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Safety and efficacy of Tirofiban in STEMI-patients

Lisa Dannenberg [a,b,1,2], Georg Wolff [a,b,1,2], David Naguib [a,b,1], Martin Pöhl [a,b,1], Saif Zako [a,b,1], Carolin Helten [a,b,1], Philipp Mourikis [a,b,1], Bodo Levkau [d,1], Thomas Hohlfeld [c,1], Tobias Zeus [a,b,1], Malte Kelm [a,b,1], Volker Schulze [a,b,1,2], Amin Polzin [a,b,*,1,2]

[a] Department of Cardiology, Pulmonology, and Vascular Medicine, Medical Faculty of the Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[b] Cardiovascular Research Institute Düsseldorf (CARID), Düsseldorf, Germany
[c] Institute for Pharmacology and Clinical Pharmacology, Heinrich Heine University, Dusseldorf, Germany
[d] Institute of Pathophysiology, West German Heart and Vascular Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

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ABSTRACT

Background: Tirofiban is recommended as bail out therapy in patients with ST-elevation myocardial infarction (STEMI). However, evidence regarding safety and efficacy of tirofiban is unclear. Tirofiban has been shown to improve ST-resolution, to decrease infarct size (IS) and to reduce incidence of major adverse cardiac and cerebrovascular events (MACCE). However, bleeding is enhanced in tirofiban treated patients. In this study, we aim to investigate efficacy and safety of Tirofiban in STEMI-patients.
Methods: 610 STEMI patients were analyzed. MACCE (death, myocardial infarction [MI], stroke) and TIMI bleeding events were registered during hospital course and 12 month follow-up.
Results: Tirofiban patients were slightly younger (tirofiban 63 ± 13 years vs. control 65 ± 14 years; $p = 0.04$). They had higher peak-high-sensitive troponin T [Hs-TnT] (tirofiban 6561 ± 11,065 vs. control 4594 ± 11,200, p-value = 0.047) and peak-creatine kinase [CK] (tirofiban 2742 ± 5097 vs. control 1416 ± 2160, p-value < 0.0001). Percutaneous coronary intervention (PCI) was more complex in tirofiban treated patients as radiation time (tirofiban 18 ± 15 vs. control 14 ± 13; p-value = 0.02) and use of contrast agent (tirofiban 240 ± 106 vs. control 209 ± 99; p-value = 0.01) was higher in tirofiban patients. However, there were no differences in MACCE (HR 0.877, 95% CI 0.62–1.25, $p = 0.47$) and bleeding (major: HR 1.494, 95% CI 0.65–3.44, $p = 0.34$; minor: HR 1.294, 95% CI 0.67–2.52, $p = 0.45$).
Conclusion: MACCE and bleeding events were similar. However, PCI was more complex and infarcts larger in tirofiban treated patients.

1. Introduction

Tirofiban is a nonpeptide tyrosine derivate acting as a reversible inhibitor of the glycoprotein (GP) IIb/IIIa receptor [1]. The 2009 European Society of Cardiology (ESC) ST-Elevation myocardial infarction (STEMI)-guidelines advised GP IIb/IIIa inhibitors as comedication next to standard dual antiplatelet therapy [2]. In patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) it has shown to reduce ischemic events [3] and thrombotic complications [4]. Early treatment with tirofiban in STEMI patients resulted in better platelet inhibition and in an improved ST-resolution [5]. Moreover, tirofiban has been shown to reduce infarct size [6] and to improve clinical outcome by lower incidence of major adverse cardiac events (MACE) [7]. However, it has been demonstrated that the reduction of MACE by additional tirofiban treatment was abolished in a sub analysis after 30 days [8]. Furthermore, there is evidence for an increased bleeding risk due to medication with GP IIb/IIIa inhibitors. Tirofiban treatment has shown to be associated with a higher risk for minor bleeding [1] and with a trend to increase major bleeding [9]. Patients undergoing elective PCI did not profit from tirofiban treatment and showed an increase in transfusions and thrombocytopenia compared to patients with acute coronary syndrome [9]. Therefore, since 2012, GP

Abbreviations: AT, Angiotensin; CAD, Coronary artery disease; CI, Confidence interval; ESC, European Society of Cardiology; GP, Glycoprotein; HR, Hazard ratio; Hs-TnT, High-sensitive Troponin T; Lv, Left ventricular; MACE, Major adverse cardiac events; MACCE, Major adverse cardiac and cerebrovascular events; MI, Myocardial infarction; NOACs, Non-vitamin K oral anticoagulants; PCI, Percutaneous coronary intervention; RCA, Right coronary artery; RCX, Ramus circumflexus; RIVA, Ramus interventricularis anterior; S.D., Standard deviation; STEMI, ST-elevation myocardial infarction; TIA, Transient ischemic attack; TIMI, Thrombolysis in myocardial infarction.

* Corresponding author at: Moorenstraße 5, 40225 Düsseldorf, Klinik für Kardiologie, Pneumologie und Angiologie, Germany.
E-mail address: amin.polzin@med.uni-duesseldorf.de (A. Polzin).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[2] Both authors contributed equally.

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Table 1
End points and bleeding.

	Tirofiban group ($N = 218$)	Control group ($N = 392$)	HR (95% CI)	p-Value*
Primary end point – no. (%)				
MACCE (composite of death, MI, stroke)	56 (25.7%)	100 (25.5%)	0.877 (0.62–1.25)	0.47
Secondary end point – no. (%)				
Death	26 (11.9%)	61 (15.6%)	0.732 (0.46–1.15)	0.18
MI	24 (11.1%)	36 (9.1%)	0.986 (0.55–1.77)	0.96
Stroke and TIA	4 (1.8%)	11 (2.8%)	0.524 (0.18–1.56)	0.25
TIMI bleeding				
TIMI major bleeding[a]	11 (5%)	14 (3.6%)	1.494 (0.65–3.44)	0.34
TIMI minor bleeding[b]	16 (7.3%)	22 (5.6%)	1.294 (0.67–2.52)	0.45

MACCE = major adverse cardiac and cerebrovascular events, MI = myocardial infarction, TIA = transient ischemic attack, TIMI = thrombolysis in myocardial infarction.
* p-Value calculated using the log-rank (Mantel-Cox) test.
[a] Any intracranial bleeding, fatal bleeding or clinically prominent bleeding with a drop in hemoglobin of ≥5 g/dl.
[b] Any clinically prominent bleeding with a drop in hemoglobin of 3 to <5 g/dl.

IIb/IIIa inhibition is only recommended as bail-out therapy and in cases of high thrombus burden, slow or no-reflow and thrombotic complications [10]. However real-life data regarding safety and efficacy are lacking. Therefore, in this study we aimed to evaluate the clinical efficacy and safety of tirofiban.

2. Methods

2.1. Study design, patient population and follow-up

A single-center analysis of 610 patients presented with STEMI from 2012 till 2015 at the Heinrich-Heine University Hospital Düsseldorf, Germany, was performed. Inclusion

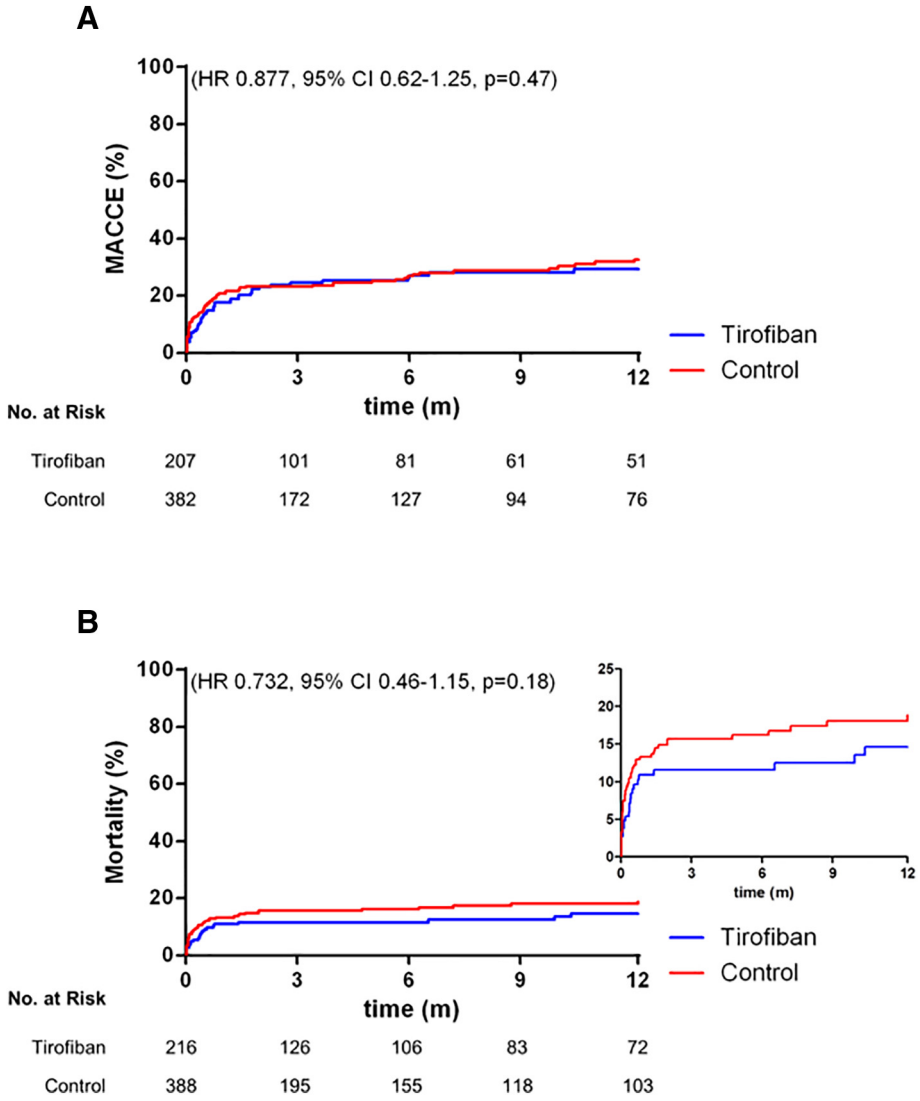

Fig. 1. Kaplan-Meier curves of tirofiban treated vs. control patients. MACCE (A) and mortality (B) did not differ between tirofiban treated and control patients ($n = 610$, log rank test; MACCE: HR = 0.877 [CI 0.62–1.25], $p = 0.47$; Mortality: HR = 0.732 [CI 0.46–1.15], $p = 0.18$).

criterion was presentation with STEMI at our department. No patients were excluded. Reasons for tirofiban administration were high thrombotic burden, coronary slow flow or complex intervention. The individual decision to use tirofiban was according to the clinical evaluation of the interventional cardiologist. 12 months follow-up was conducted at our department during ambulatory care. The study conformed to the Declaration of Helsinki and was approved by the University of Düsseldorf Ethics Committee.

2.2. Study end points

The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE). MACCE was defined as previously described [11]. Components of MACCE and bleeding events (TIMI major/minor) were the secondary end points [11,12]. Both were analyzed during hospitalization and follow-up [13].

2.3. Statistical analysis

Statistical analyses were conducted using IBM SPSS©-Software (New York, USA) and GraphPad-Prism© statistical software (GraphPad software Inc., San Diego). Hazard ratios (HR) with 95% confidence interval (CI) and log-rank test were applied. Normally distributed continues variables were analyzed using the *t*-test; non-normally distributed variables using the Mann-Whitney *U* test. Categorical variables were analyzed using the chi square test or the Fisher's exact test as appropriate. For multivariate analysis, cox regression analysis was conducted. *p*-Values below 0.05 were defined significant.

3. Results

3.1. Study patients - baseline characteristics

Overall, patients were 64 ± 14 years of age. Patients receiving tirofiban were on average 63 ± 13 years old. The control group was slightly older (65 ± 14 years of age). 75.2% of tirofiban and 71.4% of control patients were male gender. Cardiovascular risk factors such as hypertension, smoking and diabetes mellitus did not differ between groups. Renal insufficiency and reduced ejection fraction were similar. Peak-high-sensitive troponin T [Hs-TnT] (6561 ± 11,065 vs. 4594 ± 11,200, *p*-value = 0.047) and peak-creatine kinase [CK] (2742 ± 5097 vs. 1416 ± 2160, *p*-value < 0.0001) were higher in the tirofiban group. Comedication did not differ between groups. (Supplemental 1, 2).

3.2. Procedural details

Procedural details differed between the two groups. In the tirofiban group radiation time (tirofiban 18 ± 15 vs. control 14 ± 13; *p*-value = 0.02) and use of contrast agent (tirofiban 240 ± 106

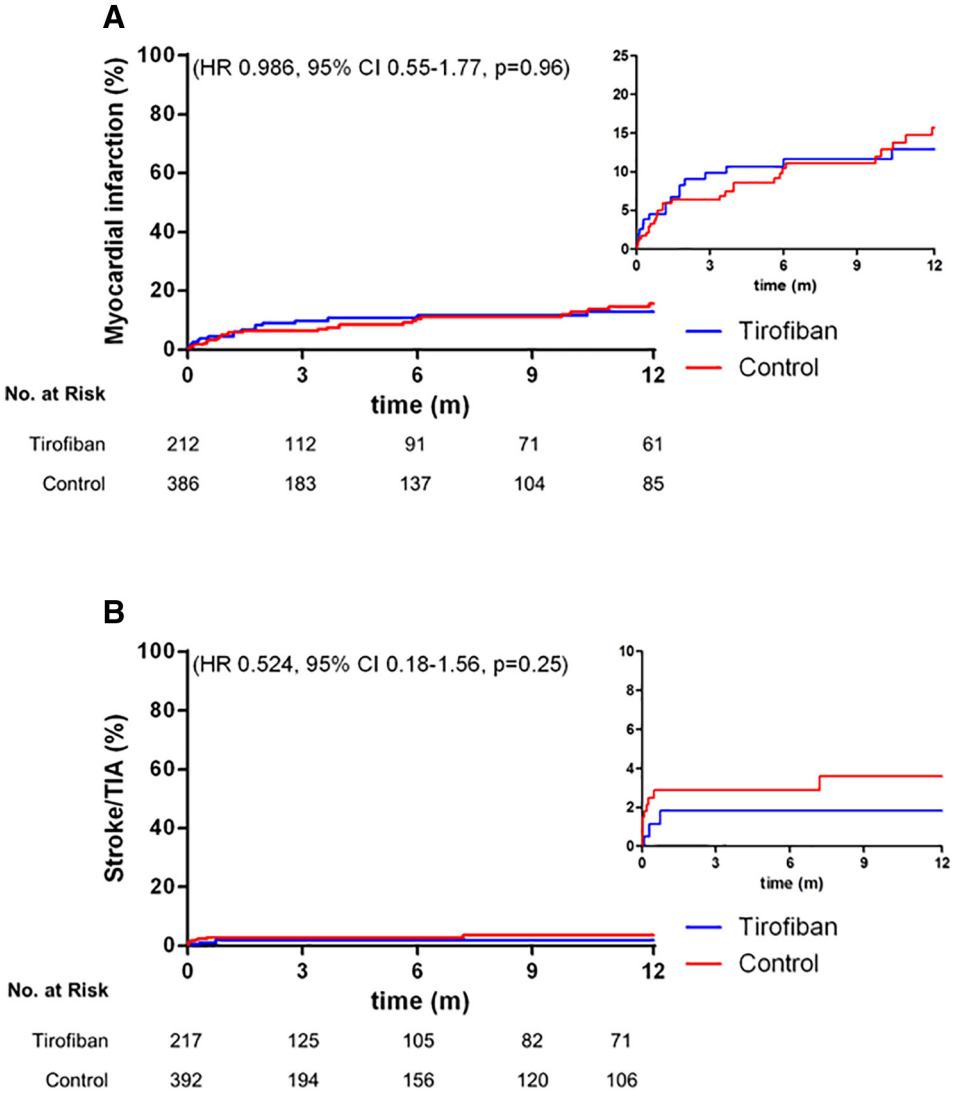

Fig. 2. Kaplan-Meier curves of tirofiban treated vs. control patients. Myocardial infarction (A) and Stroke/TIA (B) did not differ between tirofiban treated and control patients ($n = 610$, log rank test; MI: HR = 0.986 [CI 0.55–1.77], $p = 0.96$; Stroke/TIA: HR = 0.524 [CI 0.18–1.56], $p = 0.25$).

vs. control 209 ± 99; *p*-value = 0.01) were significantly higher. Target vessels did not differ between the two groups (Supplemental 3).

3.3. Tirofiban administration

Tirofiban was less frequently used over study period. In 2012 it was administrated in 40%, in 2013 in 36%, in 2014 in 33% and in 2015 only in 28% of STEMI-patients (Chi^2 for trend: *p*-value = 0.047, Supplemental 4).

3.4. Study end points

MACCE were similar during hospital course and at 1 year follow-up (tirofiban 56 events [25.7%] vs. control 100 events [25.5%]; HR 0.877, 95% CI 0.62–1.25; log-rank *p*-value = 0.47, Table 1, Fig. 1A). Comparing the components of MACCE as secondary endpoint there was no significant difference: death (tirofiban 26 [11.9%] vs. control 61 [15.6%]; HR 0.732, 95% CI 0.46–1.15; log-rank *p*-value = 0.18, Table 1, Fig. 1B), MI (24 tirofiban [11.1%] vs. 36 control [9.1%]; HR 0.986, 95% CI 0.55–1.77; log-rank *p*-value = 0.96, Table 1, Fig. 2A), stroke and transient ischemic attack (TIA) (4 tirofiban [1.8%] vs. 11 control [2.8%]; HR 0.524, 95% CI 0.18–1.56; log-rank *p*-value = 0.25, Table 1, Fig. 2B).

TIMI bleeding did not differ between groups (major: tirofiban 11 [5%] vs. control 14 [3.6%], HR 1.494, 95% CI 0.65–3.44; log-rank *p*-value = 0.34, Table 1, Fig. 3A; minor: tirofiban 16 [7.3%] vs. control 22 [5.6%], HR 1.294, 95% CI 0.67–2.52; log-rank *p*-value = 0.45, Table 1, Fig. 3B).

Multivariate analysis for MACCE and bleeding events was conducted for left ventricular (lv) function, cardiovascular risk factors, procedural details and cardiac enzymes. Lv function, age, male gender and contrast agent volume were shown to be relevant covariates for the occurrence of MACCE (lv function: HR 1.35 CI 1.16–1.58, *p*-value 0.0001; age: HR 1.04 CI 1.01–1.06, *p*-value 0.0005; male gender HR 2.89 CI 1.55–5.39, *p*-value 0.0001; contrast agent volume: HR 1.003 CI 1.001–1.006, *p*-value 0.02, supplemental 5).

4. Discussion

The major findings of this registry analysis were that tirofiban treated patients had enhanced infarct sizes and a more complex PCI. However, neither bleeding events nor MACCE differed between both groups.

Several studies have shown a protective effect of tirofiban in terms of ST-resolution [5], ischemic and thrombotic events [4], infarct size [14] and clinical outcome [5]. However, other studies did not show any differences in clinical outcome after 30 days [8]. Furthermore, infarct size measured by magnetic resonance imaging did not differ between tirofiban and control patients [15]. Additionally, tirofiban has been shown to increase the incidence minor bleeding [1] and a trend to increase the risk of major bleeding [9]. In this analysis, patients with

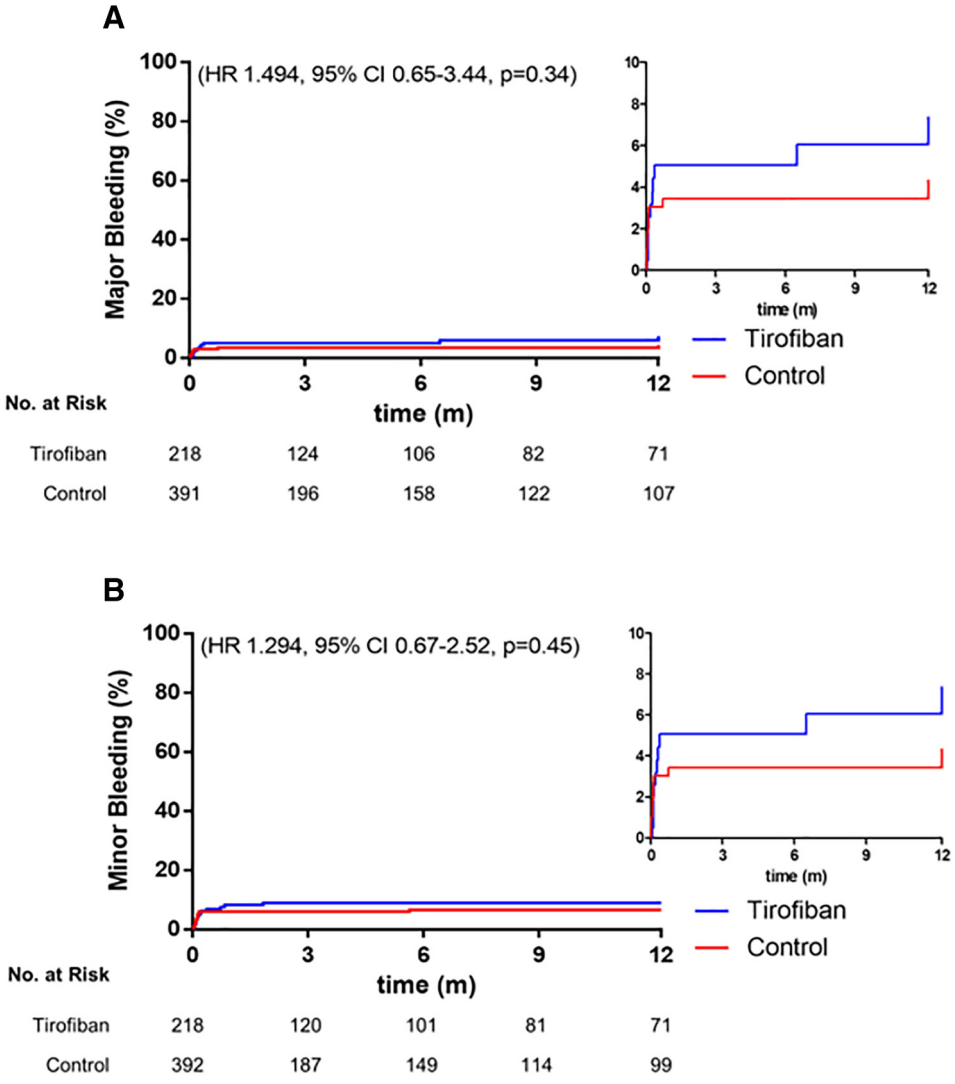

Fig. 3. Kaplan-Meier curves of tirofiban treated vs. control patients. Major (A) and minor bleeding (B) did not differ between tirofiban treated and control patients ($n = 610$, log rank test, Major bleeding: HR = 1.494 [CI 0.65–3.44], $p = 0.34$; Minor bleeding: HR = 1.294 [CI 0.67–2.52], $p = 0.45$).

additional tirofiban treatment did not show significant differences in clinical outcome and bleeding rates. However, it should be mentioned that tirofiban treated patients showed a non-significantly reduced risk of mortality in this study. This needs further investigation and should be reevaluated in large scaled clinical trials.

Recommendations for the use of tirofiban have changed. Since 2012, it is restricted to the use as bail-out therapy [10]. Only in cases of high thrombotic burden, thrombotic complications and slow- or no-reflow the use of GP IIb/IIIa seems to be reasonable [16]. This is reflected in the present analysis. Tirofiban administration decreased during study period in our center.

In the last years prasugrel and ticagrelor were used as first choice for adenosine diphosphate receptor blocker therapy in STEMI patients [10]. Data concerning tirofiban efficacy in dependence of P2Y12 inhibitor subtype is rare. This should be evaluated in further studies.

Moreover, dosing, time of administration and application form should be considered. It was shown that only high dose-bolus administration of tirofiban improved infarct size and segment ST-resolution [17]. Furthermore, it has been demonstrated that intracoronary administration was superior to intravenous application [18]. In most of the studies administration of tirofiban was conducted before PCI [4,5,19]. In our study, tirofiban was administrated as intracoronary high-dose bolus during PCI followed by an infusion in maintenance dose for 24 h.

This study has several limitations. Especially, sample size was rather small in this single center analysis. Therefore it was not sufficiently powered to detect differences in MACCE. Furthermore, this trial was not randomized and all decisions were left to the treating physician. However, this resembles a real-world cohort. Moreover, this study was designed to evaluate clinical endpoints. TIMI or Gensini score for severity of coronary artery disease (CAD) as well as pre- to post-procedural changes in lv function and electro cardiogram morphology was not assessed. These parameters might have influenced the results.

Patient characteristics should be considered while interpreting results. In our study, tirofiban patients were slightly younger, showed enhanced infarct sizes and received a more complex catheter intervention. Nevertheless, MACCE and bleeding rates did not differ. Multivariate analysis revealed lv function, age and male gender as relevant covariates for the occurrence of MACCE. This is not surprising, as these are known cardiovascular risk factors or clinical manifestations of CAD. However, tirofiban patients were slightly younger. Therefore, age should be considered as potential reason next to tirofiban medication for the equality in clinical outcome. Male gender and lv function did not differ between tirofiban and control patients. Moreover, contrast agent volume was shown to be associated with the occurrence of MACCE but cardiac enzymes as cardiac biomarkers did not. In our study, tirofiban patients had a more complex PCI with an enhanced use of contrast agent volume and enhanced infarct sizes demonstrated by increased cardiac enzymes. Nevertheless, clinical outcome was equal between groups which underlines a potential therapeutic benefit due to tirofiban. However, as non-significant differences, tirofiban patients showed a trend to increased bleeding risk and to a reduction of death. After adjustment for cardiovascular and bleeding risk factors in the multivariate-analysis, tirofiban medication still showed a trend towards an increased risk for major bleeding.

In conclusion, there were no differences in MACCE events and bleeding rates in tirofiban treated patients in this study. However, patients with tirofiban were slightly younger, had enhanced infarct sizes and a more complex PCI. The results of this pilot study should be reconfirmed in large scale clinical analysis.

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Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.052.

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