NT-proBNP level before primary PCI and risk of poor myocardial reperfusion: Insight from the On-TIME II trial

Enrico Fabris, MD, PhD[a,b], Jurrien M. ten Berg, MD, PhD[c], Renicus S. Hermanides, MD, PhD[a], Jan Paul Ottervanger, MD, PhD[a], Jan Henk E Dambrink, MD, PhD[a], AT Marcel Gosselink, MD, PhD[a], Gianfranco Sinagra, MD[b], Petra C. Koopmans, PhD[d], Evangelos Giannitsis, MD, PhD[e], Christian Hamm, MD, PhD[f], and Arnoud W.J. van 't Hof, MD, PhD[a,g,h] ***Zwolle, The Netherlands; Trieste, Italy; Nieuwegein, The Netherlands; Heidelberg, Germany; Bad Nauheim, Germany; Maastricht, The Netherlands; Heerlen, The Netherlands***

Background N-terminal fragment of the brain natriuretic peptide prohormone (NT-proBNP), a marker for neurohumoral activation, has been associated with adverse outcome in patients with myocardial infarction. NT-proBNP levels may reflect extensive ischemia and microvascular damage, therefore we investigated the potential association between baseline NT-proBNP level and ST-resolution (STR), a marker of myocardial reperfusion, after primary percutaneous coronary intervention (pPCI).

Methods we performed a post-hoc analysis of the On-TIME II trial (which randomized ST-elevation myocardial infarction (STEMI) patients to pre-hospital tirofiban administration vs placebo). Patients with measured NT-proBNP before angiography were included. Multivariate logistic-regression analyses was performed to investigate the association between baseline NT-proBNP level and STR one hour after pPCI.

Results Out of 984 STEMI patients, 918 (93.3%) had NT-proBNP values at baseline. Patients with STR <70% had higher NT-proBNP values compared to patients with complete STR (>70%) [Mean ±SD 375.2 ±1021.7 vs 1007.4 ±2842.3, Median (IQR) 111.7 (58.4-280.0) vs 168.0 (62.3-601.3), $P < .001$]. At multivariate logistic regression analysis, independent predictors associated with higher risk of poor myocardial reperfusion (STR <70%) were: NT-proBNP (OR 1.17, 95%CI 1.04-1.31, $P = .009$), diabetes mellitus (OR 1.87, 95%CI 1.14-3.07, $P = .013$), anterior infarct location (OR 2.74, 95% CI 2.00-3.77, $P < .001$), time to intervention (OR 1.06, 95%CI 1.01-1.11, $P = .021$), randomisation to placebo (OR 1.45, 95%CI 1.05-1.99, $P = .022$).

Conclusions In STEMI patients, higher baseline NT-proBNP level was independently associate with higher risk of poor myocardial reperfusion, supporting the potential use of NT-proBNP as an early marker for risk stratification of myocardial reperfusion after pPCI in STEMI patients. (Am Heart J 2021;233:78–85.)

In patients with ST-elevation myocardial infarction (STEMI), early recanalization of the infarct-related artery and achievement of early myocardial reperfusion is one of the main goals for improving prognosis, and timely reperfusion with primary percutaneous coronary intervention (PCI) is considered the treatment of choice.[1] The Ongoing Tirofiban In Myocardial Infarction Evaluation II (On-TIME II) trial[2] randomized patients undergoing primary PCI to pre-hospital tirofiban administration vs placebo. In most of these patients, levels of N-terminal fragment of the brain natriuretic peptide prohormone (NTproBNP), on admission before angiography were measured. The NTproBNP, an established marker for neurohumoral activation and heart failure, has been shown to liberate from myocardium following acute myocardial infarction,[3] and elevated levels have

From the [a]Department of Cardiology, Isala Heart Center, Zwolle, The Netherlands, [b]Cardiovascular Department, University of Trieste, Trieste, Italy, [c]Department of Cardiology, St Antonius Hospital, Nieuwegein, The Netherlands, [d]Diagram CRO, Zwolle, The Netherlands, [e]Department of Cardiology, Universitats Klinik, Heidelberg, Germany, [f]Department of Cardiology, Kerckhoff Klinik, Bad Nauheim, Germany, [g]Maastricht University Medical Center, Department of Cardiology, Maastricht, The Netherlands, [h]Zuyderland Medical Center, Department of Cardiology, Heerlen, The Netherlands

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Reprint requests: Arnoud van 't Hof, MD, PhD, Head of the department of Interventional Cardiology, Maastricht University Medical Center and Zuyderland Medical Center in Heerlen, P Debyelaan 25 | 6229 HX Maastricht, Locatie: MUMC+, level 3, Postbus 5800 | 6202 AZ , Maastricht, The Netherlands.

E-mail address: arnoud.vant.hof@mumc.nl.

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been associated with poor outcomes also in the setting of acute coronary syndrome.[4-10] NT-proBNP levels may reflect ischemic and microvascular damage, however, whether NTproBNP level before angiography may be associated with poor myocardial reperfusion expressed by ST-segment resolution (STR), a surrogate for tissue-level reperfusion,[11] is poorly studied. Therefore, we undertook a post hoc analysis of the On-TIME II trial in order to investigate the potential association between NT-proBNP level on admission before angiography, and STR 1 hour after primary PCI

Methods

Study design

The On-TIME II trial (ISRCTN06195297) was an international, multicenter, prospective, placebo-controlled, double-blind, randomized trial. The rationale and design of the study have been previously described[12] and the results of the study, showing that early initiation of tirofiban improved STR compared to placebo, have been previously published.[2] In brief, the trial randomized patients undergoing primary PCI to pre hospital tirofiban administration (25 mcg/kg bolus and 0.15 mcg/kg/min maintenance infusion for 18 h) vs placebo. Tirofiban is a reversible antagonist of fibrinogen that binds to the glycoprotein IIb/IIIa receptor, thereby blocking the final common pathway to platelet aggregation. In the ambulance or referring center, all patients also received a bolus of 5,000 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 (2,500 IU) was only given if the activated clotting time was less than 200 sec. 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.

Study population

The study population consisted of patients with STEMI who were candidates for primary PCI treatment. Eligible patients were men and women, 21 to 85 years of age, with symptoms of acute myocardial infarction (MI) for >30min but <24 h, and ST-segment elevation of >1 mV in 2 adjacent electrocardiogram leads. Exclusion criteria were known severe renal dysfunction (defined as glomerular filtration rate <30 mL/min or serum creatinine >200 mmol/L [>2•5 mg/dL]), 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 center. The study protocol was approved by all local ethics committees involved. In this posthoc analysis only patients with measured NT-proBNP before angiography were included. This study was partly funded by Medicure. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Blood samples for NT-proBNP measurement

Blood samples were taken on admission before angiography and NT-proBNP was measured by a sandwich immunoassay on a fully automated analyzer (NT-pro BNP ELECSYS 2010, Roche Diagnostics, Mannheim, Germany).

Main outcome

The main outcome investigated in this post hoc analysis was myocardial reperfusion after primary PCI, expressed as STR. Indeed, the electrocardiographic analysis of STR is a well-established and easy method to assess myocardial perfusion after reperfusion therapy for STEMI.[13] All ECGs were analyzed as previously described.[2] Briefly, the sum of ST-segment deviation was measured 20 milliseconds after the end of the QRS complex. The analysis of STR was based on the comparison between the cumulative millimeters of ST-segment deviation at pre- and postprocedural (1 hour) ECGs. Patients were divided into three groups of STR: complete: >70% resolution; partial: >30% but <70% resolution; and no resolution: <30% resolution). Poor myocardial reperfusion was defined as no or partial STR (<70%). An independent core lab (Diagram BV, Zwolle, Netherlands) analyzed all ECGs.

Statistical analysis

Continuous data were expressed as mean ± SD or median with interquartile range. Categorical data were expressed as percentages. Categorical variables were analyzed with the $\chi 2$ test or Fischer's exact test, and continuous variables with the Mann-Whitney *U*-test (2 sided). Values of $P < .05$ were considered statistically significant. We performed uni and multivariable logistic regression analyses, in order to investigate the potential association between baseline NTproBNP level and STR 1 hour after primary PCI (No or Partial ST Resolution versus Complete ST resolution).

Baseline NTproBNP level and appropriate predictors that were found to be significantly associated with STR 1 hour after primary PCI (P value <.05) at univariable analysis were then entered into a multivariable logistic regression model, using backward selection. NTproBNP (divided by 1,000) was logarithmically transformed and was entered as a continuous variable into the multivariate model. We did a graphical check on the assumption that there is a linear relationship between baseline NT-proBNP and the logit of No or Partial ST resolution. The logit function is $\text{logit}(p) = \log(p/(1-p))$, where P is the probability of No or Partial ST resolution.

Table I. Baseline characteristics of patients with a baseline NTproBNP level <= median versus > median*

	NT-proBNP level <= median (*N*=459)	NT-proBNP level > median (*N*=459)	*P*-value
Age (years)	57.3±9.9	66.3±11.8	<.001
Male gender	384/459 (83.7%)	311/459 (67.8%)	<.001
Current smoking	246/456 (53.9%)	185/456 (40.6%)	<.001
Diabetes mellitus	42/458 (9.2%)	64/459 (13.9%)	.024
Body mass index (kg/m2)	27.2±3.8	26.4±3.6	.009
Hypertension	113/459 (24.6%)	195/459 (42.5%)	<.001
Hypercholesterolaemia	111/457 (24.3%)	133/459 (29.0%)	.109
Killip>I	10/458 (2.2%)	31/458 (6.8%)	<.001
Prior myocardial infarction	25/458 (5.5%)	52/458 (11.4%)	.001
Prior CABG	6/459 (1.3%)	11/459 (2.4%)	.221
Prior PCI	31/459 (6.8%)	52/459 (11.3%)	.016
Anterior infarct location	164/409 (40.1%)	177/405 (43.7%)	.297
Time to intervention*	152 (122; 202)	193 (137; 292)	<.001
Heart rate > 100 bpm	15/456 (3.3%)	35/455 (7.7%)	.004
Systolic blood pressure < 100 mmHg	32/453 (7.1%)	33/456 (7.2%)	.919
Randomisation to Tirofiban	237/459 (51.6%)	227/459 (49.5%)	.509

Median=137

All analyses were performed according to the intention-to-treat principle. Statistical analysis was performed with PASW Statistics 24 (SPSS Inc, Chicago, Illinois).

Results

The On-TIME II trial recruited a total of 984 patients who were randomized to either placebo or tirofiban treatment. There were 918 (93.3%) patients with samples available for NT-proBNP at baseline. Patients with baseline NTproBNP level above the median value exhibited a higher risk profile compared to patients with level below the median, as presented in Table I. Indeed, patients with baseline NT-proBNP level above the median were older, more frequently female, presented higher rate of diabetes, hypertension, history of myocardial infarction, history of PCI, Killip class > 1, had a higher baseline heart rate and a longer time to intervention as compared to patient with baseline NT-proBNP levels below the median who had a higher BMI and were more frequently smokers.

876 patients had available STR evaluation after one hour after PCI. Interestingly patients with poor myocardial reperfusion (no or partial STR) had higher baseline NT-proBNP values compared to patients with complete STR (Mean ± SD 375.2 ± 1021.7 vs 1007.4 ± 2842.3, Median (IQR) 111.7 (58.4-280.0) vs 168.0 (62.3-601.3), *P* <.001) (Table II).

Moreover, patients with poor myocardial reperfusion were older, presented higher rate of diabetes, hypertension, Killip class > 1, Prior myocardial infarction, anterior infarct location, longer time to intervention and higher heart rate as compared to patient with complete STR who were more frequently smokers (Table II). Baseline cumulative ST deviation was not related to baseline Log NTproBNP (per 1000) (Pearson $r = 0.031$), see Supplementary Figure 1.

Predictors of myocardial reperfusion

Univariate logistic regression analysis is presented in Table III. At multivariate logistic regression analysis, independent predictors associated with higher risk of poor myocardial reperfusion after primary PCI were: baseline logarithmic (Log) NT-proBNP (OR 1.17, 95%CI 1.04-1.31, *P* = .009), diabetes mellitus (OR 1.87, 95%CI 1.14-3.07, *P* =.013), anterior infarct location (OR 2.74, 95% CI 2.00-3.77, *P* <.001), time to intervention (OR 1.06, 95%CI 1.01-1.11, *P* =.021), randomization to placebo (OR 1.45, 95%CI 1.05-1.99, *P* = .022). Conversely current smoking was associated with lower risk of poor myocardial reperfusion (OR 0.66, 95%CI 0.48-0.91, *P* = .011) (Table III).

The relationship between baseline NTproBNP level and the logit of poor myocardial reperfusion was linear (Figure 1), ROC curve is presented in Supplementary Figure 2. These independent variables were confirmed also when an ordinal logistic regression with 3 categories of STR post PCI (Complete versus Partial versus No Resolution) was performed, (Supplementary Table 1).

Interestingly, at multivariate analysis higher baseline Log NTproBNP, was independently associated with poor reperfusion as expressed as TIMI <3 post PCI (OR 1.29, 95% CI 1.10-1.53, *P* = .002), (Supplementary Table 2). Moreover, higher baseline Log NTproBNP was independently associated with poor reperfusion as expressed as Myocardial Blush grade (MBG) <3 (OR 1.25, 95% CI 1.10-1.43), *P* =.001 (supplementary table 3). Finally, higher baseline Log NTproBNP, was independently associated with a composite of Death and/or Recurrent MI and/or Urgent target vessel revascularization at 30 days follow-

Table II. Baseline characteristics by ST resolution post PCI‡.

		Complete ST resolution (n=550)	No or Incomplete ST resolution (N=326)	p-value
NT-proBNP baseline	Mean ± SD	375.2 ± 1021.7	1007.4 ± 2842.3	<0.001
	Median (IQR)	111.7 (58.4-280.0)	168.0 (62.3-601.3)	
Age (years)		60.9 ± 11.0	62.3 ± 12.7	0.049
Male gender		408/550 (74.2%)	256/326 (78.5%)	0.147
Current smoking		284/548 (51.8%)	134/324 (41.4%)	0.003
Diabetes mellitus		49/549 (8.9%)	51/326 (15.6%)	0.003
Body mass index (kg/m2)		26.7 ± 3.8	26.8 ± 3.5	0.623
Hypertension		168/550 (30.5%)	125/326 (38.3%)	0.018
Hypercholesterolaemia		131/549 (23.9%)	96/325 (29.5%)	0.064
Killip>I		16/550 (2.9%)	20/325 (6.2%)	0.020
Prior myocardial infarction		34/549 (6.2%)	33/326 (10.1%)	0.035
Prior CABG		6/550 (1.1%)	8/326 (2.5%)	0.120
Prior PCI		40/550 (7.3%)	33/326 (10.1%)	0.140
Anterior infarct location		168/516 (32.6%)	170/326 (58.0%)	<0.001
Time to intervention*		161 (124-230)	178 (129-274)	0.004
Heart rate > 100 bpm		21/547 (3.8%)	24/321 (7.5%)	0.020
Systolic blood pressure < 100 mmHg		39/545 (7.2%)	23/321 (7.2%)	0.996
Randomisation to Tirofiban		286/550 (52.0%)	150/326 (46.0%)	0.087

‡ ST resolution diagnosis-1 h after angiography/PCI (see Lancet manuscript Table II)
* From onset of symptoms to intervention in minutes, median (25^{th} 75^{th} IQR)

Table III. Univariate and Multivariate model for poor myocardial reperfusion (Post PCI STR <70%)

	Univariate logistic regression^		Multivariate logistic regression^	
	OR (95% CI) of No or Partial ST Resolution versus Complete ST resolution‡	p-value	OR (95% CI) of No or Partial ST Resolution versus Complete ST resolution‡	p-value
Log Baseline NTproBNP	1.28 (1.16-1.42)ǂ	<0.001	**1.17 (1.04-1.31)** ǂ	**0.009**
Age (years)	1.01 (1.00-1.02)	0.081		
Male gender	1.27 (0.92-1.76)	0.147		
Current smoking	0.66 (0.50-0.87)	0.003	**0.66 (0.48-0.91)**	**0.011**
Diabetes mellitus	1.89 (1.24-2.88)	0.003	**1.87 (1.14-3.07)**	**0.013**
Body mass index (kg/m2)	1.01 (0.97-1.05)	0.570		
Hypertension	1.41 (1.06-1.89)	0.018		
Hypercholesterolaemia	1.34 (0.98-1.82)	0.065		
Killip>I	2.19 (1.12-4.29)	0.022		
Prior myocardial infarction	1.71 (1.03-2.81)	0.036		
Prior CABG	2.28 (0.78-6.63)	0.130		
Prior PCI	1.44 (0.89-2.33)	0.142		
Anterior infarct location	2.86 (2.13-3.85)	<0.001	**2.74 (2.00-3.77)**	**<0.001**
Time to intervention	1.08 (1.03-1.12)¶	<0.001	**1.06 (1.01-1.11)** ¶	**0.021**
Heart rate > 100 bpm	2.02 (1.11-3.70)	0.022		
Systolic blood pressure < 100 mmHg	1.00 (0.59-1.71)	0.996		
Randomisation to Placebo	1.27 (0.96-1.67)	0.087	**1.45 (1.05-1.99)**	**0.022**

Log= logarithmic
^ Dependent variable: No or Partial ST Resolution versus Complete ST resolution
‡ ST resolution diagnosis-1 h after angiography/PCI
ǂ per 1000
¶ per hour

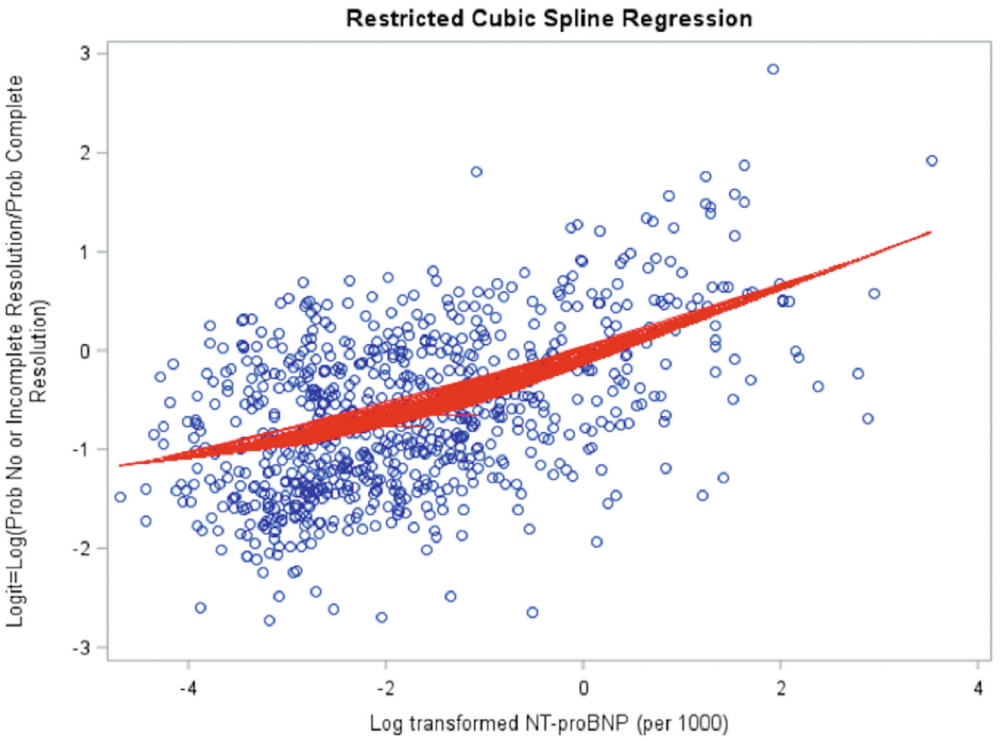
up (OR 1.50, 95% CI 1.23-1.82, P <.001) (Supplementary Table 4).

Discussion

In this post-hoc analysis of the On-TIME II trial, we have showed, in a large cohort of STEMI patients, that higher NTproBNP level before primary PCI is independently associated with a higher risk of poor myocardial reperfusion expressed by STR. Interestingly NTproBNP level was independently associated also with poor reperfusion expressed by TIMI <3 as well as MBG <3 post PCI.

These findings are particularly relevant considering the prognostic importance of the assessment of early

Figure 1



Cubic spline regression plot of the probability of no or incomplete resolution/ probability complete resolution and log-transformed Nt-proBNP/1,000.

reperfusion[14-17] and that higher levels of NT-proBNP have been associated with poor short and long term outcomes in the setting of acute myocardial infarction.[4-10,18,19] Indeed, higher baseline NTproBNP was independently associated with a composite of death/recurrent MI/urgent target vessel revascularization at 30 days follow-up. Moreover, in the On-TIME II population, baseline NT-proBNP level independently predicted also 5-year mortality.[10] In this perspective, a major explanation of the poor outcome observed in patients with heart failure at presentation[20,21] could be the association found in our study between the degree of NT-proBNP activation and myocardial perfusion.

In this current analysis, the independent association between baseline NTproBNP levels and STR may support the potential use NT-proBNP as an early marker for risk stratification of myocardial reperfusion after PCI in STEMI patients. Indeed, potential identification of patients who may derive the greatest benefit from more aggressive antithrombotic regimen is relevant for a tailored and optimized therapy for STEMI patients.

In a smaller study baseline NT-proBNP has been correlated to ST-segment recovery independently of other biochemical markers [22]; therefore, whether neurohumoral activation appears as a unifying feature for identify patients at higher risk, it has to be noted that an high-risk subset of patients, as identified by higher levels of NT-proBNP upon presentation, may derive particular benefit from early tirofiban treatment in terms of reduced short term and long term mortality.[10] The significant association between higher baseline NTproBNP level and poor myocardial reperfusion may support the concept that patients at higher risk of poor myocardial reperfusion could benefit from tirofiban administration, an outcome in which tirofiban has a proven role.[2]

Mechanisms behind the actual association between NT-proBNP and reperfusion remain speculative, however NT-proBNP elevation may be the expression of profound myocardial ischemia and extensive microvascular damage leading to relevant ventricular dysfunction. Importantly clinical characteristics (diabetes mellitus, killip class, heart rate, time to intervention) associated with higher baseline NT-proBNP levels reflect the ischemic burden of this high-risk population. Moreover, 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.[23] Higher level of NT-proBNP at presentation may be therefore a consequence of a larger infarction that may be associated with more severe damage of microcirculation and thus explain the impaired postprocedural myocardial perfusion observed in our study. This in line with the fact that anterior location of myocardial infarction and longer time to intervention were both associated with higher risk of poor myocardial reperfusion.

However, elevated NT-proBNP concentrations may also result directly from cardiac ischemia, even in the absence of left ventricular dysfunction.[24] Ischemic 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.

Our study provides insights into the biomarker pre-PCI risk profile for suboptimal myocardial reperfusion and it is in line with the recent study from Shavadia et al[25] that showed higher pre-PCI expression levels of platelet activation proteins and NT-proBNP were associated with impaired post-PCI microvascular reperfusion. Interestingly, a strong interbiomarker relationships were evident between NT-proBNP and proteins associated with inflammation, suggesting close relationships between myocardial stretch and inflammatory pathways in STEMI. These pathophysiologic mechanistic links in STEMI needs further exploration especially in patients with suboptimal reperfusion. Regardless of the mechanism, patients at risk of microvascular damage, may have particular benefit from adjunctive measures, such as early tirofiban administration which may also modulate NT-proBNP course.[26] 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 restoration of myocardial tissue reperfusion[2] and this analysis confirmed the higher risk of poor myocardial reperfusion in patients treated with placebo compared to patients treated with pre-H tirofiban administration. Furthermore, we confirmed that diabetic patients are at higher risk of poor tissue-level reperfusion despite prompt epicardial recanalization of the infarct-related artery.[16,27] In this perspective also diabetic patients are potential candidates who may benefit from adjuvant therapies, including intracoronary bolus of abciximab[28] and early high-dose tirofiban administration.[29]

Interestingly smoking was found to be associated with lower risk of poor myocardial reperfusion. This could be explained by theoretical protective mechanisms related to ischemic preconditioning, or may be determined by the effects of the carbon monoxide, a component of cigarette smoke which has vasodilator properties similar to nitric oxide.[30] Another mechanism may be related to the more thrombotic than atherogenic lesions due to the effects of smoking on platelets and endothelial function.

Finally, measurement of NT-proBNP has become easy to perform and fast[31]; 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. Additional research is required to develop further approaches to enhance myocardial perfusion and improve clinical outcomes in this high-risk subset of patients identified by elevated NT-proBNP during the acute STEMI.

Limitations

This is a post-hoc analysis of a randomized trial, therefore, our conclusions should be considered only as hypothesis generating. Only adequate randomized controlled trial can evaluate wheatear patients with high NT-proBNP level could have benefit from early aggressive antiplatelet therapy.

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. Baseline NT-proBNP measurements were made at admission (before angiography) when tirofiban was already started; although the time between tirofiban administration and first NTproBNP measurement was very short we cannot exclude a small effect of the drug on the baseline values of NT-proBNP. Finally, we cannot exclude that patients with higher baseline NT-proBNP level presenting with advanced cardiac damage may be less prone to receive complete reperfusion.

Conclusions

In a large cohort of STEMI patients, higher baseline NT-proBNP level was independently associated with higher risk of poor myocardial reperfusion, supporting the potential use of NT-proBNP as an early marker for risk stratification of myocardial reperfusion after PCI in STEMI patients. Further approaches to enhance myocardial perfusion in high-risk subset of patients are needed.

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Conflict of interest

Authors have no conflict of interest related to this manuscript to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2020.12.017.

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