Long-term mortality and prehospital tirofiban treatment in patients with ST elevation myocardial infarction

Enrico Fabris,[1,2] Sinem Kilic,[1] Dirk A A M Schellings,[3] Jurrien M ten Berg,[4] Mark W Kennedy,[1] K Gerts van Houwelingen,[5] Evangelos Giannitsis,[6] Evelien Kolkman,[7] Jan Paul Ottervanger,[1] Christian Hamm,[8] Arnoud W J van't Hof[1,9]

[1]Department of Cardiology, Isala Klinieken, Zwolle, The Netherlands
[2]Cardiovascular Department, University of Trieste, Trieste, Italy
[3]Slingeland Ziekenhuis, Doetinchem, The Netherlands
[4]Department of Cardiology, St Antonius Hospital, Nieuwegein, The Netherlands
[5]Cardiology Department, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, The Netherlands
[6]Department of Cardiology, Universitats Klinik, Heidelberg, Germany
[7]Diagram CRO, Zwolle, The Netherlands
[8]Department of Cardiology, Kerckhoff Klinik, Bad Nauheim, Germany
[9]Department of Cardiology, Maastricht University Medical Center, Maastricht, The Netherlands

Correspondence to
Professor Arnoud W J van't Hof, Department of Cardiology, Maastricht University Medical Center, Maastricht, The Netherlands; awjhof@xs4all.nl

Accepted 10 May 2017

ABSTRACT

Objective We undertook a subgroup analysis of the On-TIME 2 (Ongoing Tirofiban In Myocardial infarction Evaluation 2), a placebo-controlled, double-blind, randomised trial, in order to evaluate the association between N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and long-term (5 years) mortality and to investigate the effect of prehospital tirofiban administration on mortality in relation to NT-proBNP levels.

Methods A total of 984 patients with ST elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) were randomised to either in ambulance tirofiban or placebo. NT-proBNP levels were evaluated on admission before angiography (baseline) and 18–96 hours thereafter (post PCI).

Results There were 918 (93.3%) patients with NT-proBNP values available at baseline and 865 (87.9%) post PCI. Patients with baseline NT-proBNP values above the median (137 pg/mL) had higher 30-day (5.1% vs 0.2%, p<0.001), 1-year (7.0% vs 0.7%, p<0.001) and 5-year (20.3% vs 4.9%, p<0.001) mortality as compared with patients with values below the median. Using multivariate Cox analysis, NT-proBNP above the median was an independent predictor for 5-year mortality (HR 2.73, 95% CI 1.47 to 5.06; p=0.002). Patients with values above the median who received early tirofiban treatment had significant lower mortality compared with patients treated with placebo at 30 days (2.7% vs 7.5%, p=0.021) and 1 year (4.5% vs 9.4%, p=0.043). At 5 years, a lower but non-significant mortality rate was maintained in the treatment group (18% vs 22.4%, p=0.265).

Conclusions In patients with STEMI, baseline NT-proBNP level independently predicts long-term mortality. In patients with baseline NT-proBNP levels above the median, early prehospital treatment with tirofiban significantly reduced 30-day and 1-year mortality, suggesting that high-risk patients may derive particular benefit. This finding should be confirmed in other studies.

Trial registration number ISRCTN06195297.

INTRODUCTION

Urgent restoration of perfusion to the myocardium supplied by the infarct-related artery is the primary therapeutic objective in ST elevation myocardial infarction (STEMI), as it improves survival.[1] Primary percutaneous coronary intervention (PCI) combined with effective antiplatelet therapy is the preferred treatment strategy in STEMI.[2] In order to increase the rates of mechanical reperfusion and so reduce ischaemic complications, large interest has focused on adjunctive administration of pharmacological therapy and its timing of administration.

Glycoprotein IIb/IIIa inhibitors (GPIs) are the most powerful class of antiplatelet therapies, and their adjunctive effects have been shown in several randomised trials.[3] In addition, early GPI administration in patients undergoing primary angioplasty for STEMI has been associated with significantly higher rates of preprocedural epicardial recanalisation and ST-segment resolution.[4–8] However, the benefit of these drugs is less certain in patients at lower risk for ischaemic events or those presenting later[9 10] and large randomised trials, conducted to explore the benefits from adjunctive GPIs in addition to clopidogrel administration, showed conflicting results.[6 11–13] Among patients with STEMI undergoing primary PCI, the greatest benefit in mortality reduction from GPI usage has been shown in patients with higher risk profiles.[14] Therefore, identification of additional subgroups of patients who may have particular benefit from GPI administration is of paramount importance to further improve outcomes.

The N-terminal pro-B-type natriuretic peptide (NT-proBNP), an established biomarker, has been shown to be liberated from myocardium following acute myocardial infarction (MI)[15] and elevated levels have been associated with poor outcome in patients with acute coronary syndrome.[16–21]

The On-TIME 2 (Ongoing Tirofiban In Myocardial infarction Evaluation 2) trial randomised patients undergoing primary PCI to prehospital tirofiban administration versus placebo to investigate the effect of pretreatment on the extent of residual ST-segment deviation 1 hour after primary PCI compared with placebo. The results of the study showing that early initiation of tirofiban improved ST-segment resolution compared with placebo have been previously published.[6]

We undertook a subgroup analysis of the On-TIME 2 trial with long-term follow-up in order to investigate (1) the potential association between NT-proBNP levels and long-term mortality; (2) the effect of early tirofiban administration on mortality in relation to NT-proBNP levels in patient with STEMI undergoing primary PCI.

METHODS

Study design

The On-TIME 2 trial (ISRCTN06195297) was an international, multicentre, prospective, placebo-controlled, double-blind, randomised trial. The rationale and design of the study have been previously described.[22] In brief, the study population consisted of patients with STEMI who were candidates for primary PCI treatment. Eligible patients were men and women, 21–85 years of age, with symptoms of acute MI for >30 min but <24 hour, and ST-segment elevation of >1 mV in two adjacent ECG leads. Exclusion criteria were known severe renal dysfunction, therapy-resistant cardiogenic shock, persistent severe hypertension and an increased risk of bleeding. Also excluded were patients with a left bundle branch block and patients with a life expectancy of <1 year. Written informed consent was obtained by an intensive care nurse in the ambulance or, in a minority of the patients, by a physician in the referral centre. The study protocol was approved by all local ethics committees involved.

Randomisation and treatment

Patients were randomly assigned to prehospital treatment with high-dose bolus tirofiban (25 mcg/kg bolus and 0.15 mcg/kg/min maintenance infusion for 18 hours) or placebo. In the ambulance or referring centre, all patients also received a bolus of 5000 IU of unfractionated heparin intravenously together with aspirin 500 mg intravenously and a 600 mg loading dose of clopidogrel orally. Before PCI, additional unfractionated heparin (2500 IU) was only given if the activated clotting time was less than 200 s. Coronary angiography and PCI were performed according to each institution's guidelines and standards. Additional treatment with thrombus aspiration was left at the discretion of the treating cardiologist.

Blood samples for NT-proBNP measurement

Blood samples were taken on admission before angiography (baseline) and 18–96 hours thereafter (post PCI). NT-proBNP was measured by a sandwich immunoassay on a fully automated analyser (NT-proBNP ELECSYS 2010; Roche Diagnostics, Mannheim, Germany). The NT-proBNP levels were assessed both as continuous values and dichotomised with median value as cut-off.

Mortality outcome

In order to investigate (1) the association between NT-proBNP levels and short-term and long-term mortality and (2) the effect of early tirofiban on mortality in relation to NT-proBNP levels, the mortality endpoints of this exploratory study were set at 30 days, 1 year and 5 years. Death was defined as all-cause mortality.

Bleeding outcome

As previously described,[6] bleeding was assessed using the thrombolysis in myocardial infarction (TIMI) criteria.[23] Major bleeding was defined as clinical overt signs of haemorrhage associated with a decrease in haemoglobin of >5 g/dL (or when haemoglobin assessment is not available, a decrease in haematocrit of >15%). For patients undergoing coronary artery bypass graft surgery, the rate of surgical re-exploration for bleeding and the postoperative volume of blood loss were also evaluated. Follow-up information was derived from visits to the outpatient clinic or from telephone contact at the 30-day follow-up.

Table 1 Baseline characteristics of the patients receiving placebo versus tirofiban

Variable	Placebo (n=454)	Tirofiban (n=464)	p Value
Age (years), mean±SD	62.0±11.8	61.5±11.7	0.504
Male gender	340/454 (74.9%)	355/464 (76.5%)	0.567
Current smoking	223/449 (49.7%)	208/463 (44.9%)	0.152
Diabetes mellitus	51/454 (11.2%)	55/463 (11.9%)	0.760
Body mass index (kg/m^2), mean±SD	26.7±4.0	26.8±3.4	0.506
Hypertension	152/454 (33.5%)	156/464 (33.6%)	0.964
Hypercholesterolaemia	112/453 (24.7%)	132/463 (28.5%)	0.195
Killip >I	24/453 (5.3%)	17/463 (3.7%)	0.234
Prior myocardial infarction	34/453 (7.5%)	43/463 (9.3%)	0.331
Prior CABG	9/454 (2.0%)	8/464 (1.7%)	0.772
Prior PCI	36/454 (7.9%)	47/464 (10.1%)	0.245
Anterior infarct location	168/407 (41.3%)	173/407 (42.5%)	0.722
Time to intervention*	167 (128–261)	165 (125–235)	0.371
Heart rate >100	26/450 (5.8%)	24/461 (5.2%)	0.705
Systolic blood pressure <100	37/450 (8.2%)	28/459 (6.1%)	0.214

*From onset of symptoms to intervention in minutes, median (25th–75th IQRs).
CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Statistical analysis

Continuous data were expressed as mean±SD or median with IQR. Categorical data were expressed as percentages. Categorical variables were analysed with the χ^2 test or Fisher's exact test, and continuous variables with the Mann-Whitney U test (two sided). Values of $p<0.05$ were considered statistically significant. We performed Cox multivariate regression analyses on mortality with NT-proBNP below or above the median as the predictor of main interest and baseline characteristics (age, gender, smoking, body mass index (BMI), diabetes, hypertension, hypercholesterolaemia, prior MI, prior PCI, admission heart rate, systolic blood pressure, anterior infarct location, ischaemic time, post-PCI TIMI flow (less than 3 vs 3) and Killip class (I vs II, III or IV) as confounders). Kaplan-Meier (KM) survival analysis was performed with the use of the log-rank test. All analyses were performed according to the intention-to-treat principle. Statistical analysis was performed with PASW Statistics V.18 (SPSS Inc, Chicago, Illinois).

RESULTS

Study population

The On-TIME 2 trial recruited a total of 984 patients who were randomised to either placebo or tirofiban treatment. The baseline clinical characteristics for patient receiving placebo or tirofiban were comparable and are reported in table 1. There were 918 (93.3%) patients with samples available for NT-proBNP at admission (baseline) and 865 (87.9%) post PCI.

There was no significant difference in NT-proBNP levels between patients randomised to tirofiban or to placebo as a continuous variable (626±SD 1850 vs 646±SD 2054 pg/mL, $p=0.11$, in tirofiban vs placebo group, respectively) nor as a binary variable dichotomised according to the median value (137, IQR 60–360 pg/mL) (48.9% vs 51.1%, $p=0.51$, in tirofiban vs placebo group, respectively).

Table 2 Baseline characteristics of patients with a baseline NT-proBNP level ≤ median versus > median

Variable	NT-proBNP level ≤ median	NT-proBNP level > median	p Value
Age (years) mean±SD	57.3±9.9	66.3±11.8	<0.001
Male gender	384/459 (83.7%)	311/459 (67.8%)	<0.001
Current smoking	246/456 (53.9%)	185/456 (40.6%)	<0.001
Diabetes mellitus	42/458 (9.2%)	64/459 (13.9%)	0.024
Body mass index (kg/m^2) mean±SD	27.2±3.8	26.4±3.6	0.009
Hypertension	113/459 (24.6%)	195/459 (42.5%)	<0.001
Hypercholesterolaemia	111/457 (24.3%)	133/459 (29.0%)	0.109
Killip >I	10/458 (2.2%)	31/458 (6.8%)	<0.001
Prior myocardial infarction	25/458 (5.5%)	52/458 (11.4%)	0.001
Prior CABG	6/459 (1.3%)	11/459 (2.4%)	0.221
Prior PCI	31/459 (6.8%)	52/459 (11.3%)	0.016
Anterior infarct location	164/409 (40.1%)	177/405 (43.7%)	0.297
Time to intervention*	152 (122; 203)	193 (136; 292)	<0.001
Heart rate >100	15/456 (3.3%)	35/455 (7.7%)	0.004
Systolic blood pressure <100	32/453 (7.1%)	33/456 (7.2%)	0.919
Randomisation to tirofiban	237/459 (51.6%)	227/459 (49.5%)	0.509

*From onset of symptoms to intervention in minutes, median (25th–75th IQRs).
NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention.

Baseline clinical characteristics of patients according to baseline NT-proBNP level below or above the median are shown in table 2. Several characteristics were significantly different in the two patient cohorts. Patients with baseline NT-proBNP level above the median were older, more frequently female, presented higher rate of diabetes, hypertension, history of MI, history of PCI, Killip class >1, had a higher baseline heart rate and a longer time to intervention as compared with patient with baseline NT-proBNP levels below the median; who conversely had a lower BMI and were less frequently smokers.

Baseline NT-proBNP and mortality

Patients with baseline NT-proBNP level above the median presented higher 30-day (5.1% vs 0.2%, p<0.001), 1-year (7.0% vs 0.7%, p<0.001) and 5-year (20.3% vs 4.9%, p<0.001) mortality compared with patients with basal NT-proBNP value below the median. KM curves are shown in figure 1.

Additionally, NT-proBNP values post PCI were also strongly related to mortality: patients with NT-proBNP levels above the median post PCI had a significant higher mortality at 30 days (3.0% vs 0.2%, p=0.001), 1 year (4.8% vs 0.9%, p=0.001) and 5 years (15.5% vs 7.3%, p=<0.001); patients with NT-proBNP levels above the median at admission had an HR for 5-year mortality of 4.28 (95% CI 2.47 to 7.41; p<0.001), and following multivariate Cox regression analysis, an HR of 2.73 (95% CI 1.47 to 5.06; p=0.002).

Effect of early administration of tirofiban on NT-proBNP levels, bleeding and mortality in relation to NT-proBNP level

NT-proBNP

Interestingly in patients treated with prehospital tirofiban as compared with placebo, the NT-proBNP levels after PCI tended to be lower when considered as a continuous variable (1732±2866 vs 2114±5019; p=0.080) and were significantly lower when considered as a binary variable dichotomised with median value as cut-off (194/426, 45.5% vs 238/439, 54.2%; p=0.011) (table 3).

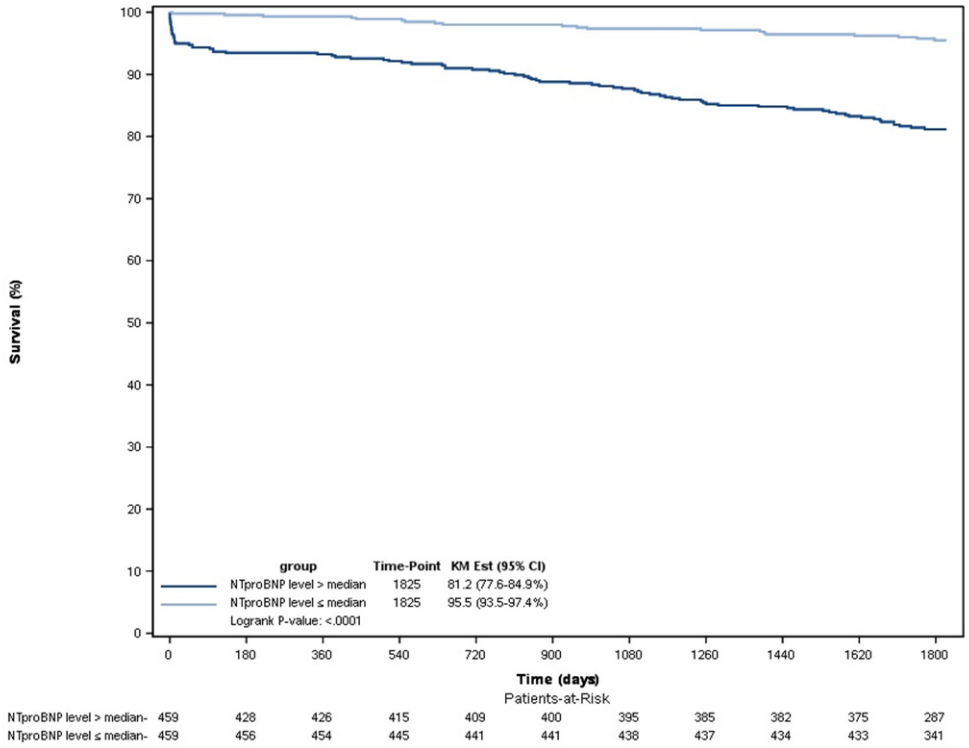

Figure 1 Kaplan-Meier survival curves according to admission NT-proBNP levels above or below the median. The p value, calculated with the use of the log-rank test, is given for the comparison between the two groups at 5 years. NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 3 NT-proBNP levels in placebo versus tirofiban groups

	NT-proBNP levels expressed as a continuous variable			NT-proBNP levels dichotomised according to the median value		
	Placebo	Tirofiban		Placebo	Tirofiban	
	Mean±SD	Mean±SD	p Value	N/Total (%)	N/Total (%)	p Value
Admission	646±2054	626±1850	0.108	232/454 (51.1)	227/464 (48.9)	0.509
After PCI	2114±2866	1732±5019	0.080	238/439 (54.2)	194/426 (45.5)	0.011

NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention.

Bleeding

Patients with NT-proBNP levels above the median at admission who received early tirofiban treatment had a similar rate of 30 days major bleeding compared with patients treated with placebo (5.8% vs 3.1%, p=0.158, for tirofiban vs placebo group, respectively) and of 30 days minor bleeding (7.6% vs 4.4%, p=0.151).

Mortality

Patients with NT-proBNP above the median at admission who received early tirofiban treatment had a significantly lower mortality at 30 days (2.7% vs 7.5%, p=0.021) and at 1 year (4.5% vs 9.4%, p=0.043) compared with patients treated with placebo (figure 2). This lower mortality rate in the treatment group was indeed maintained as far as 5 years, although at this point was associated with a non-significant difference (18% vs 22.4%, p=0.265). KM curves are shown in figure 2.

DISCUSSION

In this post hoc subgroup analysis of the On-TIME 2 trial, we have shown in a group of patients with STEMI only that NT-proBNP level above the median is an independent predictor of long-term (5-year) mortality outcome. Moreover, we have shown that in patients with baseline NT-proBNP levels above the median, early prehospital treatment with tirofiban significantly reduces 30-day and 1-year mortality compared with placebo. Furthermore, we have shown that tirofiban, compared with placebo, reduces NT-proBNP levels post PCI. These findings are clinically relevant and novel; however, they should be considered as hypothesis generating.

We have previously reported the long-term clinical outcomes benefit of a GPI-facilitated PCI strategy[7]; however, in this current analysis we provide further insight, showing that a high-risk subset of patients, as identified by higher levels of NT-proBNP upon presentation (figure 1), represents a subgroup who derives particular benefit from early GPI treatment in terms of significant mortality reduction up to 1 year (figure 2). This lower mortality rate was maintained up to 5 years, although at this point with a non-significant difference probably because other factors may influence very long-term outcomes.

Previously, a significant relationship between the benefits in mortality reduction from the use of GPIs and patient's risk profile has been suggested,[14] and the identification of patients who may incrementally benefit from GPI administration is important in the ongoing search for a more tailored and optimised therapy for patients with STEMI. Therefore, our findings

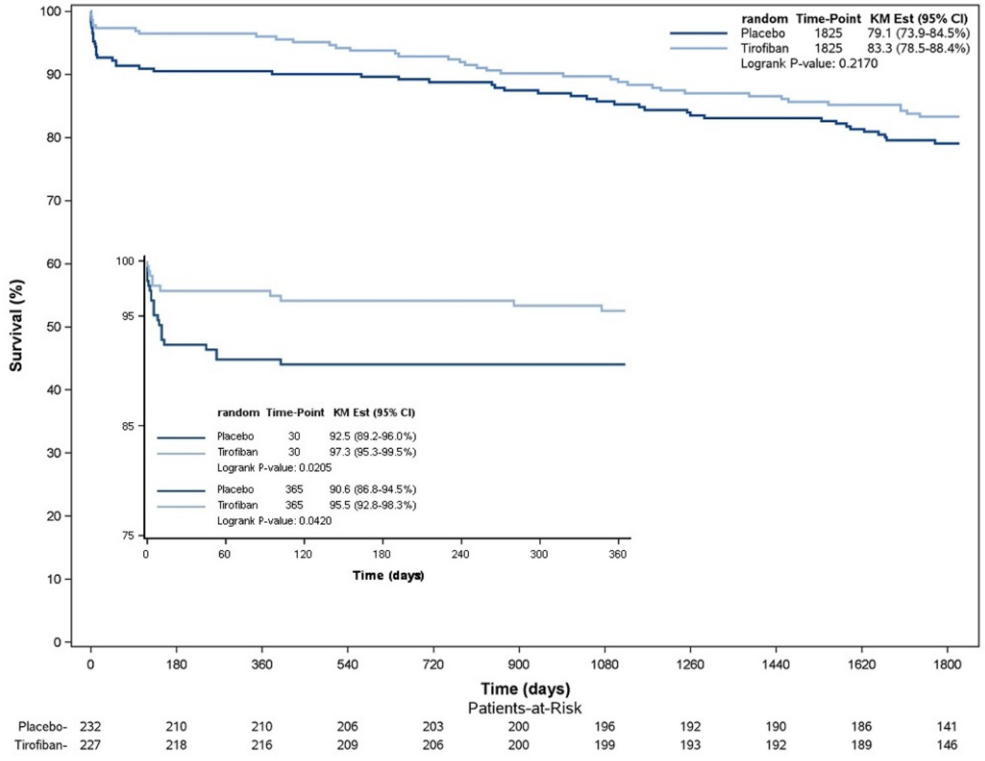

Figure 2 Kaplan-Meier survival curves among patients with admission NT-proBNP level above the median, according to treatment group. The p values, calculated with the use of the log-rank test, are given for the comparison between the two treatment groups at 30 days, 1 year and 5 years. The inset shows the same data on a magnified scale. NT-proBNP, N-terminal pro-B-type natriuretic peptide.

may help to further refine the identification of patients likely to derive the greatest benefit from prehospital GPI administration. Importantly, the mortality reduction was without a significant increase in either major or minor bleeding complications. However, it should be noted that patients receiving tirofiban had a numerically higher rate of both 30-day major and minor bleeding compared with placebo. Therefore, tirofiban should be always used with caution in patients at high bleeding risk.

It is widely believed that the predominant process underlying increased NT-proBNP concentrations is impairment of cardiac function, leading to increased left ventricular wall stretch with resultant synthesis and secretion of NT-proBNP.[24] Ischaemic injury due to coronary artery occlusion may first cause diastolic dysfunction, followed by elevation in filling pressures and associated left ventricular wall stretch resulting in the early elevation of serum NT-proBNP levels. However, elevated NT-proBNP concentrations may also result directly from cardiac ischaemia, even in the absence of left ventricular dysfunction.[25] Previous studies highlighted that, in patients with STEMI, NT-proBNP, drawn within 24 hours of the onset of chest pain, is more accurate in predicting mortality than the TIMI risk score.[26] Indeed, our group recently revealed that baseline NT-proBNP values predict 30-day mortality in patients with STEMI, treated with primary PCI independently and even more strongly than the Zwolle risk score alone.[27] However, in patients with STEMI the prognostic value of NT-proBNP on long-term, 5-year mortality outcomes to date has never been reported.

NT-proBNP measured before primary PCI has been previously shown to be the strongest, independent predictor of suboptimal microvascular reperfusion.[28] Mechanisms behind the actual association between NT-proBNP and suboptimal reperfusion remain speculative[28]; however, biomarker elevation may be the expression of profound myocardial ischaemia and extensive microvascular damage leading to relevant ventricular dysfunction, alternatively one could argue that primary microvascular dysfunction, by itself, may influence left ventricular wall stretch and so BNP values in the setting of acute MI. Regardless of the mechanism, patients at risk of suboptimal microvascular reperfusion after PCI may have particular benefit from adjunctive measures, such as early GPI administration. In fact, it has been shown that an antithrombotic therapy, which is already active and effective at the time of PCI, plays a crucial role in the prevention of microvascular damage and restoration of myocardial tissue reperfusion.[6]

Interesting, in this study, NT-proBNP level at baseline (before angiography) was not different with respect of the treatment strategy initiated in the ambulance. However, early tirofiban administration significantly reduced the number of patients with an NT-proBNP above the median after PCI. This suggests that the time course of NT-proBNP level may be positively influenced by early tirofiban administration and could potentially be dependent on the effectiveness of microvascular reperfusion after PCI, an outcome in which early tirofiban administration has a proven role.[6] This may be relevant considering that in patients with heart failure a change in NT-proBNP has been recently associated with a change in the subsequent risk of cardiovascular mortality and heart failure hospitalisation.[29]

Finally, measurement of NT-proBNP has become easy to perform and fast; its early measurement in the ambulance setting, aimed at stratifying patients and guiding early antiplatelet therapy, could represent a possible new strategy to be tested in further studies. Further prospective evaluation of high-risk subgroups identified by elevated NT-proBNP during the acute STEMI phase is warranted.

LIMITATIONS

This is a post hoc analysis of a randomised trial, therefore, our conclusions should be considered as exploratory. NT-proBNP levels were drawn at variable periods after onset of symptoms, therefore it has to be noted that some patients with the highest values of NT-proBNP at admission may include a subgroup of patients with a long ischaemia time in which the benefit of early GPI treatment remains uncertain.[30] Despite the fact that the prognostic value of NT-proBNP above the median was independent from ischaemia time, further studies are warranted to evaluate the efficacy of early tirofiban administration in subgroup presenting with long ischaemia time and high level of NT-proBNP. Moreover, this study was performed with clopidogrel, which is not the contemporary guideline-recommended oral therapy for primary PCI. Therefore, the results cannot be directly translated to patients treated with novel P2Y12 inhibitor. Finally, baseline NT-proBNP measurements were made at admission (before angiography) when tirofiban was already started; although the time between tirofiban administration and first NT-proBNP measurement was very short, we cannot exclude a small effect of the drug on the baseline values of NT-proBNP.

CONCLUSIONS

In patients with STEMI, NT-proBNP level above the median on admission independently predicts long-term (5-year) mortality. Patients with NT-proBNP levels above the median who were treated with prehospital treatment with tirofiban, as compared with placebo, had significantly reduced 30-day and 1-year mortality rates. Early tirofiban administration may be particularly effective in reducing mortality in high-risk patients, as identified by higher admission levels of NT-proBNP. This finding should be confirmed in other studies.

Key messages

What is already known on this subject?
Large randomised trials, conducted to explore the benefits from adjunctive glycoprotein IIb/IIIa inhibitor (GPI) administration in patients with ST elevation myocardial infarction (STEMI), showed conflicting results. The identification of patients who may particularly benefit from GPI administration is important in the ongoing search for a more tailored and optimised therapy for patients with STEMI.

What might this study add?
We have shown that a high-risk subset of patients, as identified by higher levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) upon presentation, may derive particular benefit from early GPI treatment in terms of reduced short-term and long-term mortality, without a significant increase in either major or minor bleeding complications.

How might this impact on clinical practice?
Our findings may help further refine the identification of patients likely to derive the greatest benefit from prehospital GPI administration. Early NT-proBNP measurement aimed at stratifying patients and guiding early antiplatelet therapy could represent a possible new strategy to be tested in further studies.

Contributors All authors have contributed significantly to the paper, in particular: EF, AWJVH: conception and design of the paper; EF, SK, MWK, AWJVH: drafting of the manuscript; EK: provided statistical expertise and analysis of data; DAS, JMTB, KGVH, EG, JPO, CH: revising critically the manuscript for important intellectual content.

Competing interests None declared.

Ethics approval The On-Time 2 trial was approved by the central Medical Ethics Review Committee (METC) of the Isala Ziekenhuizen of Zwolle (Netherlands) and by all local ethics committees involved.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993;329:1615–22.
2 Windecker S, Kolh P, Alfonso F, *et al*. ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;2014:2541–619.
3 Valgimigli M, Biondi-Zoccai G, Tebaldi M, *et al*. Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials. *Eur Heart J* 2010;31:35–49.
4 De Luca G, Gibson CM, Bellandi F, *et al*. Early glycoprotein IIb-IIIa inhibitors in primary angioplasty (EGYPT) cooperation: an individual patient data meta-analysis. *Heart* 2008;94:1548–58.
5 Herrmann HC, Lu J, Brodie BR, *et al*. Benefit of facilitated percutaneous coronary intervention in high-risk ST-segment elevation myocardial infarction patients presenting to nonpercutaneous coronary intervention hospitals. *JACC Cardiovasc Interv* 2009;2:917–24.
6 Van't Hof AW, Ten Berg J, Heestermans T, *et al*. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet* 2008;372:537–46.
7 ten Berg JM, van't Hof AW, Dill T, *et al*. Effect of early, pre-hospital initiation of high bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short- and long-term clinical outcome. *J Am Coll Cardiol* 2010;55:2446–55.
8 Huber K, Holmes DR, van't Hof AW, *et al*. Use of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention: insights from the APEX-AMI trial. *Eur Heart J* 2010;31:1708–16.
9 Stone GW, Grines CL, Cox DA, *et al*. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002;346:957–66.
10 Ellis SG, Tendera M, de Belder MA, *et al*. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 2008;358:2205–17.
11 Stone GW, Witzenbichler B, Guagliumi G, *et al*. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008;358:2218–30.
12 Mehilli J, Kastrati A, Schulz S, *et al*. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation* 2009;119:1933–40.
13 Le May MR, Wells GA, Glover CA, *et al*. Primary percutaneous coronary angioplasty with and without eptifibatide in ST-segment elevation myocardial infarction: a safety and efficacy study of integrilin-facilitated versus primary percutaneous coronary intervention in ST-segment elevation myocardial infarction (ASSIST). *Circ Cardiovasc Interv* 2009;2:330–8.
14 De Luca G, Navarese E, Marino P. Risk profile and benefits from gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. *Eur Heart J* 2009;30:2705–13.
15 Gill D, Seidler T, Troughton RW, *et al*. Vigorous response in plasma N-terminal pro-brain natriuretic peptide (NT-BNP) to acute myocardial infarction. *Clin Sci* 2004;106:135–9.
16 de Lemos JA, Morrow DA, Bentley JH, *et al*. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001;345:1014–21.
17 Heeschen C, Hamm CW, Mitrovic V, *et al*. N-terminal pro-B-type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes. *Circulation* 2004;110:3206–12.
18 James SK, Lindahl B, Siegbahn A, *et al*. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a global utilization of strategies to open occluded arteries (GUSTO)-IV substudy. *Circulation* 2003;108:275–81.
19 Galvani M, Ottani F, Oltrona L, *et al*. N-terminal pro-brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes. *Circulation* 2004;110:128–34.
20 Grabowski M, Filipiak KJ, Karpinski G, *et al*. Serum B-type natriuretic peptide levels on admission predict not only short-term death but also angiographic success of procedure in patients with acute ST-elevation myocardial infarction treated with primary angioplasty. *Am Heart J* 2004;148:655–62.
21 Hong SN, Ahn Y, Hwang SH, *et al*. Usefulness of preprocedural N-terminal pro-brain natriuretic peptide in predicting angiographic no-reflow phenomenon during stent implantation in patients with ST-segment elevation acute myocardial infarction. *Am J Cardiol* 2007;100:631–4.
22 van't Hof AW, Hamm C, Rasoul S, *et al*. Ongoing tirofiban in myocardial infarction evaluation (On-TIME) 2 trial: rationale and study design. *EuroIntervention* 2007;3:371–80.
23 Rao AK, Pratt C, Berke A, *et al*. Thrombolysis in myocardial infarction (TIMI) Trial – phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol* 1988;11:1–11.
24 Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med* 1998;339:321–8.
25 Goetze JP, Christoffersen C, Perko M, *et al*. Increased cardiac BNP expression associated with myocardial ischemia. *Faseb J* 2003;17:1105–7.
26 Khan SQ, Quinn P, Davies JE, *et al*. N-terminal pro-B-type natriuretic peptide is better than TIMI risk score at predicting death after acute myocardial infarction. *Heart* 2008;94:40–3.
27 Schellings DA, Adiyaman A, Giannitsis E, *et al*. Early discharge after primary percutaneous coronary intervention: the added value of N-terminal pro-brain natriuretic peptide to the Zwolle risk score. *J Am Heart Assoc* 2014;3:e001089.
28 Verouden NJ, Haeck JD, Kuijt WJ, *et al*. Comparison of the usefulness of N-terminal pro-brain natriuretic peptide to other serum biomarkers as an early predictor of ST-segment recovery after primary percutaneous coronary intervention. *Am J Cardiol* 2010;105:1047–52.
29 Zile MR, Claggett BL, Prescott MF, *et al*. Prognostic implications of changes in N-terminal Pro-B-type natriuretic peptide in patients with heart failure. *J Am Coll Cardiol* 2016;68:2425–36.
30 Heestermans T, van't Hof AW, ten Berg JM, *et al*. The golden hour of prehospital reperfusion with triple antiplatelet therapy: a sub-analysis from the ongoing tirofiban in myocardial evaluation 2 (On-TIME 2) trial early initiation of triple antiplatelet therapy. *Am Heart J* 2010;160:1079–84.