[8,9]_ENREF_4. However, since a number of randomized clinical trials failed to show mortality benefit and revealed a higher bleeding risk from GPIs[10-15]_ENREF_9_ENREF_9, peri-angioplasty adjunctive GPI therapy is currently a class IIa recommendation and, under contemporary guidelines for STEMI management, is considered a bailout therapy if there is evidence of no-reflow or a thrombotic complication.[1,2] As a result, much depends on the clinician's judgement and it is crucial to determine which specific populations of STEMI patients would benefit from the use of adjunctive GPIs._ENREF_2

Tirofiban, a small-molecule GPI, has frequently been used as a peri-PCI adjunctive therapy for STEMI in Taiwan. A meta-analysis study showed that tirofiban reduced mortality and the composite of death and myocardial infarction.[9] According to some case series studies, tirofiban may be associated with more peri-procedure bleeding events, but reduce the incidence of MACE during long-term clinical follow-up.[16,17] A further case series study on PCI for STEMI patients showed similar death, myocardial infarction, stroke and bleeding events, but PCI was more complex and the infarcts were larger in tirofiban-treated patients.[18] The objective of this study was to investigate the clinical outcome of tirofiban use in STEMI patients undergoing PCI treatment.

Methods

Study Design and Population

This study was a retrospective analysis of a prospective database of patients diagnosed with STEMI who presented with acute chest pain to the emergency department (ED) within 12 hours from onset, and who received primary PCI. Those referred for emergency bypass surgery were not included in the database. The study was conducted between 2007-2018 at the Far Eastern Memorial Hospital, a tertiary medical center in New Taipei City, an administrative district in northern Taiwan with approximately 4 million residents. Our hospital is a high-volume PCI center, performing PCI in more than 2000 cases per year and primary PCI in more than 150 cases per year. The study protocol was approved by the Institutional Review Board of our hospital, and all the data were retained in the hospital database only for academic research.

The diagnostic criteria of STEMI were either (1) $\geq$ 0.2 mV (anterior myocardial infarction) or 0.1 mV (non-anterior myocardial infarction) ST elevation in 2 contiguous electrocardiographic leads, or (2) left bundle branch block that was new or presumed to be new.

Treatment Protocol

Patients were administered loading doses of oral dual antiplatelet therapy with aspirin (300 mg) and clopidogrel (300 mg) or ticagrelor (180 mg) along with heparin boluses and infusion at the ED. Coronary angiography was carried out mainly via the transfemoral approach. When there was angiographic evidence of a large thrombus burden, and following the interventionist's judgement, tirofiban was administered at the catheterization laboratory at a bolus intracoronary dose of 10 μg/Kg, followed by 24-hour infusion at a rate of 0.15 μg/Kg/min. Patients received

primary PCI with stenting if feasible in the infarct-related artery. Post-angioplasty care was carried out at the cardiovascular care unit in standard fashion according to contemporary guidelines. Therapy with oral beta blockers, statins, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers was initiated during hospitalization. This study was approved by the Research Ethics Committee of Far Eastern Memorial Hospital (IRB number: IRB101091-F).

Primary Endpoint and Data Collection

The primary endpoint was 30-day all-cause mortality. Mortality data were collected by chart review for in-hospital death. Past medical history was collected by interviews during hospitalization and by chart review. Venous blood was drawn at the time of admission for evaluation of hemoglobin levels, creatinine levels, and white blood cell counts. The Killip classification and locations of the infarctions were assessed by the attending cardiologist. Angiographic data were collected from cardiac catheterization reports.

Statistical Analysis

Categorical variables are presented as numbers and percentages, and continuous variables are expressed as medians and interquartile ranges. Hazard ratios (HR) with 95% confidence interval (CI) and log-rank test were determined. Normally distributed continuous variables were analyzed using the t-test; non-normally distributed variables using the Mann-Whitney U test. Categorical variables were compared using the chi-square test, and continuous ones were compared with the Mann-Whitney U test. Mortality rates were compared using Log-Rank test.

Baseline characteristics, laboratory data, angiographic features, and presentation factors were analyzed to identify potential modulators of survival benefits conferred by peri-PCI tirofiban use. The screening and analyzing were performed as follows: (1) Patients were divided into subgroups according to the factor of interest. (2) A multivariate Cox proportional regression model was used to calculate the adjusted hazard ratio for 30-day all-cause mortality associated with tirofiban use in each subgroup. The logistic regression model comprised all known potential outcome predictors or confounders, including age, sex, body mass index (BMI), cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, current or ex-smoker, previous myocardial infarction and known coronary artery disease), laboratory data (hemoglobin level, creatinine level and white blood cell counts obtained at the ED) and other presentation factors (anterior myocardial infarction, number of diseased vessels, door-to-balloon time and the Killip class).

All P-values were 2-tailed, and P-values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS statistical software version 19.0 (IBM Corp., Armonk, New York) and were reviewed and revised by a professional statistical consultant.

Results

Patient Characteristics

A total of 1659 consecutive patients who underwent primary PCI between January 1, 2007, and December 31, 2018, were enrolled in the database. Table 1 shows the baseline characteristics of our study population. Overall, patients were 58 ± 9 years of age. Patients receiving tirofiban were on average 56 ± 8 years old, slightly younger than the control group (59 ± 12 years, p=0.047). 90.2% of the tirofiban patients, and 84.7% of the control patients were male (p=0.001). Cardiovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus, renal insufficiency and underlying coronary artery disease did not differ between the groups. The tirofiban group had fewer smokers (72.2% vs. 76.9%, p=0.039) but higher average body mass index (BMI) (25.4 ± 2.8 vs. 24.6 ± 3.2, p=0.035). About half of the patients presented with anterior myocardial infarction, and notably, 45.5% presented with Killip > 1. The angiographic,

Table 1. Baseline Characteristics and 30-day All-cause Mortality of Patients With or Without Adjunctive Tirofiban

Characteristics	All (n =1659)	Tirofiban (n = 1006)	No Tirofiban (n = 653)	P-value*
Age, years (IQR)	58 (48-67)	56 (47-64)	59 (48-72)	0.047
Male, n (%)	1460 (88.0)	907 (90.2)	553 (84.7)	0.001
Body mass index, Kg/m^2 (IQR)	25.3 (22.8-28.1)	25.4 (23.2-28.3)	24.6 (22.6-27.8)	0.035
Diabetes mellitus, n (%)	445 (26.8)	254 (25.2)	191 (29.2)	0.103
Hypertension, n (%)	1093 (65.9)	691 (64.8)	402 (61.6)	0.228
Dyslipidemia, n (%)	731 (44.1)	434 (43.1)	297 (45.5)	0.132
Previous myocardial infarction, n (%)	87 (5.2)	44 (4.4)	43 (6.6)	0.137
Known coronary artery disease, n (%)	245 (14.8)	147(14.6)	98 (15.0)	0.952
Current or ex-smoker, n (%)	1228 (74.0)	726 (72.2)	502 (76.9)	0.039
Creatinine, mg/dL (IQR)	0.92 (0.75-1.23)	0.93 (0.75-1.18)	0.91(0.77-1.21)	0.832
Hemoglobin, g/dL (IQR)	14.7 (13.4-16.2)	14.6 (13.5-16.3)	14.7 (13.3-15.9)	0.748
White blood cell counts, /μL (IQR)	10860 (8895-14870)	10920 (9060-15120)	10790 (8740-14640)	0.380
Anterior myocardial infarction, n (%)	850 (51.2)	517 (51.4)	333 (51.0)	0.751
Killip class, n (%)				0.261
I	904 (54.5)	569 (56.6)	335 (51.3)	
II	470 (28.3)	278 (27.6)	192 (29.4)	
III	78 (2.9)	37 (3.7)	41 (6.3)	
IV	207 (12.5)	122 (12.1)	85 (13.0)	
Peak creatine kinase-MB, U/L (IQR)	288 (104-394)	272 (108-386)	294 (92-403)	0.584
TIMI major bleeding, n (%)	30 (1.8)	17 (1.7)	13 (2.0)	0.129
30-day all-cause death, n (%)	84 (5.1)	41 (4.1)	43 (6.6)	0.023
Killip Class I, n (%)	12 (1.3)	7 (1.2)	5 (1.5)	0.740
Killip Class II~III, n (%)	38 (6.9)	20 (6.3)	16 (7.7)	0.532
Killip Class IV, n (%)	34 (16.4)	14 (11.5)	20 (23.5)	0.021
Number of diseased vessels, n (%)				0.217
1	533 (32.1)	315 (31.3)	218 (33.4)	
2	496 (29.9)	321 (31.9)	175 (26.8)	
3	630 (38.0)	370 (36.8)	260 (39.8)	
Door-to-balloon time, minutes (IQR)	70 (46-138)	66 (48-93)	76 (54-133)	< 0.001

* P for tirofiban and no tirofiban group. IQR: interquartile range.

procedural, and pharmacological characteristics of the patients are described in Table 2. Around 70% of the patients had multi-vessel disease, and 61% had received peri-PCI tirofiban. The stenting rate and the stent type did not differ. There was a smaller proportion of Killip class IV (11.5% vs. 23.5%, p=0.021) patients and shorter door-to-balloon time (66 ± 19 mins vs. 76 ± 34 mins, p<0.001) in the tirofiban group. All patients were prescribed dual anti-platelet therapy during hospitalization and co-medications did not differ between the groups. There was no difference in peak serum CKMB or TIMI major bleeding rate (1.7% vs. 2.0%, p=0.129). For the primary endpoint of 30 days all-cause mortality, the tirofiban group showed better results with 4.1%, vs. 6.6% in the control group (p=0.023). Since the Killip class is the major impacting factor for mortality, we further stratified the patients by Killip class. Tirofiban use was associated with reduced 30 days all-cause mortality in the Killip class IV group (11.5% vs 23.5%, p=0.021), but had no statistical impact in the Killip class I~III groups. Baseline, angiographic and procedural characteristics of patients stratified by Killip class categories and characteristics are shown in Table 3. There was more diabetes, more renal insufficiency, and more ECMO use in Killip class

Table 2. Angiographic, Procedural, and Pharmacological Characteristics With or Without Adjunctive Tirofiban

Characteristics	All (n = 1659)	Tirofiban (n = 1006)	No Tirofiban (n = 653)	P-value*
Number of diseased vessels, n (%)				0.217
1	533 (32.1)	315 (31.3)	218 (33.4)	
2	496 (29.9)	321 (31.9)	175 (26.8)	
3	530 (38.0)	370 (36.8)	260 (39.8)	
Door-to-balloon time, minutes (IQR)	70 (46-138)	66 (48-93)	76 (54-133)	< 0.001
Peri-PCI use of tirofiban, n (%)	1006 (60.6)	1006 (100)	0 (0)	
IABP, n (%)	238 (14.3)	164 (16.3)	74 (11.3)	0.37
ECMO, n (%)	56 (3.4)	26 (2.6)	30 (4.3)	0.05
Stent type, n (%)				
Bare metal stents	792 (47.7)	485 (48.2)	307 (47.0)	0.74
Drug-eluting stents	739 (44.5)	439 (43.6)	300 (45.9)	0.69
No stenting	128 (7.7)	82 (8.2)	46 (7.0)	0.56
Medications at discharge, n (%)				
Aspirin	1659 (100)	1006 (100)	653 (100)	1.0
Clopidogrel	1362 (82.1)	865 (86.0)	497 (76.1)	0.35
Ticagrelor	297 (17.9)	141 (14.0)	156 (23.9)	0.07
β-blockers	1379 (83.1)	822 (81.7)	557 (85.3)	0.52
ACE inhibitors or ARBs	1395 (84.1)	828 (82.3)	567 (86.8)	0.57
Statins	1613 (97.2)	975 (96.9)	638 (97.7)	0.84

PCI: percutaneous coronary intervention; IABP: intra-aortic balloon pump; ECMO: extracorporeal membrane oxygenation; ACE: angiotensin-converting enzyme; ARB: aldosterone receptor blocker; IQR: interquartile range.

Table 3. Baseline, Angiographic and Procedural Characteristics of Patients Stratified by Categories of Killip Class

Characteristics	Category 1 (Killip I) (n = 904)	Category 2 (Killip II & III) (n = 548)	Category 3 (Killip IV) (n = 207)	P-value
Age, years (IQR)	55 (48-64)	59 (51-69)	57 (51-66)	0.136
Male, n (%)	794 (87.8)	482 (88.0)	184 (88.9)	0.952
Body mass index, Kg/m^2 (IQR)	25.7 (22.9-27.5)	25.3 (22.7-28.2)	26.1 (22.5-27.6)	0.429
Diabetes mellitus, n (%)	208 (23.0)	152 (27.7)	85 (41.1)	0.001
Hypertension, n (%)	575 (63.6)	382 (69.7)	136 (65.6)	0.054
Dyslipidemia, n (%)	379 (41.2)	260 (47.4)	92 (44.4)	0.132
Previous myocardial infarction, n (%)	45 (5.0)	30 (5.5)	12 (5.8)	0.096
Known coronary artery disease, n (%)	137(15.2)	69 (12.6)	39 (18.8)	0.067
Current or ex-smoker, n (%)	669 (74.0)	405 (73.9)	154 (74.4)	0.585
Creatinine, mg/dL (IQR)	0.89 (0.74-1.09)	0.94 (0.80-1.20)	1.15 (0.88-1.52)	< 0.001
Hemoglobin, g/dL (IQR)	15.4 (14.1-16.1)	14.8 (13.1-15.9)	14.9 (12.5-15.9)	0.382
White blood cell counts, /μL (IQR)	10680 (8780-14830)	10768 (8890-14670)	12430 (9760-16500)	0.042
Anterior myocardial infarction, n (%)	458 (50.7)	266 (48.5)	126 (60.9)	0.031
Peak creatine kinase-MB, U/L (IQR)	190 (102-334)	255 (103-435)	382 (180-875)	< 0.001
TIMI major bleeding, n (%)	16 (1.8)	9 (1.6)	5 (2.4)	0.043
30-day all-cause death, n (%)	12 (1.3)	38 (6.9)	34 (16.4)	< 0.001
Number of diseased vessels, n (%)				0.045
1	294 (32.5)	192 (35.0)	47 (22.7)	
2	282 (31.2)	145 (26.5)	69 (33.3)	
3	328 (36.3)	211 (38.5)	91 (44.0)	
Door-to-balloon time, minutes (IQR)	68 (53-96)	75 (56-117)	85 (65-125)	< 0.001
Peri-PCI use of tirofiban, n (%)	569 (62.9)	315 (57.5)	122 (58.9)	0.067

IQR: interquartile range.

IV patients. From the multi-variant regression analysis, tirofiban can be seen as an independent beneficial prognostic factor for 30-day all-cause mortality (hazard ratio: 0.73, 95% CI: 0.059-0.824; P = 0.039) in Killip class IV patients.

Discussion

In this retrospective analysis from a single medical center, we show that for patients with STEMI undergoing primary PCI, peri-angioplasty adjunctive use of tirofiban carried a survival benefit in 30-day mortality, primarily in Killip class IV patients. The TIMI major bleeding rate and peak serum CKMB levels were similar in both groups, suggesting that, in our study, tirofiban therapy had similar safety and therapeutic effects in reducing myocardium damage. Several randomized placebo-controlled trials have demonstrated that GPIs conferred

significant clinical benefits with regard to myocardial perfusion and protection from distal embolization for STEMI, but may be associated with a higher bleeding rate.[16,17] Another case series study involving PCI for STEMI patients in Germany showed similar MACE and bleeding events but PCI was more complex and the infarcts were larger in tirofiban treated patients.[18] Despite the clinical benefits found in these observational studies, several large-scale randomized trials, including CADILLAC[10], BRAVE-3[11], On-TIME 2[12]_ENREF_10, and ASSIST[13] failed to show significant mortality benefits in patients receiving GPIs, as shown by meta-analyses studies[8,9]_ ENREF_5. This discrepancy could be explained by the low-risk profiles of the patients in these randomized trials (30-day mortality < 3%, small proportion of Killip > I, and lack of patients with Killip IV); also, the mortality benefits of GPIs became significant in meta-analyses when these trials were pooled with other observational studies which did not have stringent criteria for patient selection. A cohort study conducted by P. Ortolani et al., also derived from real-world practice,[19] reported that mortality reduction associated with early administration of GPIs at the ED appeared magnified in patients with TIMI risk index > 25 or Killip > I, when compared to late administration at the catheterization laboratory. Several meta-regression analyses have demonstrated that the benefits from GPIs correlated with the risk profiles of study patients, and have suggested using validated risk scores to identify those who would most likely benefit from adjunctive GPIs.[14,15] Currently, the STEMI guidelines suggest peri-angioplasty adjunctive GPI as a bailout therapy if there is evidence of no-reflow or a thrombotic complication. Much therefore depends on the clinician's judgement during the procedure, and there is a lack of evidence regarding which specific STEMI populations could benefit from adjunctive GPIs. Our data shows that for high-risk Killip class IV STEMI patients, tirofiban use has survival benefit and may be considered for use. Previously, we developed a novel Killip-BMI score (KBS = 2.5 × Killip category - | BMI - 24 |) to select the most-benefitting populations. A KBS ≥ 2 was associated with significant mortality benefit, whereas a KBS < 0 predicted increased 30-day mortality without tirofiban use.[20] This score may be used to guide peri-angioplasty use of adjunctive tirofiban in patients with STEMI undergoing primary angioplasty.

Our database provided real-world, long-term data on peri-PCI adjunctive use of tirofiban for STEMI patients undergoing primary angioplasty. The study population comprised 46% who were Killip > I, 12.5% who were Killip IV, 14.3% who had received IABP, and 3.4% with ECMO support, indicating the non-selective nature of the study and the real-world risk profiles of our study population. The use of tirofiban depends on the physician's clinical judgement, and the data showed that the tirofiban group had shorter door to balloon time and fewer ECMO patients. The clinician may consider the bleeding risk from tirofiban in an ECMO setting and choose not to use it if the clinical condition is too critical. Our data showed ECMO had a non-statistically significant trend of survival benefit in Killip class IV STEMI patients. After adjusting for these factors, tirofiban still showed benefits in 30-day survival. We still had Killip class IV cases completing PCI procedure with tirofiban use under ECMO support. Given the bleeding risk, there was less concomitant ticagrelor use than clopidogrel in the tirofiban group. Selection bias with regard to different anti-platelet agents may have been present but finally the bleeding rates were similar in our data. No significantly increased bleeding rate was noted while tirofiban was used in combination with ticagrelor.

Another issue regards thrombus aspiration therapy during primary PCI for STEMI. Since most tirofiban use is as a result of large thrombus or no-reflow phenomenon during PCI, it is usually used in combination with thrombosuction or thrombectomy. In the ITTI study,[21] a 2*2 trial examined the effect of thrombus aspiration with or without tirofiban during primary PCI for STEMI.

Tirofiban may augment thrombus aspiration therapy in myocardial reperfusion, giving a better myocardial blush grade in primary PCI, but it has a similar 6-month MACE rate, including mortality. While thrombus aspiration could be a factor impacting the outcome in our study, the number of thrombus aspirations is not available in our database, and we cannot tell the impact of thrombus aspiration in this study.

Our study has several limitations that have to be acknowledged. First, due to insufficient patient numbers, our study might be underpowered to detect some potentially significant modulators. Second, since our study was restricted to patients with acute STEMI undergoing primary PCI, it is unknown if these findings can be applied to guide the early administration of GPIs for patients with non-ST-elevation acute coronary syndrome or those referred for bypass surgery. Further studies are needed to elucidate this. Third, our database did not register TIMI minor or minimal bleeding complications. However, peri-PCI adjunctive use of tirofiban did not lead to a significant increase in TIMI major bleeding in our registry. Fourth, the tirofiban regimen in this study involved a bolus dose of 10 μg/Kg, and any modulating effects with the high-dose regimen (bolus of 25 μg/Kg) remain unknown. Fifth, it is not clear whether the modulators of tirofiban are the same as those of other GPIs, and this needs further investigation.

Conclusions

In this retrospective analysis study from a single medical center, we showed that for patients with STEMI undergoing primary PCI, peri-angioplasty adjunctive use of tirofiban had a survival benefit in 30-day mortality, primarily in Killip class IV patients. The safety profile was maintained since TIMI major bleeding did not increase. The use of tirofiban could be considered for high risk STEMI patients during PCI.

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Conflict of Interest

All the authors have no potential conflicts of interest to disclose. They have no relationships with industry.

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