Review

Natriuretic peptides in unstable coronary artery disease

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Received 1 March 2004; revised 5 June 2004; accepted 10 June 2004
Available online 14 August 2004

Patients with unstable coronary artery disease (CAD), i.e., unstable angina or non-ST-elevation myocardial infarction, vary widely in clinical presentation, prognosis and response to treatment. To select appropriate therapy, early risk stratification has become increasingly important. This review focuses on the emerging role of natriuretic peptides in the early assessment of patients with unstable CAD. We conclude that levels of brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are strongly associated to mortality and the risk of future congestive heart failure, and carry important prognostic information independent from previously known risk factors in unstable CAD. There are some data indicating that these markers can also be helpful in the selection of appropriate therapy in these patients but further studies are needed. Before a routine use of BNP or NT-proBNP in unstable CAD can be recommended, the cost-effectiveness of adding these new markers to the currently routine markers and their impact on selection of treatment needs further evaluation.

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KEYWORDS
Natriuretic peptide; Unstable angina; Myocardial Infarction; Prognosis

Introduction

Unstable coronary artery disease (CAD), i.e., unstable angina or non-ST-elevation myocardial infarction (MI), is the most common cause of admission to the coronary care unit and accounts for 60–70% of all admissions because of acute coronary syndrome.\textsuperscript{1,2} Patients with unstable CAD encompass a heterogeneous group that varies widely regarding severity of the underlying coronary artery disease, prognosis and response to treatment. Patients with the highest risk of subsequent events usually have the largest benefit of an intensified pharmacological treatment and early mechanical intervention.\textsuperscript{3,4} The prognosis for low-risk patients, on the other hand, is often difficult to improve further and these patients usually benefit more from a conservative management with a lower risk of side effects. Therefore, risk stratification is essential and should be initiated early and updated continuously throughout the hospital stay.

Early risk stratification is usually performed by the use of clinical background factors, clinical presentation, electrocardiography, and biochemical markers of myocardial damage.\textsuperscript{5} Markers of inflammation and renal function have also shown to be useful.\textsuperscript{6,7} Moreover, measurements of cardiac performance, such as left ventricular ejection fraction and wall motion index, have an important impact on the prognosis.\textsuperscript{8,9} Levels of natriuretic peptides have been shown to reflect cardiac per-
formance. This review focuses on the emerging role of these peptides in the early risk stratification of unstable CAD patients. For this purpose, we searched the Medline database using the key words natriuretic peptide, brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), together with unstable angina or myocardial infarction. Articles about BNP or NT-proBNP in patients with unstable CAD were reviewed. We also searched the references of the selected articles.

Natriuretic peptides

The biochemistry and physiology of natriuretic peptides have been thoroughly reviewed by several authors.10–13 There are two natriuretic peptides secreted from the heart. Atrial natriuretic peptide (ANP) is produced primarily in the cardiac atria, whereas brain (B-type) natriuretic peptide (BNP) is mainly synthesised in the ventricular myocardium. Both these peptides are produced as pro-hormones (proANP and proBNP), that upon secretion are split into biologically active peptides (ANP and BNP) and N-terminal pro-hormone fragments (NT-proANP and NT-proBNP). ProANP is released from storage granules, whereas the BNP regulation takes place during BNP gene expression, which can increase rapidly under appropriate conditions. ANP and BNP are released mainly in response to increased stretch or wall-tension and are broadly involved in the regulation of blood pressure, blood volume and sodium balance. The actions are performed by natriuresis, vasodilatation, and inhibition of the renin–angiotensin–aldosterone axis and the sympathetic nervous system. Natriuretic peptide receptor A (NPR-A), which is linked to the cGMP-dependent signaling cascade, mediates these effects. ANP and BNP are cleared by natriuretic peptide receptor C (NPR-C) as well as by degradation by neutral endopeptidase, whereas the N-terminal fragments have a renal clearance. As a result, the N-terminal pro-hormone fragments have a longer half-life than the biologically active hormones.

In disease states, BNP and NT-proBNP have a greater proportional rise than ANP and NT-proANP, and have therefore received most of the interest regarding their usefulness in clinical practice. Both markers are highly sensitive and fairly specific markers for diagnosing congestive heart failure (CHF) and to detect left ventricular dysfunction.14–19 Levels of BNP and NT-proBNP are related to the severity of disease and are strongly associated to outcome in patients with heart failure.20,21 They have also been found to be related to the subsequent response to treatment and have been suggested to be useful tools to guide treatment in heart failure patients.21,22 There is a close correlation between BNP and NT-proBNP levels.23 Although NT-proBNP has a longer half-life than BNP (60–120 vs. 20 min) and the fact that NT-proBNP has a greater incremental rise above baseline values during cardiac decompensation,23 studies have so far not revealed any differences regarding clinical utility.24,25

Unstable coronary artery disease

It has been known for some years that natriuretic peptides can be used for detection of left ventricular dysfunction after MI and that elevated levels of these peptides are related to a worse outcome.26–30 However, the first studies mainly included patients with ST-elevation MI. Not until recently have studies including patients with unstable CAD been published. Table 1 summarises the findings in these studies. The first published study was by de Lemos et al.31 BNP was measured in a cohort including 2525 patients with acute coronary syndrome, of which 1698 patients had unstable angina or non-ST-elevation MI. In the group with unstable CAD, the 10-month mortality increased with increasing levels of BNP, with a mortality of approximately 1% in the lowest quartile and 7–15% in the highest quartile. Later, the same research group validated these findings in another study,32 including 1676 patients with unstable CAD. In that study, a prospectively defined decision-limit of 80 ng/L was able to identify a group of patients with a 30-day and 6 months mortality of 5.0% and 8.4%, respectively, compared to 1.2% and 1.8% in the group with lower levels of BNP. Similar to the first study, the level of BNP was strongly associated to mortality even when adjusted for well-known risk factors, such as age, gender, diabetes, ST-segment depression, history of CHF, CHF at presentation and baseline level of troponin. BNP was also associated to the risk of subsequent CHF, whereas there was no significant association to the risk of future MI.

There are now four studies evaluating NT-proBNP in patients with unstable CAD. In the first study by our group,33 NT-proBNP was analysed on admission in a non-selected group of 755 patients (407 with unstable CAD) consecutively admitted to coronary care unit because of symptoms suggestive of an acute coronary syndrome and no ST-segment elevations. Patients were followed concerning death for 40 months (median). Compared to the lowest quartile, patients in the 2nd, 3rd, and 4th quartile had a relative risk (95%CI) of subsequent death of 4.2 (1.6–11.1), 10.7 (4.2–26.8) and 26.6 (10.8–65.5), respectively (Fig. 1). The predictive value of NT-proBNP was evident in patients with unstable CAD as well as in those with other cardiac or non-cardiac conditions. When added to a Cox regression model including clinical background factors, electrocardiography and troponin T, NT-proBNP levels were independently associated with prognosis. These findings were later confirmed in a study by Omland et al.,34 including 609 patients with ACS, of which 405 had unstable CAD. Patients with unstable CAD and an elevated NT-proBNP level had 3- to 5-fold increased mortality compared to those with lower levels of NT-proBNP. More important, the level of NT-proBNP was strongly associated to mortality even when adjusted for age, Killip class and left ventricular ejection fraction determined by echocardiography.

Our group, together with others, has recently reported the NT-proBNP substudy of the GUSTO-IV trial,35 including 6809 patients with unstable CAD. In this very large material, the associations between the NT-proBNP
<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Method</th>
<th>Median time from onset of symptoms (h)</th>
<th>Follow up</th>
<th>Cut-off (ng/L)</th>
<th>Mortality</th>
<th>Congestive heart failure</th>
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<tbody>
<tr>
<td>De Lemos31</td>
<td>2525 patients with ACS of which 1698 had unstable CAD</td>
<td>BNP</td>
<td>40</td>
<td>10 months</td>
<td>&lt;44/44–81/81–138/&gt;138</td>
<td>1%/3%/4.5%/7–15%</td>
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<tr>
<td>Morrow32</td>
<td>1676 patients with unstable CAD</td>
<td>BNP</td>
<td>?</td>
<td>30 d</td>
<td>&lt;80/&gt;80</td>
<td>1.2%/5.0%</td>
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<tr>
<td>Morrow32</td>
<td></td>
<td>BNP</td>
<td>6</td>
<td>6 months</td>
<td>&lt;80/&gt;80</td>
<td>1.8%/8.4%</td>
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<tr>
<td>Jernberg33</td>
<td>775 patients with suspected unstable CAD</td>
<td>NT-proBNP</td>
<td>6</td>
<td>35 months</td>
<td>&lt;113/113–400/401–1653/&gt;1653</td>
<td>2.6%/8.8%/23.2%/46.1%</td>
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<tr>
<td>Omland34</td>
<td>609 patients with ACS of which 405 had unstable CAD</td>
<td>NT-proBNP</td>
<td>&gt;72</td>
<td>51 months</td>
<td>&lt;545/&gt;545</td>
<td>RR (95%CI): 5.6 (2.2–14.5) in NSTEMI</td>
<td>1.8%/3.9%/7.7%/19.2%</td>
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<tr>
<td>James35</td>
<td>6609 patients with unstable CAD</td>
<td>NT-proBNP</td>
<td>9.5</td>
<td>12 months</td>
<td>&lt;238/238–668/669–1869/&gt;1869</td>
<td>RR (95%CI): 5.6 (2.2–14.5) in UAP</td>
<td>1.8%/3.9%/7.7%/19.2%</td>
</tr>
<tr>
<td>Jernberg44</td>
<td>1008 patients with unstable CAD treated non-invasively</td>
<td>NT-proBNP</td>
<td>39</td>
<td>24 months</td>
<td>Men: &lt;294/294–905/&gt;905</td>
<td>2.5%/2.7%/10.8%</td>
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<td>Women: &lt;395/395–1344/&gt;1344</td>
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<td>1011 patients with unstable CAD treated invasively</td>
<td>Men: &lt;294/294–905/&gt;905</td>
<td>1.4%/2.6%/7.2%</td>
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<td>Women: &lt;395/395–1344/&gt;1344</td>
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</table>

In all studies, the differences in outcome between the groups are statistically significant in overall tests.

a The minimum time all patients were followed.

b Only risk ratios stated for these subgroups.
levels and other patient characteristics were clearly outlined. Higher levels of NT-proBNP were related to age, hypertension, diabetes, renal dysfunction and previous history of cardiovascular disease. In the acute setting, the level of NT-proBNP was related to the magnitude of myocardial damage (i.e., level of troponin T) and inflammatory activity (i.e., level of C-reactive protein [CRP]). Again, there was an increase in mortality with higher levels of NT-proBNP, with significant separation of the survival curves already at 48 h (mortality in lowest vs. highest quartile: 0.2% vs. 1.4%). The survival rates continued to separate and at one-year follow-up the mortality was 1.8% in the lowest quartile and 19.2% in the highest. In a multiple logistic regression analysis, including a large number of covariates and other predictors, the NT-proBNP level continued to be an important predictor of outcome. The overall risk stratification was further improved when NT-proBNP was combined with a marker of renal dysfunction, myocardial damage or inflammation (Fig. 2). In univariable analysis, a higher level of NT-proBNP was also associated with a higher risk of future MI. However, after adjustment for the multitude of covariates, there remained no independent association between the level of NT-proBNP and the risk of subsequent MI.

Mechanisms behind the predictive value

The reason for the strong association between the BNP or NT-proBNP level and mortality in unstable CAD is so far not fully understood but probably includes several cooperating mechanisms. One reason seems to be that the level of natriuretic peptide is an indicator of several co-morbidities: age, hypertension, diabetes mellitus and renal dysfunction which are all associated with a worse outcome in unstable CAD. Secondly, an elevated BNP or NT-proBNP may reflect a permanent left ventricular dysfunction established prior to or during the current
episode of instability, which is an important predictor of outcome in patients with acute coronary syndromes. Previous studies have also shown that the neurohormonal response itself, including raised levels of NT-proBNP, is independently associated to mortality in patients with left ventricular dysfunction. Thirdly, the acute phase elevation of BNP and NT-proBNP can also reflect the temporary left ventricular dysfunction secondary to the acute ischaemic event with magnitude corresponding to the size of the jeopardised myocardium. Previous studies have demonstrated an elevation of BNP shortly after percutaneous coronary intervention and that the level of BNP is correlated to the size of the ischaemic territory. Thus, an elevated BNP or NT-proBNP level might be an indicator of a neurohormonal activation secondary both to reversible myocardial ischaemia and myocardial necrosis.

The lack of an independent association between the natriuretic peptide level and the risk of future MI is probably explained by the fact that BNP and NT-proBNP level are not related to processes that increases the likelihood of a new coronary plaque destabilisation or formation of coronary thrombi. In contrast, the BNP level has been shown to be associated to the risk of sudden death. Thus, an increased level of BNP or NT-proBNP may indicate an increased risk of ventricular arrhythmias, ventricular rupture, or terminal heart failure rather than MI.

**Cut-off value**

A single cut-off value can be convenient to use in clinical practice and in decision algorithms. Regarding BNP, a cut-off value of 80 ng/L has been suggested. In the study by Morrow et al., there was a step-wise relationship between increasing levels of BNP and mortality where the increase in mortality appeared at 80 ng/L (Fig. 3). In the large GUSTO IV substudy, on the other hand, there was a continuous increase in mortality with increasing NT-proBNP levels (Fig. 4).

One important issue is whether cut-off values should be related to age and gender. It is well known that both BNP and NT-proBNP levels increase with age and are higher in women. The reasons for the sex-related difference is still unclear. One reason is probably the higher prevalence of diastolic dysfunction found in older women. Hormone replacement therapy has also been shown to increase levels of natriuretic peptides in women, suggesting that the gender difference is partly due to oestrogenic action. The fact that the age-related mortality is lower in women than in men suggests that the reason for this gender-difference does not cause increased mortality. Therefore, gender differences should be considered when determining suitable cut-off values, especially in order to identify low risk patients. Since the higher levels of BNP and NT-proBNP found in the elderly are presumably explained by a higher prevalence of subclinical cardiac conditions, age-dependent cut-off values would not be necessary when using these methods for risk stratification.

The optimal decision limit depends on the purpose of using the analytical results. Therefore, based on available data two different decision limits might be proposed; one to identify low-risk patients and another to identify high-risk patients. The low-risk group would be defined as those with a BNP or NT-proBNP level lower than the upper reference limit in a healthy population. According to our data, the 97.5th percentile values for NT-proBNP in men and women below 65 years of age can be approximated to 200 and 300 ng/L, whereas these values are somewhat higher in those older than 65 (about 300 ng/L for men and 400 ng/L for women). For BNP, the reference values differ between assays and studies and there is a lack of standardisation, but seem to be in the same range as the cut-off value (80 ng/L) tested be Morrow et al. In the GUSTO IV substudy, the levels of NT-proBNP even below the upper reference limit in a healthy population were associated with an increased mortality. However, cut-off values below the reference...
value would probably lead to an unacceptably low specificity.

A cut-off value to identify the high-risk group, with a probably greater benefit from a more aggressive treatment strategy (including early revascularisation), is difficult to define and tends to be somewhat arbitrary. We suggest a level corresponding to an NT-proBNP level above 1000 ng/L. In the GUSTO IV substudy, a decision limit of 1000 ng/L identified 40% of the patients with a 1-year mortality of 15.3% compared to 3.4% for patients with lower levels of NT-proBNP, resulting in a sensitivity of 75% and a specificity of 63%. In the FAST-study, including an older population with higher mortality, this decision limit identified 33% of the patients with 35 months mortality of 43%, compared to 9% for patients with lower NT-proBNP levels (sensitivity 70% and specificity 77%). Finally, in the FRISC II trial, a cut-off value of 1000 ng/L identified 33% of the patients, who had a markedly higher 2-year mortality (8.6% vs. 2.5%, \( p < 0.001 \)). Thus, this decision limit identifies a definite high-risk group, which according to the FRISC II trial might have the greatest beneficial effect of early revascularisation (see also below).

**Should BNP and NT-proBNP be used in clinical practice**

To be clinically useful, a marker should meet several criteria. Firstly, the marker should have a significant additive value regarding diagnosis, pathophysiology and prognosis compared to pre-existing tests. Secondly, the marker should be helpful in the identification of patients who will benefit from a certain treatment strategy. Thirdly, the assay for the marker should be reliable and rapidly obtained. Fourthly, the use of the marker should be cost-effective. In unstable CAD, BNP and NT-proBNP meet the first and third criteria. Several studies have demonstrated the powerful association between these markers and the subsequent risk of death and CHF, and the assays used for these markers are both fast and reliable.

Regarding the use of BNP or NT-proBNP to guide the clinician to select an appropriate therapeutic regimen data are still limited. In the TACTICS-TIMI 18 trial, there was no appreciable difference in the reduction of death or MI by an invasive vs. conservative strategy in those with higher levels of BNP compared to those with lower levels. However, the markers do not predict the risk of future MI and the trial did not have the power to look at the reduction of mortality alone. In the FRISC 2 trial, on the other hand, patients with elevated NT-proBNP had a greater survival benefit of an early invasive strategy compared to those with lower NT-proBNP levels. An invasive strategy reduced the 2-year mortality by 3.6% from 10.8 to 7.2% \( (p = 0.11) \) in those with higher levels of NT-proBNP, whereas there was no effect in those with lower levels of NT-proBNP (Fig. 5). Interestingly, this apparent treatment effect was mainly present in patients with elevated markers of inflammation, with a 7.3% absolute reduction of mortality in the group with elevated interleukin-6 and NT-proBNP, while there was no significant reduction in mortality in patients with lower levels of NT-proBNP or interleukin-6. Thus, although these data need to be confirmed in future studies, they suggest that BNP and NT-proBNP might be useful to identify those unstable CAD patients with a mortality benefit by an early invasive management. Whether patients with
unstable CAD and high levels of natriuretic peptides will obtain any specific benefit from intensified treatment with anti-thrombotics, β-blockers or angiotensin converting enzyme inhibitors is still unknown. One study, including patients with congestive heart failure, suggested a larger benefit from β-blocker treatment in patients with elevated levels of NT-proBNP, whereas studies testing an intensified neurohormonal antagonism in unstable CAD are still lacking.

The last question is about cost-effectiveness. Thus, although we now have fast and reliable assays for peptides that are strongly associated to outcome and also seem to be helpful when determining further management, the added cost must be acknowledged. Therefore, studies relating the additive value of these peptides to the cost are required before any firm recommendations for their routine use can be given.

Need for future studies

In addition to studies regarding the value of these markers in treatment decision making and cost-effectiveness of using these markers, other studies are also warranted. One issue is when and how often these markers optimally should be measured. In previous studies, the median time from onset of symptoms has varied from 6 to 40 h. In one report from our group, there was no difference in the prognostic utility between the sample obtained on admission compared to that taken after 6 h. In the GUSTO IV study, the predictive capacity was as good in patients admitted within 6 h after symptom onset as in patients admitted later than 16 h after symptom onset. However, as well as in unstable CAD as in patients with acute MI, NT-proBNP continues to increase during the first 12–24 h. Thus, further studies are needed regarding the optimal time points or intervals to analyse these peptides. Moreover, not only is the release of natriuretic peptides in the acute phase of interest, but also the subsequent course of plasma concentrations. It can be hypothesised that patients whose levels of BNP and NT-proBNP return to normal might have a better outcome than patients who maintain or even increase their levels. Thus, natriuretic peptides might be useful to monitor patients after an episode of unstable CAD, and thereby identify responders and non-responders to a given treatment. Therefore, studies investigating the value of serial measurements of these markers after an episode of unstable CAD are needed.

Finally, studies with the power to make a valid comparison between the clinical value of BNP and that of NT-proBNP would be of interest. BNP and NT-proBNP are released in a 1:1 ratio and the results from studies using BNP and NT-proBNP have been comparable. In addition, small studies comparing these markers regarding the ability to diagnose congestive heart failure have not shown any significant differences. As a result, these markers have been considered to be interchangeable. Still, there are differences in the kinetics that might be of importance when evaluating a dynamic condition such as unstable CAD. Moreover, due to differences in clearance, there may be larger differences when comparing the markers in patients with abnormal renal function. Therefore, a large study directly comparing and combining these markers in patients with unstable CAD and acute MI would be of value.

Conclusions

In conclusion, fast and reliable assays for BNP and NT-proBNP are now commercially available. These markers of cardiac performance are strongly associated to mortality and the risk of future congestive heart failure, and carry important prognostic information independent from previous known risk factors in unstable CAD. As such, natriuretic peptides can be added to previously existing risk stratification models and multi-marker approaches. There are some data indicating that these markers might also be helpful in the selection of the appropriate therapy in these patients but further studies are needed. Before a routine use of BNP or NT-proBNP in unstable CAD can be recommended, the cost-effectiveness of adding these new markers to the currently routine markers of creatinine, troponin and CRP and their impact on selection of treatment needs further evaluation.

References

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