Current opinion

BNP in acute coronary syndromes: the heart expresses its suffering

Alf Inge Larsen*, Kenneth Dickstein

Cardiology Division, University of Bergen, Central Hospital in Rogaland, Stavanger, Norway

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The use of N-BNP is well established in the diagnosis and staging of patients with heart failure and its ability to predict prognosis in this population has been verified in several frequently cited studies. Recently, measurement of N-BNP has also been shown to be a useful prognostic tool in the population of patients with ACS. In a past issue of this journal, Bazzino et al., further extended our knowledge in that they demonstrated the prognostic value of elevated levels of N-terminal B-type natriuretic peptide (N-BNP) in addition to standardised risk-stratification schemes in patients (n = 1483) that were included consecutively with acute coronary syndromes (ACS).

Risk stratification of patients with ACS

Although, early treatment with fibrinolytic agents or percutaneous coronary intervention is well documented in acute ST-elevation myocardial infarction (STEMI), the optimal treatment strategy for the considerable and increasing population with non-STEMI is still being developed. These patients have an elevated risk for subsequent cardiac events despite substantial progress in management during the last decade. Therefore, risk stratification is important for selection of medical therapy and the optimal use of invasive procedures explaining the interest in a biomarker potentially identifying the most appropriate target population.

Treatment of the patients with the highest risk scores with an early invasive strategy and intensive anticoagulation has shown to lower rates of death, myocardial infarction (MI), and re-admission. Various risk-stratification algorithms have been developed to identify those patients at highest risk who deserve priority with regard to intensive care and aggressive medical and interventional treatment. Commonly employed variables include age >65 years, ST-deviation on ECG, known coronary artery disease or previous coronary artery bypass grafting (CABG), prior use of aspirin and accelerating symptoms.

More recently, certain cardiac biomarkers have been identified which are associated with increased risk. Sensitive and specific biochemical markers of minor myocardial damage include troponin-T (TnT) and creatinine kinase MB isoforms. Myeloperoxidase levels and high-sensitivity C-reactive protein (hsCRP) levels, may identify patients at risk for cardiac events even in the absence of substantial myocardial necrosis. Patients with a TnT level >0.1 ng/mL have been shown to carry a substantially elevated risk for death, cardiogenic shock, MI, and heart failure. In that each of these variables may provide unique prognostic information, combining these markers further strengthens their prognostic power and permits risk stratification over a broad range of short and long-term major cardiac events.

Identifying patients with ACS at risk of developing subsequent acute heart failure

In the report by Bazzino et al., the authors evaluated the use of N-BNP in addition to the variables employed in conventional risk scores (TIMI risk score and the ACC/AHA prognostication schemes) in a large population with 180 day follow-up. 1226 patients presented with unstable angina and 257 with non-STEMI. 20% of the population had prior myocardial infarction and 17% had previously undergone previous coronary revascularisation (PCI/CABG). 67% were treated for hypertension. Measurements of N-BNP, TnT, hsCRP and myoglobin were taken at 3 h.

The median level of N-BNP was 232 pg/mL. The area of the ROC curve relating N-BNP level with 6 month mortality was 0.78 (95% CI: 0.73–0.83), and the highest likelihood ratio relating N-BNP level with 6 month mortality corresponded to a value of 586 pg/ml. This is in...
accordance with a previous report in patients with ACS that showed that N-BNP and markers for inflammation identified the patients who benefited most from an early invasive strategy.\textsuperscript{18} In the study by Bazzino et al., N-BNP was also correlated to a marker of inflammation (hsCRP), and both N-BNP and hsCRP in addition to elevated CK-MB, were independently associated with 180 day mortality. Only N-BNP and a marker for myocardial necrosis (TnT) were independent predictors of in-hospital death, whereas only TnT, CK-MB and diabetes, but not N-BNP, were associated with increased risk for ischemic events. In TACTICS TIMI 18, revascularisation did not benefit patients with increased BNP at admission,\textsuperscript{19} whereas in the FRISC II study the combination of increased levels of an inflammatory marker and increased levels of BNP identified patients with a survival benefit from an early invasive strategy.\textsuperscript{17}

As expected, the authors showed that the risk of death or non-fatal MI at six months increased with the TIMI categories from 5\% to 25\%. However, for each TIMI category, elevated levels of N-BNP further increased the risk. Moreover, elevated N-BNP levels were significantly associated with adverse outcome, independently of risk according to the ACC/AHA classification.

Although prior myocardial infarction and the presence of Q-waves in ECG are included as risk factors in the ACC/AHA Classification, neither the TIMI risk score nor the ACC/AHA prognostication scheme include variables that directly evaluate myocardial function. The novel finding in this report was that the use of N-BNP adds independent prognostic information to conventional variables, and is in accordance with recent reports suggesting that natriuretic peptide measurement might be integrated into the routine evaluation of patients with ACS.\textsuperscript{19,20}

The study had some important limitations. Although the use of N-BNP has been shown to have prognostic significance both beyond LVEF and Killip class,\textsuperscript{4} the prognostic value of N-BNP was not adjusted for the level of left ventricular function as assessed by ejection fraction or wall motion score. In addition, the authors did not collect N-BNP data during follow up to provide longitudinal information and predict risk of clinical events.

The definition of MI was based on CK-MB elevation in that the initiation of the enrolment into the study was prior to the current recommendations concerning the use of troponins.\textsuperscript{21} The population of patients with a non-STEMI might have been larger than actually reported if troponins had been used as the diagnostic marker. The measurement of troponins was performed only once at a mean time of 3.2 hours after admission. In that the authors did not take serial measurements of this marker, patterns compatible with necrosis may not have been detected. It would also have been of interest to compare the prognostic performance of the two BNP fragments, BNP and N-BNP.

The likely mechanistic explanation is that elevated BNP levels indicate the degree of ischaemic induced left ventricular dysfunction in patients with acute coronary syndromes. The elevation of N-BNP in patients with highest risk reflects pathological left ventricle strain and overload.\textsuperscript{22} However, the development of acute left ventricular strain in connection with ischaemia is not necessarily accompanied by myocardial necrosis as measured by elevated levels of troponins. Stunned myocardium,\textsuperscript{23} ischaemic induced diastolic dysfunction, reversible border zone injury, apoptosis,\textsuperscript{24} acute papillary muscle dysfunction and arrhythmia may precipitate the development of acute heart failure in both STEMI and non-STEMI patients. Therefore, even in patients without substantial loss of myocardial tissue, the development of acute heart failure is an important threat to patients admitted with ACS.

**Clinical implications?**

Bazzino and co-workers quantify the contribution of N-BNP measurement in assessing prognosis in this population in addition to conventional risk classification and markers of myocardial necrosis. The report focuses on the risk associated with potential left ventricular dysfunction as assessed by N-BNP in patients with ACS. This is in accordance with recently published results confirming the poor prognosis of patients with ACS and signs of heart failure including patients without elevated markers of necrosis.\textsuperscript{15} Identification of patients and an appropriate treatment strategy for patients at this deadly intersection between ACS and acute heart failure might improve survival substantially. 80\% of all in-hospital morbidity and mortality is concentrated in the group of patients with ACS and acute heart failure.\textsuperscript{26,27} Tailored medical treatment may be as important as early revascularisation in selected patients with ACS. The challenge has been to identify the patients at highest risk. Has the time now come to recommend that clinicians routinely assay BNP in order to better identify patients who should be targeted for aggressive therapy? Perhaps.

**References**

7. Sabatine MS, Morrow DA, Giugliano RP et al. Implications of upstream glycoprotein IIb/IIa inhibition and coronary artery stenting in the


