Reperfusion before percutaneous coronary intervention in ST-elevation myocardial infarction patients is associated with lower N-terminal pro-brain natriuretic peptide levels during follow-up, irrespective of pre-treatment with full-dose fibrinolysis

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Aims
N-terminal pro-brain natriuretic peptide (NT-proBNP) levels predict outcomes in ST-elevation myocardial infarction patients treated with fibrinolysis or primary percutaneous coronary intervention (PCI). However, its role in facilitated PCI has not yet been assessed; it may be a tool to evaluate the lower event rates with primary PCI in ASSENT-4.

Methods and results
In ASSENT-4, 1667 patients were randomized to tenecteplase (TNK) followed by PCI or primary PCI alone. Baseline, discharge/Day 7, and 90-day NT-proBNP levels were available for 1008, 971, and 813 patients. Increasing quartiles of baseline NT-proBNP levels were associated with a higher risk of the combined endpoint of death, heart failure, and shock at 90 days and 1-year mortality (P < 0.001). Events were more common with TNK + PCI, regardless of baseline NT-proBNP quartile. When analysing baseline NT-proBNP as a continuous variable, no treatment interaction was observed for the primary endpoint (P = 0.17) or 1-year mortality (P = 0.08). Overall, NT-proBNP levels at Day 7 or 90 were not different between the two treatments. In patients with TIMI 2–3 flow before PCI, NT-proBNP at Day 90 was lower in PCI-only patients (P = 0.01), although no interaction was observed (P = 0.14). In TNK-pre-treated patients without reperfusion (TIMI 0–1) after PCI, NT-proBNP levels at Day 7 or 90 were not significantly higher than in PCI patients.

Conclusion
Baseline NT-proBNP predicts outcome at 90 days and 1 year in patients undergoing PCI with or without facilitation with TNK. A higher rate of reperfusion in lytic-pre-treated patients did not result in lower NT-proBNP during follow-up. Thus, baseline and subsequent NT-proBNP levels do not explain the lower mortality rate with PCI alone seen in this trial.

Keywords
STEMI • Facilitated PCI • BNP • Reperfusion

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Introduction

Brain natriuretic peptide (B-type, BNP) is an emerging cardiac hormone belonging to the family of natriuretic peptides and acts as a marker of ventricular function. Apart from being useful in the diagnosis and prognosis of chronic heart failure, BNP also predicts outcomes after non-ST-elevation and ST-elevation myocardial infarction (STEMI).\(^1\)\(^-\)\(^5\) N-terminal proBNP (NT-proBNP) measured early after an acute myocardial infarction predicts death and heart failure independently of left ventricular ejection fraction,\(^6\) and NT-proBNP levels at hospital discharge accurately predicts left ventricular dilation 1 year after myocardial infarction.\(^7\) In acute coronary syndrome patients, serial BNP measurements accurately predict the risk of death or congestive heart failure.\(^8\)\(^-\)\(^9\)

After the acute phase, elevated BNP reflects the extent of left ventricular dysfunction and adverse remodelling of non-infarcted myocardium\(^10\)\(^-\)\(^13\) and is related to subsequent adverse cardiac events.\(^14\)\(^-\)\(^15\) However, the relationship of BNP to reperfusion or patency of the infarct-related artery in STEMI remains unclear. Failure of fibrinolytic therapy to achieve epicardial or myocardial reperfusion has been shown to be associated with elevated BNP levels.\(^5\)\(^,\)\(^16\) Likewise, reocclusion of a previously successfully open infarct-related artery is associated with higher BNP levels during follow-up.\(^17\) The impact of fibrinolytic therapy before planned early percutaneous coronary intervention (PCI) on NT-proBNP levels after STEMI remains unclear, however.

In the Assessment of the Safety and Efficacy of a New Thrombo-lytic Regimen (ASSENT)-4 PCI study, full-dose fibrinolysis followed by early planned PCI was associated with a higher risk of the primary 90-day composite endpoint of death, congestive heart failure, or shock compared with primary PCI alone.\(^18\) The reason behind these unexpected findings remains unclear, but possibly relates to suboptimal concomitant antithrombotic therapy with subsequent reocclusion, or to shorter than expected treatment delays, or other unexplored pathophysiological processes.

In a pre-specified substudy of the ASSENT-4 PCI trial, we hypothesized that the natriuretic peptide system would offer a unique insight into the mechanisms through which primary PCI and facilitated PCI differ; more specifically, we assumed that compared with primary PCI alone, pre-treatment with a lytic would result in better pre-PCI reperfusion and a reduction in myocardial necrosis and hence cardiogenic shock or heart failure and that this would result in treatment-dependent differences in NT-proBNP. In the present analysis, we investigated whether NT-proBNP levels at randomization, discharge (or Day 7), and at 90 days were related to epicardial reperfusion before and after PCI. Furthermore, the utility of these three sequential measurements of NT-proBNP was explored in relation to 1-year outcome in a large contemporary high-risk STEMI population.

Methods

The ASSENT-4 PCI protocol has been described before.\(^18\) Briefly, 1667 patients with high-risk STEMI presenting within 6 h to tertiary care hospitals, community hospitals without PCI facilities and ambulances, were randomized to full-dose weight-adjusted tenecteplase (TNK) followed by early planned PCI vs. primary PCI alone. Per protocol, clopidogrel was started after stenting, and the administration of glycoprotein IIb/IIIa inhibitors was prohibited in lytic-treated patients. The trial was halted prematurely because of higher in-hospital mortality in the combination therapy arm.

Core NT-proBNP and angiographic measures

NT-proBNP samples were collected at randomization, discharge or Day 7 (whichever came first), and Day 90. Samples were collected in plastic tubes, frozen at \(-20^\circ\)C, and batch shipped after collection of the last sample. N-terminal proBNP was measured centrally in the clinical core lab (University Hospitals Leuven, Belgium) using the Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, IN, USA; coefficient of variation 3.38% at 134.5 pg/mL and 2.76% at 5087.5 pg/mL). TIMI flow perfusion grades before and after the index PCI were analysed blindly by the AngioCore Lab, University Hospital Gasthuisberg, Leuven, Belgium.

Statistical methods

NT-proBNP measurements and 1-year mortalities were pre-specified per protocol. The primary combined endpoint was death, and centrally adjudicated congestive heart failure or cardiogenic shock at 90 days, for a given subject. Subjects were categorized in quartiles according to their baseline NT-proBNP value. Descriptive statistics for baseline characteristics are presented for each quartile. Differences between the quartiles were tested with a \(\chi^2\) or Kruskal–Wallis test, whichever was appropriate. \(\chi^2\) analysis was used to examine the difference in stratified BNP levels and the primary endpoint or 1-year mortality among the quartiles. Kaplan–Meier survival curves with a log-rank test were used to compare 1-year survival curves and time to the 90-day primary endpoint in the different NT-proBNP level quartiles. In addition, mean NT-proBNP levels were compared between treatment groups for pre-specified (per protocol) subgroups of patients. To satisfy statistical conditions, a logarithmic transformation was performed for analyses using continuous NT-proBNP levels at Day 7 or discharge and Day 90. Finally, a multivari-able logistic regression was used to predict 90-day primary outcome or 1-year mortality. Variables included in the multivariable model were clinically statistically important variables from prior studies (age, weight, gender, systolic blood pressure, time from symptom onset to randomization, infarct localization, Killip class or congestive heart failure at randomization, history of hypertension, or diabetes) and NT-proBNP as a continuous covariate.\(^2\)\(^-\)\(^3\) The statistical analysis was performed using SAS version 9.1.3 (Cary, NC, USA). Testing was done two-sided, and a \(P\)-value of \(P < 0.05\) was considered significant.

Results

N-terminal pro-brain natriuretic peptide levels at randomization were available for 1008 patients at randomization, 971 patients at discharge/Day 7, and 813 patients at 90 days. Median baseline NT-proBNP was 152 pg/mL (25th–75th inter-quartile range 56–514 pg/mL). Median NT-proBNP values at discharge/Day 7 and 90 days were 696 pg/mL (316–1665) and 370 pg/mL (142–853), respectively. There was no significant difference in baseline characteristics, primary endpoint, or 1-year mortality rates between those with and without NT-proBNP measurements available at the different time points.

Baseline characteristics

Baseline characteristics according to NT-proBNP quartile at randomization are listed in Table 1. Patients in the upper quartiles of...
NT-proBNP were older, more frequently female, had higher heart rates, more advanced Killip class, and were more likely to have a history of hypertension, diabetes, previous myocardial infarction, and present with an anterior wall infarction. Symptom-to-treatment delays were significantly longer with increasing NT-proBNP levels. Half of the patients in the lowest NT-proBNP quartile were treated within 2 h of symptom onset vs. less than one in four patients (23.3%) in the upper quartile of NT-proBNP (Table 1). Of the 16.7% of the patients treated after 4 h from symptom onset, only 11.2% had an NT-proBNP level of <56 pg/mL, whereas 34.6% had levels >514 pg/mL.

### N-terminal pro-brain natriuretic peptide and outcome

Of the 1008 patients, 161 (16.0%) experienced a primary endpoint at 90 days: 56 (5.6%) died, 107 (10.6%) developed CHF, and 59 (5.9%) developed cardiogenic shock. Increasing quartiles of baseline NT-proBNP were associated with a higher risk of the primary combined endpoint at 90 days: 7.5% (n = 19), 9.6% (n = 24), 16.5% (n = 42), and 30.2% (n = 76), respectively. Kaplan–Meier analysis for the primary endpoint show diverging curves for the four quartiles during the first 2 months (log-rank P < 0.001, Figure 1A), with few events occurring beyond this time point. The primary 90-day endpoint occurred rarely and early after randomization in patients below the median NT-proBNP: 12 deaths (2.4%), 29 CHF (5.8%), and 17 shock (3.4%).

One-year mortality rate was 1.2% (n = 3), 5.0% (n = 12), 6.9% (n = 17) to 14.1% (n = 35) per increasing NT-proBNP quartile, respectively (log-rank P < 0.001, Figure 1B). Except for subjects in the first quartile, in whom there were no additional deaths beyond the initial in-hospital phase, mortality rates were similar beyond the first 2–3 months after randomization.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics per baseline N-terminal pro-brain natriuretic peptide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1 (&lt;56 pg/mL), n = 256</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53 ± 11</td>
</tr>
<tr>
<td>Age ≥75 years (%)</td>
<td>3.5</td>
</tr>
<tr>
<td>Female (%)</td>
<td>12.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79 ± 15</td>
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<tr>
<td>Weight &lt;60 kg (%)</td>
<td>5.9</td>
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<tr>
<td>Weight &gt;90 kg (%)</td>
<td>22.6</td>
</tr>
<tr>
<td>Killip class 1 (%)</td>
<td>95.7</td>
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<tr>
<td>Killip class 2 (%)</td>
<td>3.1</td>
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<tr>
<td>Killip class 3 (%)</td>
<td>0</td>
</tr>
<tr>
<td>Killip class 4 (%)</td>
<td>1.2</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>130 ± 22</td>
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<tr>
<td>Heart rate (b.p.m.)</td>
<td>73 ± 15</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>0.8</td>
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<tr>
<td>Anterior MI (%)</td>
<td>42.2</td>
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<tr>
<td>Hypertension (%)</td>
<td>34.4</td>
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<tr>
<td>Diabetes (%)</td>
<td>9.4</td>
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<tr>
<td>Previous MI (%)</td>
<td>5.9</td>
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<tr>
<td>TIMI flow grade after PCI (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>1</td>
<td>0.4</td>
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<tr>
<td>2</td>
<td>7.0</td>
</tr>
<tr>
<td>3</td>
<td>91.0</td>
</tr>
<tr>
<td>Symptom-to-UFH (min)</td>
<td>140 ± 68</td>
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<tr>
<td>Symptom-to-UFH ≤ 2 h (%), n</td>
<td>50.4 (119)</td>
</tr>
<tr>
<td>Symptom-to-UFH &gt;2 h (%), n</td>
<td>49.6 (117)</td>
</tr>
<tr>
<td>Ambulance (%)</td>
<td>9.4</td>
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<tr>
<td>Non-PCI site (%)</td>
<td>33.2</td>
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<tr>
<td>PCI site (%)</td>
<td>57.4</td>
</tr>
</tbody>
</table>

Values are mean ± SD unless otherwise stated. CHF, congestive heart failure; PCI, percutaneous coronary intervention; MI, myocardial infarction; BP, blood pressure; UFH, unfractionated heparin.
Treatment effect, outcome and baseline N-terminal pro-brain natriuretic peptide

We assessed the effect of treatment on 90-day outcome and 1-year mortality per NT-proBNP quartile (Figure 2). The combined 90-day outcome was worse for patients randomized to facilitated PCI across all baseline NT-proBNP quartiles ($P < 0.001$). However, there was no significant interaction between treatment and NT-proBNP by quartile ($P = 0.50$). Likewise, 1-year mortality was higher with facilitated PCI vs. primary PCI, especially in patients in the second and third quartile, but no significant interaction between treatment and NT-proBNP was observed as well (interaction $P = 0.39$).

When analysing baseline log-transformed NT-proBNP as a continuous variable, no significant treatment interaction was observed.
for the primary combined 90-day endpoint ($P = 0.17$, Figure 3A). A treatment interaction was found for 1-year mortality ($P = 0.04$), but it did not remain significant after adjusting for baseline risk factors ($P = 0.08$, Figure 3B).

### Treatment and N-terminal pro-brain natriuretic peptide levels at 90 days

We analysed the influence of treatment allocation on NT-proBNP levels at 90 days. N-terminal pro-brain natriuretic peptide levels were available for 813 subjects (49% of the overall population; 403 patients in the facilitated PCI arm and 410 patients in the primary PCI arm). In patients who survived 3 months after STEMI, log-NT-proBNP at 90 days was not significantly different for facilitated PCI vs. PCI-alone ($P = 0.47$). When analysing log-NT-proBNP as continuous variable, there was no significant interaction between treatment and NT-proBNP levels at 90 days for the primary combined endpoint as well ($P = 0.15$).

### TIMI flow grades and treatment
We also investigated whether epicardial blood flow before and after PCI had an impact on NT-proBNP levels during follow-up and whether this was influenced by pre-treatment with full-dose fibrinolysis. Figure 4 demonstrates that TIMI flow grades 0–1 before PCI was associated with higher NT-proBNP levels at Day 7/discharge and at Day 90, regardless of treatment allocation. In patients having TIMI grade 2 or 3 flow before PCI, NT-proBNP at Day 90 was significantly lower in patients treated with primary PCI alone compared with TNK-pre-treated patients ($P = 0.01$). There was no significant treatment interaction, however ($P = 0.14$).

N-terminal pro-brain natriuretic peptide levels during follow-up were especially high in patients without reperfusion after PCI (TIMI flow grades 0–1) compared with those with epicardial reperfusion (TIMI flow grades 2–3), irrespective of treatment. In patients with TIMI grades 0–1 flow after PCI, NT-proBNP levels at Day 7 as well as at 90 days were higher with TNK pre-treatment than...
Discussion

In this pre-specified analysis of the ASSENT-4 PCI study, we present the largest analysis on acute and post-discharge NT-proBNP levels in STEMI patients to date. In high-risk STEMI patients randomized to either TNK plus PCI vs. PCI alone, high baseline NT-proBNP levels were associated with a higher incidence of death, congestive heart failure, or cardiogenic shock at 90 days, and worse 1-year mortality. Patients treated with primary PCI alone had a significantly lower risk of the primary combined endpoint or death at 1 year, irrespective of NT-proBNP level at the time of randomization. N-terminal pro-brain natriuretic peptide levels at Day 90, however, were not significantly affected by treatment allocation. We also found that better TIMI flow grades before PCI were associated with significantly lower NT-proBNP levels at 3 months after randomization. Subjects with an open artery before PCI had significantly lower NT-proBNP levels at follow-up when receiving fibrinolytic therapy before PCI than PCI-only patients, although no significant treatment interaction was found. Likewise, follow-up NT-proBNP levels were higher in patients with incomplete epicardial reperfusion after the intervention, but this difference could also not be shown to be affected by treatment strategy.

Several studies have found an association between high NT-proBNP levels early after a myocardial infarction and adverse outcome, although the relative value of NT-proBNP levels taken later during follow-up remains unclear. In the present study, we found that baseline NT-proBNP levels predict 1-year mortality and the risk of death, congestive heart failure, or cardiogenic shock at 90-day follow-up. Higher baseline NT-proBNP levels are an especially strong negative prognostic marker during the first 2 months after randomization. The burden of readmissions for congestive heart failure in the highest BNP quartiles might be even higher than suggested by our analysis, however, as we only recorded death or the first occurrence of congestive heart failure or cardiogenic shock during the first 90 days; only death was captured from 90 days to 1 year. Also, our results indicate that the risk of adverse outcome after a myocardial infarction increases in a graded manner even at lower thresholds than previously suggested.

The 90-day combined endpoint was lower in patients treated with primary PCI alone than those randomized to facilitated PCI, regardless of NT-proBNP. In contrast, for 1-year mortality, the benefit of primary PCI only appeared to be present in patients within the two middle NT-proBNP quartiles; those with a very high or very low quartile had similar outcomes, regardless of what treatment strategy was used. Given the lack of significant treatment interaction for the primary endpoint, however, and because the number of subjects with very high NT-proBNP levels is relatively small, the implications of these findings remain unclear.

Reperfusion, as assessed with ST-segment resolution and TIMI flow grade, was associated with lower BNP levels during follow-up in primary PCI patients in a substudy of the COMMA trial. In the present analysis, we examined whether epicardial patency before PCI had an impact on NT-proBNP levels during follow-up, and found significantly higher NT-proBNP levels at discharge and Day 90 in patients with TIMI flow grades 0–1 vs. 2–3. When designing the BNP substudy, we hypothesized that earlier reperfusion in the combination therapy group would be associated with less extensive myocardial necrosis and hence with lower NT-proBNP values during follow-up. However, despite a substantially higher proportion of patients with TIMI flow grade 3 in the facilitated PCI group (56 vs. 20% in the primary PCI arm), NT-proBNP levels at discharge or Day 90 were not significantly...
lower in patients pre-treated with fibrinolysis. In contrast, primary PCI alone appeared to be associated with significantly lower NT-proBNP levels during follow-up in patients with TIMI flow grade 2 or 3 before PCI. These findings suggest that an early planned intervention in an already successfully reperfused infarct-related artery after fibrinolysis might not necessarily be beneficial. Although speculative, this might relate to prothrombotic side effects of fibrinolysis, especially when insufficiently opposed by adequate antithrombotic therapy as might has been the case in ASSENT-4 PCI.

Several limitations apply to the present analysis. First, baseline and serial NT-proBNP measurements were not available for all patients included in ASSENT-4 PCI; however, the overall trial population and our a priori substudy population were similar. Survival bias might impact our analysis of NT-proBNP levels later during follow-up. In addition, our study might have been underpowered to detect a significant treatment interaction. We also have only recorded the first occurrence of congestive heart failure or cardiogenic shock, which might lead to an underestimation of the prognostic power of NT-proBNP or the treatment effect. Finally, we were not able to run a formal analysis on the primary combined 90-day outcome since a large proportion of heart failure and shock events occurred before Day 7 or discharge.

In conclusion, we found that NT-proBNP at presentation is an excellent marker of unfavourable outcome in patients presenting with a myocardial infarction, even at relatively low cut-off values. The prognostic properties of baseline BNP measurements at the time of STEMI appear to be for the most part irrespective of the reperfusion strategy chosen, but should stimulate further risk-stratification efforts with NT-proBNP. Higher BNP values during follow-up in lytic-pre-treated patients with patent arteries before PCI also confirm that an early planned intervention after fibrinolysis might be harmful. These findings suggest that a more balanced approach of delaying PCI in successfully reperfused arteries and reserving immediate PCI only for occluded arteries after fibrinolysis plus clopidogrel might be wiser. This hypothesis is currently being tested prospectively in the Strategic Reperfusion (with Tenecteplase and Antithrombotic Treatment) Early after Myocardial Infarction (STREAM) study.

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**References**