Editorial Comment

Use of Brain Natriuretic Peptide Levels for Risk Assessment in Non–ST-Elevation Acute Coronary Syndromes*

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Risk assessment of patients with non–ST-elevation acute coronary syndromes (NSTEACS) plays an important role in determining the prognosis. This enhances the cost-effectiveness of patient care by allowing evidence-based treatments (such as antiplatelet, anti-thrombotic, and revascularization therapies) to be targeted at the patients who are most likely to benefit from their use. The clinical history, examination findings, electrocardiographic (ECG) changes, and cardiac troponin levels are all crucial factors in assessing risk (1–8). In patients with NSTEACS, troponin levels predict the likelihood of benefit from treatment with low-molecular-weight heparins, glycoprotein IIb/IIIa antagonists, and early revascularization (9–11).

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Risk assessment should be considered a dynamic process, and refractory ischemia or evidence of ongoing (including silent) ischemia on ECG monitoring should mandate early angiography. Risk assessment may be enhanced by determining the number and severity of flow-limiting coronary artery stenoses and the presence or absence of left ventricular (LV) impairment.

There has been extensive research into the roles of inflammation and inflammatory markers in NSTEACS. Elevated levels of C-reactive protein and serum amyloid-A were first reported in patients with NSTEACS in the early 1990s (12,13). The levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 and, more recently, CD-40 ligand (which has prothrombotic effects) have been shown to have independent prognostic significance (14). Elevated levels of other inflammatory markers, such as adhesion molecules (13), interleukin-7 (15), and matrix-metalloproteinases (including pregnancy-associated plasma protein-A) (16) have also been observed in patients with NSTEACS. Conversely, levels of the anti-inflammatory cytokine, interleukin-10, have been shown to be reduced in patients with NSTEACS, and patients with higher levels of interleukin-10 suffer fewer events during follow-up (17). There have been no prospective trials of therapies aimed at modulating the levels of these markers. Neither the American College of Cardiology/American Heart Association (1) nor the European Society of Cardiology treatment guidelines (18) for NSTEACS currently recommend measurement of inflammatory marker levels (18).

In this issue of the Journal, the Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease (FRISC-II) investigators (19) expand upon their previous work on markers of myocardial necrosis and inflammation in patients with NSTEACS (20) with a report describing an association between amino-terminal brain natriuretic pro-peptide (NT-proBNP) levels and two-year mortality. When patients were classified into tertiles based on their NT-proBNP levels at admission, the risk ratios for two-year mortality in the upper tertile (NT-proBNP levels of >905 ng/l in men and >1,345 ng/l in women) were 4.1 (95% confidence interval [CI] 2.4 to 7.2) in the conservative treatment limb and 3.5 (95% CI 1.8 to 6.8) in the invasive treatment limb, as compared with patients in the lowest tertile. Invasive treatment resulted in absolute mortality reductions of 3.6% (risk ratio 0.67, 95% CI 0.41 to 1.10) in the upper tertile and 0.6% (risk ratio 0.78, 95% CI 0.39 to 1.57) in the lowest and middle NT-proBNP tertiles. This association was independent of other prognostic markers such as interleukin-6 and troponin T levels. The largest mortality reduction achieved by invasive treatment (7.3% absolute) was in patients who were in the upper NT-proBNP tertile and who also had interleukin-6 levels of ≥5 mg/l. Troponin T levels were not an independent predictor of mortality.

There are three classes of natriuretic peptides: atrial natriuretic peptide (ANP) (first identified in 1981) (21), brain natriuretic peptide (BNP) (first identified in porcine brains in 1988) (22), and the more recently described C-type natriuretic peptide, which is derived from endothelial cells and cells expressed in the nervous system. The release of natriuretic peptides from myocardial cells is provoked by a variety of stimuli, including hypoxia, ischemia, exercise, increased wall stress, and dilation of the atria and/or ventricles; the latter may be due to transient (including silent) ischemia, stunning, or hibernation. Other cardiac pathologies, such as hypertensive heart disease, atrial fibrillation, and valvular heart disease, are also associated with elevation of natriuretic peptide levels (19,23). In normal individuals, the blood levels of BNP (amino acids 77 to 108) and NT-proBNP (amino acids 1 to 76) are similar and significantly lower than the ANP levels (24). The cost of natriuretic peptide assays is approximately US$20.

The release of ANP, BNP, and NT-proBNP is markedly increased in patients with heart failure (HF), whether it is due to diastolic dysfunction or to systolic LV dysfunction,
and thus natriuretic peptide levels cannot be used to differentiate between these two causes of HF. Natriuretic peptide levels have prognostic significance in patients with chronic HF, including those who are receiving combination beta-blocker and angiotensin-converting enzyme inhibitor therapy and those with asymptomatic or minimally symptomatic LV dysfunction (25). Natriuretic peptide levels predict the response to treatment and the likelihood of readmission, and may be used for titration of pharmacologic therapies (26). Elevated BNP levels have also been used to identify patients at increased risk of sudden death (27). Atrial natriuretic peptide, BNP, and NT-proBNP levels have been shown to have similar correlations with both the extent of LV dysfunction and the risk of late mortality in patients with ST-elevation acute coronary syndromes (28).

The Treat Angina With Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI-18) investigators (29) have previously reported an association between BNP levels at admission and six-month mortality in patients with NSTEACS. In patients with NSTEACS in the Orbofibin in Patients with Unstable Coronary Syndromes-Thrombolysis in Myocardial Infarction 16 (OPUS-TIMI-16) trial, the levels of troponin I, hsCRP, and BNP at admission were independent predictors of the composite six-month end point of death, myocardial infarction (MI), or congestive HF, a finding validated in a cohort of 1,635 patients from the TACTICS-TIMI-18 trial (30).

In previous studies of patients with NSTEACS, NT-proBNP levels have been shown to be an independent prognostic factor for mortality (31–33). In an observational study of 755 patients, the risk ratios for death in patients with NT-proBNP levels in the second, third, and fourth quartiles (vs. the lowest quartile) were 4.2, 10.7, and 26.6, respectively (31). In another study of 609 patients (all of whom underwent echocardiography), NT-proBNP levels measured on day 3 provided prognostic information independently of the Killip class and LV ejection fraction (32). In the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study, NT-proBNP levels measured at 72 h were the only independent predictor of the composite 30-day end point of death and infarction, whereas troponin and hsCRP levels were not predictive (33).

The findings of the current FRISC-II substudy indicate that NT-proBNP levels at admission predict the benefit of revascularization and add prognostic information to that obtained from clinical and ECG data and from markers of myocyte necrosis and inflammation. However, in TACTICS-TIMI-18, revascularization did not benefit patients with elevated BNP levels (>80 ng/l) at admission (34). There are various possible explanations for this observation, which appears to conflict with the FRISC-II findings.

First, in patients with NSTEACS, the rise in NT-proBNP levels may be greater than the rise in BNP levels. Only 19% of patients in TACTICS-TIMI-18 had BNP levels of >80 ng/l, whereas at least 30% of patients in FRISC-II had NT-proBNP levels of >1,000 ng/l, and the distribution was less skewed.

Second, the patient characteristics of the TACTICS-TIMI-18 and FRISC-II populations differed somewhat in that the TACTICS-TIMI-18 patients had a higher incidence of previous MI (39% vs. 23%). In both studies, natriuretic peptide levels were related to the angiographic severity of coronary artery disease. In TACTICS-TIMI-18, the incidence of left main or triple-vessel disease (reported by the core laboratory) (31) was 22%, whereas in FRISC-II it was 34%, and the rate of surgical revascularization in patients randomized to undergo invasive treatment was lower in TACTICS-TIMI-18 than in FRISC-II (21% vs. 35%).

Third, early revascularization did not reduce the overall mortality rate in TACTICS-TIMI-18 (3.3% vs. 3.5% with conservative treatment), although it did reduce the incidence of recurrent ischemic events. It is therefore unlikely that revascularization would have reduced mortality in the subgroup of patients with elevated BNP levels. However, the nonsignificant 13% relative reduction in six-month mortality seen in TACTICS-TIMI-18 patients with BNP levels of >80 ng/ml (odds ratio 0.87, 95% CI 0.4 to 1.9) is not inconsistent with the 41% relative reduction in two-year mortality seen in patients in the highest tertile of NT-proBNP levels in FRISC-II.

The FRISC-II investigators chose interleukin-6, rather than hsCRP, as the inflammatory marker for inclusion in their multivariate models, because they had previously found that interleukin-6 was superior to hsCRP in predicting risk in the same FRISC-II population (19). When NT-proBNP was added to the multivariate model of two-year mortality predictors, the interleukin-6 level was no longer a significant predictor (95% CI 0.92 to 3.09). Considering that hsCRP testing is more readily available and there is more extensive literature on its use (14), it would have been interesting to evaluate the prognostic information added by NT-proBNP levels to that obtained from hsCRP levels.

What are the pathophysiologic mechanisms that make elevated natriuretic peptides levels adverse risk factors in patients with NSTEACS? These peptides have salutary effects on the cardiovascular system, including diuretic and natriuretic effects, blood pressure reduction, inhibition of the angiotensin system, and modulation of endothelial function. Their independent association with risk may be due to multiple mechanisms.

First, elevation of natriuretic peptide levels may result from acute LV dysfunction caused by acute or old myocyte necrosis, and the risk associated with elevated levels could therefore be related to the effect of LV impairment on mortality (including sudden death) or to new or progressive HF.

Second, elevation of natriuretic peptide levels may result from acute myocardial stretch caused by ischemia without myocyte necrosis, and the risk associated with elevated levels
could therefore be related to the extent of ischemia and the consequent risks of future infarction and arrhythmia (possibly sudden cardiac death). Brain natriuretic peptide levels have been shown to rise after transient myocardial ischemia resulting from inflation of an angioplasty balloon (35). In TACTICS-TIMI-18, 6.6% of patients without elevated troponin I levels (i.e., with levels of <1.0 μg/l) had elevated BNP levels. The TACTICS-TIMI-18 and FRISC-II investigators found that natriuretic peptide levels were associated with the extent of angiographic coronary disease, and in these trials BNP/NT-proBNP levels were higher in patients with ST depression. In view of previous data showing correlations between BNP levels and the size of the ischemic area measured by nuclear stress imaging (36), it is surprising that elevated natriuretic peptide levels were not predictors of recurrent ischemic events or MI in TACTICS-TIMI-18 and FRISC-II. In FRISC-II, the only predictor of reinfarction was an elevated troponin level, and it is not clear why natriuretic peptide levels were not found to be a predictor, whereas in the PRISM study, there was a correlation between higher NT-proBNP levels and the risk of MI (p < 0.01) (33). It would enhance our understanding of the associations between natriuretic peptides and ischemia to know how well natriuretic peptide levels correlated with the extent of ischemia, documented electrocardiographically, in TACTICS-TIMI-18 and FRISC-II.

Third, interpretation of natriuretic peptide levels in the setting of NSTEMI may be confounded by the fact that elevations of these markers can result from various pathophysiologic mechanisms (or possibly even a combination of different mechanisms) unrelated to acute myocardial ischemia or necrosis causing LV dysfunction. Interpretation of natriuretic peptide levels may also be confounded by age, gender, or severe renal impairment.

The natriuretic peptides themselves may also have therapeutic applications. Natriuretic peptide receptor-A knockout mice have been shown to develop hypertension with marked cardiac hypertrophy and fibrosis (37). In BNP knockout mice, ventricular pressure overload leads to increased cardiac fibrosis because the production and release of BNP may inhibit collagen accumulation (38). Exogenously administered BNP has been shown to limit the infarct size in a rat heart model of acute MI (34). Intravenous nesiritide (recombinant human BNP) has been shown to have beneficial hemodynamic effects, reducing pulmonary capillary wedge pressure in patients with acute HF (39).

To enhance risk stratification, measurement of BNP or NT-proBNP levels should be performed at admission in patients presenting with NSTEMI. However, the optimal timing of measurement has not yet been defined, and different prognostic information may be obtained if levels are measured at a later stage. The treatment implications of elevated natriuretic peptide levels may include more appropriate targeting of revascularization and aggressive anti-platelet (33) and antithrombotic therapies. It is yet to be determined whether therapies directed at cardiac neurohormonal activation, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, should be used in all patients with NSTEMI and elevated natriuretic peptide levels.

Future trials should be designed to evaluate targeted therapies based on elevations in the levels of one or more markers occurring in conjunction with the pathophysiologic mechanisms of necrosis, inflammation, or ischemia causing myocardial stretch. Such trials will provide further insights into the interaction between troponins, inflammatory markers, and natriuretic peptides in the pathogenesis and dynamic risk assessment of NSTEMI.

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