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ORIGINAL SCIENTIFIC PAPER
Acute Coronary Syndromes

Prehospital tirofiban increases the rate of disrupted myocardial infarction in patients with ST-segment elevation myocardial infarction: insights from the On-TIME 2 trial

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Aims

In patients with ST-segment elevation myocardial infarction (STEMI), prehospital tirofiban significantly improved myocardial reperfusion. However, its impact on the rate of disrupted myocardial infarction (MI), particularly in the context of high-sensitivity cardiac troponin (hs-cTn) assays, is still unclear.

Methods and results

The On-TIME 2 (Ongoing Tirofiban In Myocardial infarction Evaluation 2) trial randomly assigned STEMI patients to prehospital tirofiban or placebo before transportation to a percutaneous coronary intervention (PCI) centre. In this *post hoc* analysis, we evaluated STEMI patients that underwent primary PCI and had measured hs-cTn levels. Troponin T levels were collected at 18–24 and 72–96 h after PCI. Disrupted MI was defined as peak hs-cTn T levels ≤ 10 times the upper limit of normal (≤140 ng/L). Out of 786 STEMI patients, 47 (6%) had a disrupted MI. Disrupted MI occurred in 31 of 386 patients (8.0%) in the tirofiban arm and in 16 of 400 patients (4.0%) in the placebo arm ($P = 0.026$). After multivariate adjustment, prehospital tirofiban remained independently associated with disrupted MI (odds ratio 2.03; 95% confidence interval 1.10–3.87; $P = 0.027$). None of the patients with disrupted MI died during the 1-year follow-up, compared with a mortality rate of 2.6% among those without disrupted MI.

Conclusion

Among STEMI patients undergoing primary PCI, the use of prehospital tirofiban was independently associated with a higher rate of disrupted MI. These results, highlighting a potential benefit, underscore the need for future research focusing on innovative pre-treatment approaches that may increase the rate of disrupted MI.

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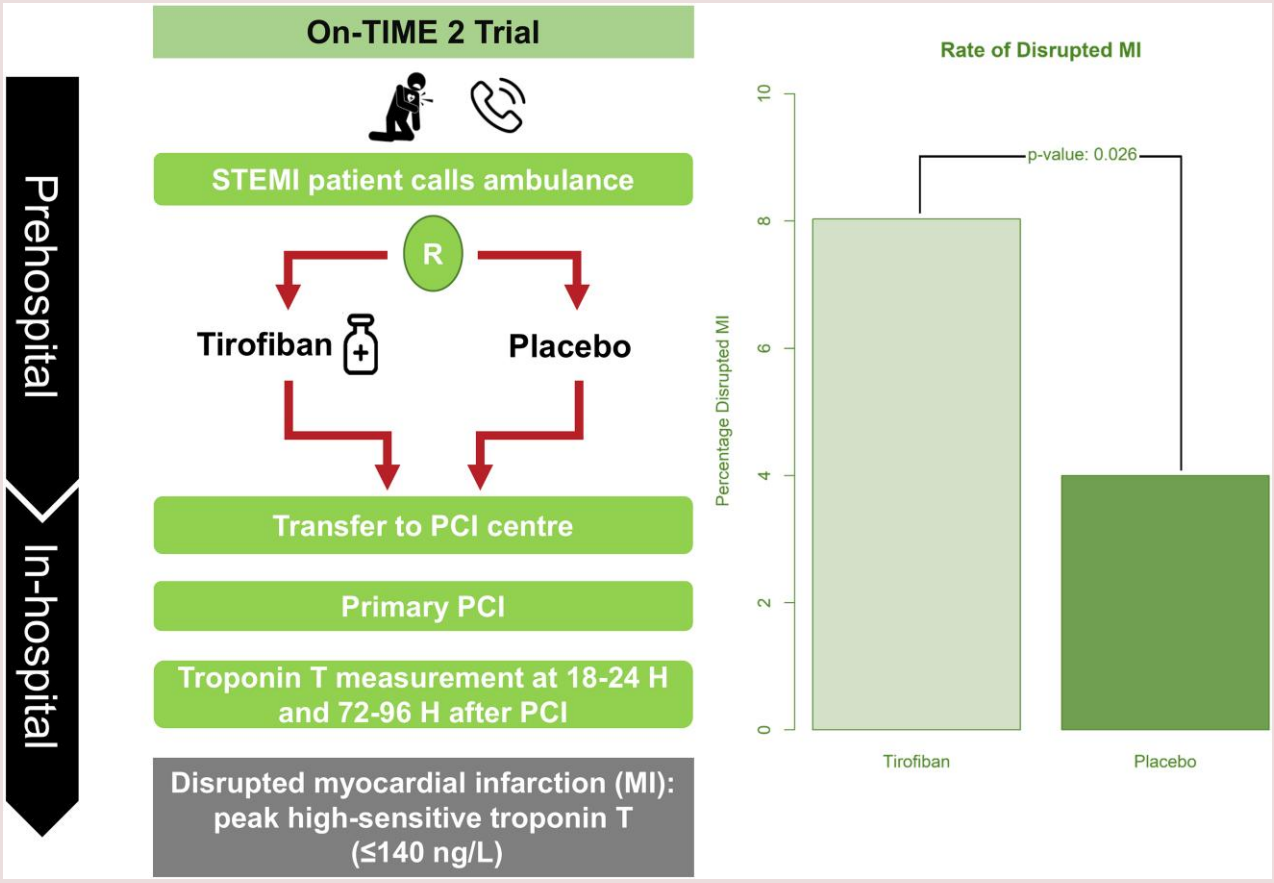
Graphical Abstract



Keywords STEMI • Tirofiban • Prehospital • Glycoprotein IIb/IIIa inhibitors • Disrupted myocardial infarction

Introduction

Timely reperfusion of the infarct-related artery is crucial in minimizing infarct size and improving survival among patients with ST-segment elevation myocardial infarction (STEMI).[1] Therefore, achieving early myocardial reperfusion is the primary therapeutic goal in STEMI patients. When reperfusion occurs very promptly after symptom onset, it can result in only a minimal rise in cardiac biomarkers. Weaver *et al.*[2] described this phenomenon in 1993 and termed it aborted myocardial infarction (MI). Despite the establishment of the fourth universal definition of MI in 2018, this framework does not reference to the concept of aborted MI.[3] This omission is noteworthy because aborted MI has been associated with smaller infarct sizes, improved ventricular ejection fraction, and better clinical outcomes compared with non-aborted MI.[4–9]

One potential strategy to increase the rate of aborted MI involves pre-treatment with glycoprotein IIb/IIIa inhibitors (GPIs) followed by primary percutaneous coronary intervention (PCI).[10] Glycoprotein IIb/IIIa inhibitor pre-treatment improved initial angiographic target vessel patency and ST-segment resolution, in particular when administered in the prehospital setting to early-presenting patients.[11–13] In contrast, prehospital pre-treatment with oral $P2Y_{12}$ inhibitors did not improve angiographic or electrocardiographic indices of reperfusion.[14] In the On-TIME 2 (Ongoing Tirofiban In Myocardial infarction Evaluation 2) trial, myocardial reperfusion was significantly improved in patients who received tirofiban in the ambulance at a median of 75 min after symptom onset compared with those receiving a placebo with standard care.[12] This effect may be attributed to the observation that fresh coronary thrombi are richer in platelets, making them more dynamic and hence more vulnerable to thrombus lysis when tirofiban is administered early after symptom onset.[15] Thus, administering tirofiban to early-presenting STEMI patients, ideally in the prehospital setting, holds promise in enhancing reperfusion and potentially increasing the rate of aborted MI. Of note, due to the ongoing politicization surrounding the term 'aborted', we choose to use the term 'disrupted' MI from here on out.

We conducted a *post hoc* analysis of the On-TIME 2 trial to specifically investigate the association between prehospital tirofiban and the rate of disrupted MI among STEMI patients undergoing primary PCI.

Methods

Study design

The On-TIME 2 trial (ISRCTN06195297) was an international, multicentre, double-blind, randomized, placebo-controlled trial investigating the extent

of residual ST-segment deviation 1 h after initial angiography. The rationale and design of the study have been previously described.[16] In brief, adult patients with (i) symptoms of acute MI of more than 30 min but less than 24 h and (ii) ST-segment elevation of more than 1 mV in two adjacent leads who were candidates to undergo primary PCI were randomly assigned to either high-dose bolus tirofiban (25 mcg/kg bolus and 0.15 mcg/kg/min maintenance infusion for 18 h) or placebo in addition to contemporary standard pharmacological care. Exclusion criteria were severe renal dysfunction, therapy-resistant cardiogenic shock, persistent severe hypertension, increased risk of bleeding, pre-existing left bundle branch block, and life expectancy of <1 year.

Written informed consent was obtained by a paramedic in the ambulance or by a physician in the referral centre. The study drug was administered in the ambulance or in a minority of patients in the referring centre. Contemporary standard pharmacological care consisted of 5000 IU unfractionated heparin, together with aspirin 500 mg intravenously and a 600 mg loading dose of clopidogrel orally. Coronary angiography and PCI were performed according to each institution's guidelines and standards. The study protocol was approved by all local ethics committees involved and complied with the Declaration of Helsinki.

In this analysis, the study population consisted of STEMI patients who underwent primary PCI and had measured high-sensitivity cardiac troponin T (hs-cTnT) levels after PCI. The primary objective was to evaluate the association between prehospital tirofiban administration and the rate of disrupted MI.

Study outcomes

The primary outcome was disrupted MI, and this was defined as peak hs-cTnT levels ≤ 10 times the upper limit of normal (ULN), corresponding to hs-cTnT levels ≤ 140 ng/L. Blood samples were collected at 18–24 and 72–96 h after primary PCI and were immediately processed for later analysis by a central core laboratory (Universitats Klinik, Heidelberg, Germany). All samples underwent hs-cTnT analysis using the Elecsys Troponin T assay (with the 99th percentile ULN set at ≤14 ng/L) from Roche Diagnostics®. The laboratory staff conducting the measurements were blinded to patient data. Secondary outcomes included major adverse clinical events at 30 days, mortality at 1 year, and reperfusion arrhythmias between groups and as function of disrupted MI.

Statistical analysis

Continuous data were presented as mean ± standard deviation or median with interquartile range, while categorical data are presented as no./total with percentages. Continuous variables were analysed with the *t*-test or Mann–Whitney *U* test, while categorical variables were analysed with the χ^2 test or Fisher's exact test. Multivariate logistic regression was used to estimate the adjusted odds ratio (OR) for the primary outcome. The key explanatory variable was a binary indicator for whether the patient was treated with tirofiban. Other covariates in the model such as age, hypercholesterolaemia, previous MI, and ischaemic time were selected based on their significance levels in a univariate model. Kaplan–Meier curves were used to determine the incidence of mortality over time at 1 year as a function of disrupted MI and were tested using the log-rank test. All statistical analyses were performed with R version 4.3.1 (R Foundation for Statistical Computing), and two-sided *P*-values <0.05 were considered to be statistically significant.

Results

Between June 2006 and November 2007, 984 patients diagnosed with STEMI were enrolled in the On-TIME 2 trial. Of these, 786 patients were included in the current analysis. The reasons for being excluded were (i) no blood samples available for analysis ($n = 133$) and/or (ii) no PCI performed ($n = 109$). Baseline characteristics for patients receiving tirofiban or placebo are reported in *Table 1*. The mean age in the present study population was 61.9 ± 11.5 years and 76.2% were male.

A total of 47 (6%) patients had disrupted MI (i.e. hs-cTnT ≤ 10 times the ULN). Disrupted MI occurred in 31 of 386 patients (8.0%) within

Table 1 Baseline characteristics of the patients according to treatment group and disrupted myocardial infarction

Characteristic	Tirofiban ($n = 386$)	Placebo ($n = 400$)	*P*-value	Disrupted MI ($n = 47$)	Non-disrupted MI ($n = 739$)	*P*-value
Age—mean (SD), years	62 (11)	62 (11)	0.459	59 (12)	62 (11)	0.063
Male sex—no./total (%)	300/386 (77.7)	299/400 (74.8)	0.371	35/47 (74.5)	564/739 (76.3)	0.911
Medical history—no./total no. (%)						
Diabetes	44/385 (11.4)	39/400 (9.8)	0.525	14/47 (29.8)	249/738 (33.7)	0.452
Current smoker	182/385 (47.3)	205/399 (51.4)	0.281	23/47 (48.9)	364/737 (49.4)	1.000
Hypertension	134/386 (34.7)	129/400 (32.2)	0.511	14/47 (29.8)	249/739 (33.7)	0.696
Hypercholesterolaemia	108/385 (28.1)	101/400 (25.2)	0.432	18/47 (38.3)	191/738 (25.9)	0.089
Family history or CVD	157/383 (41.0)	157/398 (39.4)	0.738	20/47 (42.6)	294/734 (40.1)	0.824
Previous myocardial infarction	31/385 (8.1)	27/399 (6.8)	0.582	8/47 (17.0)	50/737 (6.8)	0.020
Previous cerebrovascular accident	5/386 (1.3)	9/400 (2.2)	0.458	1/47 (2.1)	13/737 (1.8)	1.000
Baseline NT-proBNP levels in pg/mL—median (IQR)	134 (64–365)	122 (56–306)	0.226	133 (60–343)	112 (45–264)	0.254
Median time intervals						
Ischaemic time—median (IQR)	164 (125–229)	165 (127–250)	0.491	148 (113–215)	165 (127–243)	0.148
Study treatment to angiography—median (IQR)	55 (42–68)	55 (42–70)	0.840	54 (42–65)	55 (42–69)	0.770
No. of vessels with coronary artery disease—no./total no. (%)			0.107			0.297
One-vessel disease	220/381 (57.7)	210/399 (52.6)		30/47 (63.8)	406/737 (54.9)	
Two-vessel disease	99/381 (26.0)	130/399 (32.6)		9/47 (19.1)	220/737 (29.8)	
Three-vessel disease	62/381 (16.3)	59/399 (14.8)		8/47 (17.0)	113/737 (15.3)	

CVD, cardiovascular disease; IQR, interquartile range; MI, myocardial infarction; NT-proBNP, N-terminal fragment of the brain natriuretic peptide prohormone.

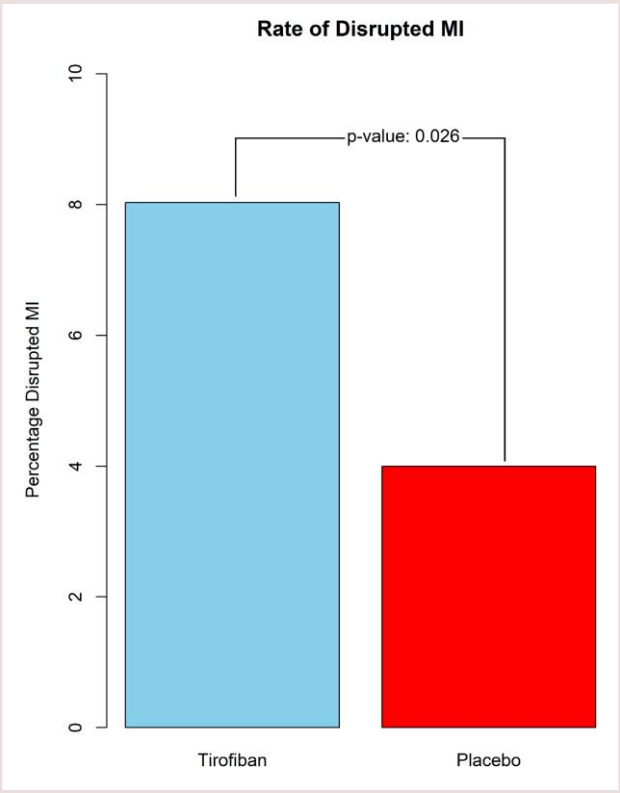


Figure 1 Rate of disrupted myocardial infarction. MI, myocardial infarction.

the prehospital tirofiban group and in 16 of 400 (4.0%) in the placebo group ($P = 0.026$, *Figure 1*). Clinical outcomes within the treatment groups were comparable with the rates reported in the primary paper.[12] Rates of reperfusion arrhythmias were similar between patients randomized to tirofiban vs. placebo (*Table 2*). Following multivariate analysis, prehospital tirofiban remained independently associated with disrupted MI (adjusted OR 2.03; 95% confidence interval 1.10–3.87; $P = 0.027$). In a sensitivity analysis using a stricter definition of disrupted MI (peak hs-cTnT ≤ 5 times the ULN), patients treated with tirofiban continued to show a higher rate of disrupted MI compared with the placebo group (4.1 vs. 1.5%, $P = 0.042$).

Patients with disrupted MI showed a higher incidence of prior MI and were more frequently treated with tirofiban compared with those with non-disrupted MI (*Table 1*). Other baseline characteristics were similar between patients with disrupted MI and with non-disrupted MI. All patients with disrupted MI were alive at the 1-year follow-up, whereas 19 patients (2.6%) with non-disrupted MI were dead. *Figure 2* shows the survival curves for patients with disrupted MI and non-disrupted MI. Moreover, patients with disrupted MI experienced fewer ventricular reperfusion arrhythmias (2.1 vs. 13.5%, $P = 0.041$) and less atrial fibrillation compared with those with non-disrupted M (0.0 vs. 14.7%, $P = 0.029$, *Table 2*).

Discussion

Our *post hoc* analysis of the On-TIME 2 trial, studying the effect of prehospital given tirofiban in STEMI patients followed by primary PCI, has uncovered several new insights. First, among STEMI patients undergoing primary PCI, prehospital tirofiban on top of standard care increased the rate of disrupted MI compared with placebo with standard care. This increase remained independently associated with tirofiban pretreatment after multivariate adjustment. Second, none of the patients

Table 2 Primary and secondary outcomes according to treatment group and disrupted myocardial infarction status

	Tirofiban ($n = 386$)	Placebo ($n = 400$)	*P*-value	aOR*	Disrupted MI ($n = 47$)	Non-disrupted MI ($n = 739$)	*P*-value
Primary outcome no./total no. (%)							
Disrupted MI (peak trop ≤ 10 times the ULN)	31/386 (8.0)	16/400 (4.0)	0.026	2.03, CI 1.10–3.87, $P = 0.027$	47/47 (100)	0/739 (0.0)	<0.001
Exploratory combination of disrupted MI +							
TIMI flow 2/3 pre-PCI	27/386 (7.0)	13/400 (3.2)	0.026		40/47 (85.1)	0/739 (0.0)	<0.001
Complete STR (≥70%) pre-PCI	18/384 (4.7)	9/400 (2.2)	0.061		27/45 (60.0)	0/739 (0.0)	<0.001
Clinical outcome at 30 days							
Stroke	1/386 (0.3)	5/400 (1.2)	0.236		0/47 (0.0)	0/739 (0.0)	1.000
Recurrent MI	10/386 (2.6)	10/400 (2.5)	1.000		0/47 (0.0)	20/739 (2.7)	0.506
Death	2/386 (0.5)	9/400 (2.2)	0.078		0/47 (0.0)	11/739 (1.5)	0.840
Reperfusion arrhythmias							
AF	39/386 (10.1)	44/400 (11.0)	0.770		0/47 (0.0)	83/739 (14.7)	0.029
VT	33/386 (8.5)	37/400 (9.2)	0.826		1/47 (2.1)	69/739 (9.3)	0.156
VF	20/386 (5.2)	18/400 (4.5)	0.780		0/47 (0.0)	38/739 (5.1)	0.214
VT/VF	49/386 (12.7)	52/400 (13.0)	0.983		1/47 (2.1)	100/739 (13.5)	0.041

Variables used for multivariate adjustment include tirofiban treatment, age, prior myocardial infarction, hypercholesterolaemia, and ischaemic time.
AF, atrial fibrillation; aOR, adjusted odds ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; STR, ST-segment resolution; TIMI, thrombolysis in myocardial infarction; ULN, upper limit of normal; VT, ventricular tachycardia; VF, ventricular fibrillation; VT/VF, ventricular tachycardia and ventricular fibrillation.

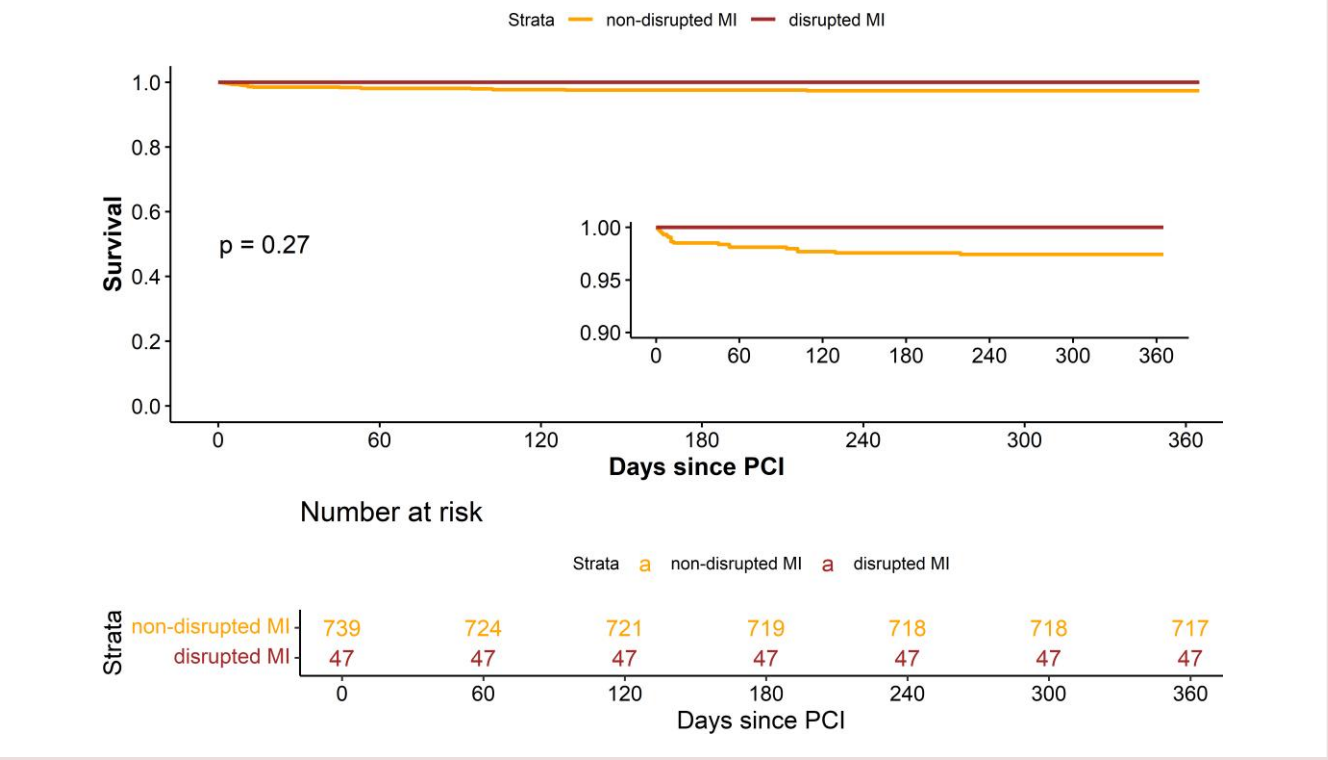


Figure 2 Kaplan–Meier curves for survival according to disrupted myocardial infarction. MI, myocardial infarction; PCI, percutaneous coronary intervention.

with disrupted MI experienced major adverse clinical events at 30-day follow-up, and notably all patients with disrupted MIs were alive at 1-year follow-up, underscoring the favourable prognosis associated with a very limited infarct size. Third, those with disrupted MIs experienced fewer reperfusion-related ventricular arrhythmias and occurrences of atrial fibrillation, suggesting potential benefits beyond just reducing infarct size.

GPI pre-treatment in STEMI patients followed by primary PCI has previously shown improvements in myocardial reperfusion indices, clinical outcomes, and N-terminal fragment of the brain natriuretic peptide prohormone levels.[11,12,17] In this analysis, we have shown for the first time that prehospital tirofiban followed by primary PCI increased the rate of disrupted MI in the era hs-cTnT testing. Prior studies have hinted at higher but non-significant rates of disrupted MI associated with GPI pre-treatment followed by primary PCI.[11] However, it is important to note that disrupted MI identification in those studies relied on creatinine kinase levels, which are less selective, sensitive, and specific, limiting direct comparisons with our findings.

Using our definition for disrupted MI (peak hs-cTnT levels ≤ 10 times the ULN), the overall rate of disrupted MI favoured prehospital tirofiban compared with placebo followed by primary PCI (8.0 vs. 4.0%, $P = 0.026$). It is interesting to compare the rates of disrupted MI in our study with those observed in the STREAM-2 (Strategic Reperfusion in Elderly Patients Early After Myocardial Infarction 2) trial, where the cut-off for disrupted MI was set to hs-cTnT levels ≤ 5 times the ULN combined with complete (≥70%) ST-segment resolution.[18] The STREAM-2 randomized early-presenting STEMI patients that could not undergo primary PCI within 1 h to prehospital fibrinolysis followed by coronary angiography and PCI if indicated (fibrinolytic-invasive) vs. primary PCI. In STREAM-2, the rates of disrupted MI between the two treatment arms were similar (4.0 vs. 4.0%). Applying the STREAM-2 definition of disrupted MI to the On-TIME 2 population, the overall rates were substantially lower (tirofiban 2.1% vs. placebo 0.5%, $P = 0.098$), but a trend towards increased rates of disrupted MI with prehospital GPI was observed. Interestingly, the fibrinolytic-invasive strategy showed significantly improved rates of epicardial and myocardial reperfusion, although this did not translate in superior clinical outcomes. In contrast, prehospital tirofiban–treated patients showed improved myocardial reperfusion coupled with better clinical outcomes.[12] Of note, strokes occurred in 2.3% in the fibrinolytic-invasive group vs. 0.5% in the primary PCI group in STREAM-2, compared with 0.3% in the prehospital tirofiban group vs. 1.2% in placebo group in the On-TIME 2.

Our findings align with previous evidence demonstrating improvements in reperfusion indices through prehospital GPI treatment in early-presenting STEMI patients.[11] While other rapid-acting antiplatelet drugs like cangrelor have not been investigated specifically in the prehospital context among STEMI patients, results from the randomized FABOLOUS-FASTER (Facilitation Through Aggrastat or Cangrelor Bolus and Infusion Over Prasugrel: A Multicenter Randomized Open-Label Trial in Patients with ST-Elevation Myocardial Infarction Referred for Primary Percutaneous Intervention) trial showed inferior platelet aggregation inhibition compared with tirofiban when cangrelor was administered in the catheterization laboratory to STEMI patients.[19] Moreover, research has demonstrated that although $P2Y_{12}$ inhibitors significantly inhibit adenosine diphosphate (ADP)–induced platelet aggregation, their effect on the more potent thrombin-induced protease-activated receptor (PAR)-1 and PAR-4 pathways remains relatively limited.[20,21] This presents a limitation in the acute setting following plaque rupture, as thrombin serves as an early and crucial primary agonist in the pathophysiology of atherosclerotic thrombotic events. This suggests that GPIs, which inhibit the final pathway of platelet aggregation, might offer greater efficacy in halting thrombus formation, promoting early reperfusion, and potentially disrupting MI. Despite superior pharmacodynamic efficacy compared with single

agonist-blocking antiplatelet drugs, GPI pre-treatment among early-presenting STEMI patients is currently not recommended according to the latest European guidelines, possibly due to concerns that the perceived benefits in reducing ischaemic events are outweighed by bleeding risks.[1] However, some of the increase in bleeding was rooted in an era of widespread use of femoral access and long GPI infusion periods, factors known to increase bleeding risk after PCI.[22–24] In the current era of primary PCI management, where radial approach is dominant, an early, short-during GPI pre-treatment regimen could result in safer outcomes in terms of access-related bleeding risk. Noteworthy, data from On-TIME 2 trial, the largest randomized clinical trial on prehospital GPI therapy, showed no increase in the risk of major or minor bleedings.[12]

First-generation GPIs present additional limitations such as their relatively long half-life, the risk of thrombocytopenia associated with their use, and the necessity for continuous infusion, which poses logistical challenges during transportation to interventional facilities.[25] To address these concerns, the potential use of the investigational second-generation subcutaneously injected GPI, called zalunfiban, holds promise for achieving early platelet inhibition, prompt reperfusion, and potential disruption of MI.[26] Zalunfiban is specifically designed for acute MI pre-treatment, exhibiting rapid and potent platelet inhibition within 15 min after administration, with its antiplatelet effects wearing off rapidly.[10,26] It effectively inhibits both ADP-induced and thrombin-induced platelet aggregation and showed superior inhibition against thrombin-induced platelet aggregation in a head-to-head *in vitro* comparison with $P2Y_{12}$ inhibitors.[20] Preliminary analyses showed that pre-treatment with the highest investigated dose of zalunfiban was associated with improved coronary and myocardial patency and reduced thrombus burden on the initial angiogram, thus warranting further investigation in larger trials.[27] Currently, zalunfiban is undergoing evaluation in the Phase 3, randomized, double-blinded, placebo-controlled trial called CELEBRATE (CELEcor Blinded RAndomized trial in sTE-elevation myocardial infarction, NCT04825743).[28] Given the observed beneficial effect of prehospital tirofiban on the rate of disrupted MI in the On-TIME 2 trial, disrupted MI has been selected as component of the hierarchically assessed primary composite outcome in the CELEBRATE trial.

Our *post hoc* analysis has several limitations that deserve attention. First, the absence of an evidence-based cut-off for defining disrupted MI based on hs-cTn levels after STEMI led us to arbitrarily choose a stringent definition (peak hs-cTnT $\leq$ 10 times the ULN).[3] However, our selection of a more sensitive and selective biomarker, hs-cTnT, contrasts with earlier definitions often relying on creatinine kinase and/or creatinine kinase muscle brain fraction levels $\geq$ 2 times the ULN.[29] It is worth noting that our definition of disrupted MI is sevenfold lower than the commonly accepted threshold for significant peri-procedural MI (a rise in cTn $\geq$ 70 times above the ULN), with the observation that only large biomarker elevations (cTn $\geq$ 70 times above the ULN) are associated with mortality.[30,31] Notably, all patients meeting our definition for disrupted MI were alive at 1-year follow-up. Second, our analysis was limited to patients with available hs-cTnT data who underwent primary PCI, potentially limiting the generalizability to patients managed by coronary artery bypass grafting surgery or medical therapy alone. Despite an equal distribution of missing values across treatment groups, undocumented reasons for missing data could have introduced bias. Third, the multivariate analysis was adjusted for a limited set of potential confounders due to the small number of patients with disrupted MI. Nevertheless, the lack of multiple differences in baseline characteristics between tirofiban and placebo groups supports tirofiban's independent association with disrupted MI.

Conclusions

Prehospital tirofiban followed by primary PCI in early-presenting STEMI patients was associated with an increased rate of disrupted MI, supporting its potential role in maximizing myocardial salvage. These results, highlighting a potential benefit, underscore the need for future research focused on innovative pre-treatment approaches that may enhance the rate of disrupted MI and validate our observed association.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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