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Editorial

Short-term follow-up BNP level and risk stratification after myocardial infarction

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In this issue of International Journal of Cardiology, Lee et al. published a very interesting study aimed at investigating the relationship between brain (B-type) natriuretic peptide (BNP) and the risk of death and major cardiovascular events in patients after myocardial infarction [1]. They performed the retrospective single-center study including 442 patients (71% males) who had BNP assayed in the acute phase as well as after discharge within 2 months (median 26 days). The relationship between initial/follow-up BNP level and all-cause mortality as well as major cardiovascular events (MACE) including all deaths, any myocardial infarction and any revascularization during the median follow-up period of 441 days was then analyzed. Patients were divided into four groups according to initial and follow-up BNP levels below or above the median: low initial-low follow-up, low initial-high follow-up, high initial-low follow-up and high initial-high follow-up. The results demonstrated that high follow-up BNP level was associated with greater risk of all-cause mortality and MACE (odds ratio 2.265 and 1.43, respectively) after adjustment for covariates such as age, sex, left ventricular ejection fraction, hemoglobin concentration, body mass index and creatinine level. In contrast, high initial BNP level did not correlate with mortality or MACE. Nevertheless, the risk of all-cause mortality but not of MACE was higher in the high-high group (odds ratio almost 3.5) than in any other group.

BNP is synthesized mostly by ventricular cardiomyocytes as the preprohormone consisting of 134 amino acids [2,3]. After cleavage of signal peptide, it is converted to proBNP containing 108 amino acids (proBNP1–108). ProBNP1–108 is partially cleaved by intracellular endoprotease, furin, and membrane-associated serine protease, corin, into N-terminal (BNP1–76) and C-terminal (BNP77–108, usually referred to as BNP1–32) fragments, respectively. Apart from proBNP1–108, BNP1–76 and BNP1–32, other shorted forms such as BNP3–32, BNP4–32, BNP5–32 and BNP8–32 have been identified in t6he blood [4]. BNP1–32 is the major biologically active form which binds to natriuretic peptide receptor-A (NPR-A) and increases intracellular cGMP concentration. The main biological activities of BNP1–32 are similar to those of atrial natriuretic peptide (ANP) and include vasodilation, natriuresis, inhibition of renin and aldosterone secretion as well as suppression of smooth muscle cell proliferation and myocardial hypertrophy [2,3].

Measurement of plasma BNP level is used for diagnosis and risk stratification in patients with heart failure for about two decades. Previous studies have demonstrated that in patients with decompensated heart failure, short-term follow-up BNP may be a better predictor of morbidity and mortality than initial BNP measured at admission [5]. Rapid increase in BNP secretion in acute myocardial infarction has also been observed in both experimental animal models and in humans [6]. However, the study of Lee et al. [1] is the first one which suggests that short-term follow-up BNP may be the better prognostic marker than initial BNP in patients with acute myocardial infarction. The reason for this is unclear at present but several possibilities may be suggested. First, myocardial infarction may be associated with biphasic increase in circulating BNP level. The first acute phase results from transiently acting humoral factors such as angiotensin II, endothelin-1, catecholamines, proinflammatory cytokines and cortisol [7]. In addition, hypoxia directly stimulates BNP secretion from cardiomyocytes even in the absence of myocardial necrosis [8]. Thus, initial increase in BNP may reflect acute neurohormonal responses, inflammatory reaction and non-lethal hypoxia which may be the transient phenomena, not necessarily correlating with prolonged detrimental alterations. In contrast, subacute or chronic elevation of BNP results from enhanced protein synthesis stimulated by myocyte stretch which is induced by left ventricle overload. Mechanical stress as well as growth factors up-regulated in hypertrophied heart up-regulate the expression of BNP-encoding gene [7]. Consequently, follow-up BNP level may better represent myocardial injury with subsequent contractile/diastolic dysfunction and remodeling. Second, all patients assessed in the study of Lee et al. were subjected to percutaneous coronary intervention. Higher initial BNP could result from peptide washout due to successful reperfusion. In contrast, delayed or incomplete reperfusion may be associated with BNP degradation by proteases in the necrotic tissue before washout. In addition, reperfusion is the direct stimulus for BNP synthesis and secretion from the heart [9]. Third, BNP1–32 has been demonstrated to be protective in experimental models of myocardial ischemia-reperfusion [9]. Thus, high initial BNP level may not be necessarily associated with detrimental clinical outcomes. Finally, it cannot be excluded that initial and follow-up rise in BNP are accounted for by

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different molecular forms of the peptide. Antibody-based BNP assays used in routine clinical practice have limited specificity. Anti-BNP1–32 antibodies may cross-react with other less active or inactive forms such as proBNP1–108, BNP3–32, BNP4–32 and BNP5–32. Recent studies demonstrate that heart failure is associated with high BNP1–108, BNP3–32, BNP4–32 and BNP5–32 but low BNP1–32. It may be speculated that early and late elevation of BNP in acute myocardial infarction are associated with various peptide forms and as such have different clinical implications. However, verification of this hypothesis requires further studies using more specific analytical methods such as mass spectrometry. Until now only one study addressed molecular forms of BNP in patients with myocardial infarction [10].

Of course, the results presented by Lee et al. need to be confirmed in large-scale multicenter prospective clinical studies including large groups of patients. Such studies could help to answer several questions, for example: (1) when exactly the follow-up BNP should be measured to offer the best prognostic value, (2) which BNP isoform is the best predictor of clinical outcomes, (3) what is the effect of comorbidities such as diabetes, hypertension or hyperlipidemia on prognostic value of this marker. In addition, studies in large groups of patients could allow to model the quantitative relationship between BNP concentration and prognosis rather than treating it as a binary variable (above or below the median) which was the only possible approach in the relatively small patients' sample in the discussed study [1]. Addressing these issues could contribute to establishing short-term follow-up BNP as the useful clinical marker in patients after acute myocardial infarction which could help to adjust further management and improve clinical outcomes.

Conflict of interest

The author reports no relationships that could be construed as a conflict of interest.

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