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COMMENTARY

Expanding the role of cardiac biomarkers—natriuretic peptides and troponins—further in pre-Stage A

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In the most recent 2013 ACCF/AHA guideline for the management of heart failure,[1] BNP and NT-proBNP are presented as indispensable biomarkers for the diagnosis/exclusion and prognostic evaluation of patients with heart failure (Class I, Evidence A) as well as for the achievement of guideline-directed medical therapy (Class IIa, Evidence B) in the acute or ambulatory setting (Stage C or D, in heart failure[1]). Studies on the application of these cardiac biomarkers were already expanded from Stage B (asymptomatic heart diseases)[1] or Stage A (hypertension, DM, etc)[1] to pre-Stage A, namely, non-diseased, general, community or company-based populations. These studies also revealed the importance of these biomarkers to predict the risk of cardiovascular events and death independently of conventional risk factors.

In this issue of the Journal, Hasegawa *et al.*[2] reported that plasma BNP measured in an area health check-up population was significantly associated with the higher risk of future events of coronary heart disease (CHD) estimated by the Framingham risk score (FRS) equation, that is, even in the conventionally normal range, the threshold level for the identification of the moderate (10 year-risk 10–20%) to high (10 year-risk >20%) risks of CHD was obtained as BNP values of 12.0 pg ml^{-1} and 22.0 pg ml^{-1} with the area under the curve 0.755 and 0.700 for men and women, respectively. For better and universal understanding, the BNP values measured using the CLEIA assay (Shionogi, Japan) in their report should be recognized as not necessarily being equal to the BNP values reported by the UA or European countries (Triage-BNP), as Triage-BNP level = 1.579 (Shionoria-BNP) minus 2.947, $r = 0.947$.[3] Thus, the optimal threshold level of BNP for Triage-BNP would be calculated as 16.2 and 32.2 pg ml^{-1} for men and women, respectively.

BNP AND OBESITY PARADOX

How obesity affects the relationship between the BNP level and the predicted risk of CHD as estimated by the FRS equation remains unclear. As mentioned by the authors, obesity has been well known to decrease plasma BNP levels. In their study, body mass index (BMI) gradually decreased with an increase in the tertile of BNP levels in men. However, subjects with multiple cardiovascular risk factors (that is, high predicted CHD risk) usually had a higher BMI, which may lead to a decrease in plasma BNP levels. Visceral fat expansion has been reported to increase the clearance of BNP due to the increased expression of a clearance receptor on adipocytes.[4] Given these observations, further studies are expected to clarify the impact of BMI (or visceral fat expansion[5]) on the relationship between BNP levels and the accumulation of cardiovascular risk factors in the general population.

ISSUE OF SMOKING HABITS

In the present study, the prevalence of current smoking status gradually decreased as the tertile of BNP increased, particularly in men. Cigarette smoking impairs vasomotor function and induces the progression of atherosclerosis in the coronary artery,[6] which may decrease coronary blood flow and cause subclinical myocardial ischemia. These symptoms may, in turn, increase cardiac overload, thereby leading to the subsequent secretion of BNP. We previously reported that the serum NT-proBNP levels were significantly elevated in current smokers compared with never smokers.[7] Therefore, the inverse relationship between the prevalence of current smoking status and plasma BNP levels seen in their study is of interest. Subjects in the high-tertile BNP group were found to be older than those in other tertile groups. Because aging is one of the important determinants of elevated plasma BNP levels, the most plausible explanation for the results of the inverse relationship between smoking and BNP would be the gradual increase in age with the increase in the tertile of BNP.

PREDICTIVE VALUE OF BNP IN THE PRE-STAGE A

The present study has raised the next question for us regarding whether the measurement of BNP levels is practically useful for identifying individuals at high risk of cardiovascular disease. The sensitivity and specificity of BNP for discriminating among individuals of moderate to high predicted CHD risk were 0.70 and 0.71, respectively, for men and 0.66 and 0.63, respectively, for women. These results suggest that the positive likelihood ratio of BNP was 2.4 for men and 1.8 for women, whereas the negative likelihood ratio of BNP was 0.4 for men and 0.5 for women; these data might be not necessarily sufficient as a diagnostic tool in daily clinical practice. As the authors mentioned in the limitation section, the present study is a cross-sectional investigation, and therefore the association between BNP levels and future cardiovascular events was not evaluated. Several community-based cohort studies in Japan have shown

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that plasma BNP or NT-proBNP levels predict the risk of cerebro- and cardiovascular diseases.[8–10] Further longitudinal studies are expected to confirm whether plasma BNP levels are useful for predicting the future onset of CHD in the present study population.

EXPANDING ROLE OF TROPONINS IN PRE-STAGE A

Furthermore, in the 2013 ACCF/AHA guideline for the management of heart failure,[1] newly presented markers of myocardial injury, such as troponins (Tpn), for additive risk stratification (Class I, Evidence A) in the acute or ambulatory setting of heart failure against the background of the pathophysiological and prognostic importance of ongoing myocardial injury detected by Tpn, which we first reported,[11] were cited. Several studies on the application of the high-sensitivity Tpn have also expanded from the diagnosis of myocardial infarction to Stage B and Stage A in heart failure[1] and further in pre-Stage A. We have reported the first study evaluating the high-sensitivity Tpn-T in a non-diseased, company-based population ($n=1072$; male) to correlate the Tpn-T levels with cardiovascular risk factors and the estimated CHD risk by the FRS equation.[12] The Tpn-T levels were significantly associated with several cardiovascular risk factors, including age, blood pressure, estimated glomerular filtration rate, current smoking, left ventricular hypertrophy and C-reactive protein levels. Using the FRS equation, individuals in the highest tertile of Tpn-T had an odds ratio of 3.98 compared with the lowest tertile for a 10-year CHD risk of $>20\%$.[12] Immediately afterwards, de Lemos *et al.*[13] demonstrated a clear association of the high-sensitivity Tpn-T levels with cardiac structure and mortality risk in the Dallas County general population ($n=3546$) based on the 6.4-year follow-up investigation, which was consistent with the odds ratio estimated in our report.[12]

The expanding role of the cardiac biomarkers, BNP, NT-proBNP and Tpn, is remarkably now beyond the stages of heart failure[1] in terms of novel risk markers or risk factors for future cardiovascular disease prediction in individuals with a pre-Stage A status.

1 Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines 2013. ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**: e147–e239.
2 Hasegawa T, Asakura M, Eguchi K, Asanuma H, Ohara T, Kanzaki H, Hashimura K, Tomoike H, Kim J, Kitakaze M. Plasma B-type natriuretic peptide is a useful tool for assessing coronary heart disease risk in a Japanese general population. *Hypertens Res* 2015; **38**: 74–79.
3 Fisher Y, Filzmaier K, Stiegler H, Graf J, Fuhs S, Franke A, Janessens U, Gressner AM. Evaluaion of a new, rapid gedsude test for quantitative determination of B-type natriuretic peptide. *Clin Chem* 2001; **47**: 591–594.
4 Clerico A, Giannoni A, Vittorini S, Emdin M. The paradox of low BNP levels in obesity. *Heart Fail Rev* 2012; **17**: 81–96.
5 Chen CY, Asakura M, Asanuma H, Hasegawa T, Tanaka J, Toh N, Min KD, Kanzaki H, Takahama H, Amaki M, Itoh Y, Ichien G, Okumoto Y, Funahashi T, Kin J, Kitakaze M. Plasma adiponection levels predict cardiovascular events in the observational Arita Cohort Study in Japan: the importance of the plasma adiponectin levels. *Hypertens res* 2012; **35**: 843–848.
6 Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol* 2004; **43**: 1731–1737.
7 Otsuka T, Kawada T, Seino Y, Ibuki C, Katsumata M, Kodani E. Relation of smoking status to serum levels of N-terminal pro-brain natriuretic peptide in middle-aged men without overt cardiovascular disease. *Am J Cardiol* 2010; **106**: 1456–1460.
8 Doi Y, Ninomiya T, Hata J, Hirakawa Y, Mukai N, Ikeda F, Fukuhara M, Iwase M, Kiyohara Y. N-terminal pro-brain natriuretic peptide and risk of cardiovascular events in a Japanese community: The Hisayama study. *Arterioscler Thromb Vasc Biol* 2011; **31**: 2997–3003.
9 Nakamura M, Tanaka F, Onoda T, Takahashi T, Sakuma M, Kawamura K, Tanno K, Ohsawa M, Itai K, Sakata K, Makita S. Gender-specific risk stratification with plasma B-type natriuretic peptide for future onset of congestive heart failure and mortality in the Japanese general population. *Int J Cardiol* 2010; **143**: 124–129.
10 Takahashi T, Nakamura M, Onoda T, Ohsawa M, Tanno K, Itai K, Sakata K, Sakuma M, Tanaka F, Makita S, Yoshida Y, Ogawa A, Kawamura K, Okayama A. Predictive value of plasma B-type natriuretic peptide for ischemic stroke: A community-based longitudinal study. *Atherosclerosis* 2009; **207**: 298–303.
11 Setsuta K, Seino Y, Takahashi N, Ogawa T, Sasaki K, Harada A, Takano T, Kishida H, Hayakawa H. Clinical significance of elevated levels of cardiac troponin T in patients with chronic heart failure. *Am J Cardiol* 1999; **84**: 608–611.
12 Otsuka T, Kawada T, Ibuki C, Seino Y. Association between high-sensitivity cardiac troponin T levels and the predicted cardiovascular risk in middle-aged men without overt cardiovascular disease. *Am Heart J* 2010; **159**: 972–978.
13 de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 2010; **304**: 2503–2512.