N-terminal Prohormone B-type Natriuretic Peptide and Cardiovascular Risk in Stable Coronary Artery Disease: A Meta-analysis of Nine Prospective Studies

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To evaluate the prognostic value of N-terminal prohormone B-type natriuretic peptide (NT-proBNP) for patients with stable coronary artery disease, we searched for all published English-language articles indexed in MEDLINE and PubMed through July 2011. Nine independent, prospective, cohort studies that assessed the association between NT-proBNP value and long-term prognosis were identified. The interested endpoints of this meta-analysis were all-cause mortality and cardiovascular mortality and cardiovascular events. A general variance-based method was used to pool the hazard ratio (HR). In a comparison of individuals in the top quartile with those in the bottom quartile of baseline values of NT-proBNP, the combined adjusted HR was 2.74 (95% confidence interval [CI], 1.85-3.62). The combined HRs for the second and third quartiles compared with the first quartile were 1.33 (95% CI, 0.83-1.82) and 1.85 (95% CI, 1.23-2.48), respectively. In a subanalysis grouped by the median value, per 1 standard deviation increase or per 1000 pg/mL increase of NT-proBNP, the overall effect also showed that poor prognosis was significantly increased with the elevation of NT-proBNP (HR, 1.58; 95% CI, 1.16-2.01). Available prospective studies indicated strong associations between the circulating concentration of NT-proBNP and long-term prognosis in patients with stable coronary artery disease.

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KEY WORDS

NT-proBNP • Stable coronary artery disease • Prognosis • Meta-analysis

N-terminal prohormone B-type natriuretic peptide (NT-proBNP) is a stable fragment of the B-type natriuretic peptide (BNP) precursor, which is a neurohormone synthesized and released primarily from the cardiac ventricles in response to increased ventricular stretch and wall tension. Measurement of circulating levels of NT-proBNP has been recommended in the diagnosis and prognosis of patients with heart failure.[1] NT-proBNP was also documented, by in vitro study, to be directly released from cardiomyocytes in response to myocardial ischemia.[2] Therefore, it has been proposed that measurement of their circulating levels can be used for stratification of cardiovascular risk in populations with ischemic heart disease.

In recent years, many clinical studies have investigated the relationship between concentrations of NT-proBNP and the subsequent risk of patients with stable coronary artery disease (CAD); most of them have not been systematically assessed. One previous meta-analysis reviewed the relationship between BNP/NT-proBNP and cardiovascular risk in general populations or in those at high risk for CAD, but not in patients with stable CAD and a clear diagnosis.[3] We also noticed that, in most relevant studies addressing NT-proBNP and stable CAD, the study populations were divided into four quartile groups according to NT-proBNP concentrations and the clinical outcomes of different groups were reported, respectively. Thus, sufficient data were available to reanalyze the prognosis in patients with different NT-proBNP concentrations. Herein we report a systematic review and meta-analysis of results from nine prospective cohort studies and address the association between long-term prognosis and NT-proBNP concentrations in patients with stable CAD.

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Methods

Study Selection

We searched for all published articles indexed in MEDLINE and PubMed through July 2011. The search terms were *N-terminal pro-brain natriuretic peptide/N-terminal-proBNP/NT-proBNP*, and *coronary artery disease*. Although no language restrictions were imposed initially, only English-language articles were analyzed. Inclusion criteria included (1) prospective design; (2) reported adjusted hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) of the relevant outcomes; (3) the interested outcomes of all-cause mortality, cardiovascular mortality, or major adverse cardiac events (MACE); and (4) stable CAD patients with angiographic evidence or history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). These patients were divided into different groups according to NT-proBNP concentrations.

Data Extraction

Data were independently extracted by two investigators (Drs. Gao and Ren) onto a preset data extraction form. Extracted data included study population, endpoints, mean duration of follow-up, cutoff point of NT-proBNP, adjustment factors, and HRs (and 95% CIs). If the study reported several HRs based on different adjustment factors, the most adjusted HR was used. The relevant endpoints were all-cause mortality, cardiovascular mortality, or MACE, which was defined as a composite of myocardial infarction, heart failure, and revascularization.

Statistical Analysis

We estimated the pooled risk for patients of the second, third, and fourth quartiles compared with those in the first quartile of NT-proBNP values when the participants were divided into four groups. If the available HRs (and 95% CIs) were reported according to the median value, per 1 standard deviation (SD) increase or per 1000 pg/mL increase of NT-proBNP, we took them together and estimated the pooled risk roughly in a subanalysis.

We used a general variance-based method that requires information on the HRs and their 95% CIs for each study to estimate the pooled risks. The degree of inconsistency across studies was assessed by standard χ^2 test and the I^2 statistic,[4] and statistical heterogeneity was measured by Q test. A fixed-effects model was used when there was no statistical heterogeneity across the included studies. Otherwise, the random effects model was used. We did not perform the meta-regression sensitivity analysis because of the small number of included studies. P values were two-tailed and the statistical significance was set at 0.05. All analysis was performed with Stata software 10.0 (StataCorp, College Station, TX).

Results

Search Results and Study Characteristics

A detailed process of the study selection is shown in Figure 1. Among the 13 potentially relevant

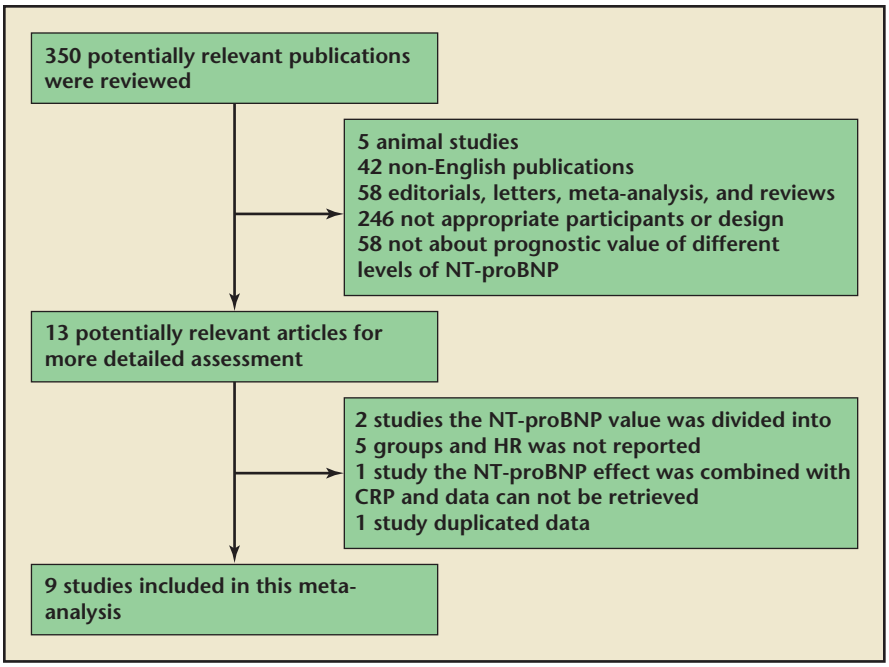

Figure 1. Flow chart of the study selection process. CRP, C-reactive protein; HR, hazard ratio; NT-proBNP, N-terminal prohormone B-type natriuretic peptide.

articles identified after a review of title or abstract, two were finally excluded because the participants were divided into five groups and the HRs were not reported[5,6]; one was excluded because the NT-proBNP effect was combined with C-reactive protein and the needed HR data could not be retrieved[7]; and another was excluded because duplicate data were used.[8] In all, nine prospective cohort studies[9-17] reporting on 16,516 individuals were identified and are detailed in Table 1. Seven studies were conducted in Europe, one in North America, and one in both North America and Europe. All participants were stable CAD patients with a history of PCI/CABG or angiographic evidence of significant coronary lesions. The average follow-up ranged from 2 to 9.2 years. For the endpoints we used all-cause mortality in seven studies, cardiovascular mortality in one study, and MACE in one study. The adjustment factors of HRs varied between studies and they are all shown in Table 1.

Five studies divided the participants into four quartiles according to NT-proBNP concentration and the authors calculated the long-term prognosis (HRs and 95% CIs) for patients in the second, third, and fourth quartiles compared with those in the first quartile. One study reported both HRs (and 95% CIs) of the fourth versus the first quartile and per 1 SD increase of log NT-proBNP. One study reported HR (and 95% CI) by the cutoff of median value of NT-proBNP. One study only reported HR (and 95% CI) per 1 SD increase of log NT-proBNP and one other reported HR (and 95% CI) per 1000 pg/mL increase of NT-proBNP.

Associations Between NT-proBNP and Long-term Prognosis

Five studies reported the HRs (and 95% CIs) of the second, third, and fourth versus the first quartile and one study only reported HR (and 95% CI) of the fourth quartile versus the first quartile. Under the fixed-effects model, the pooled HR was 1.33 (95% CI, 0.83-1.82) for the second versus the first quartile. In the comparison between the third and fourth versus the first quartile, the HRs were 1.85 (95% CI, 1.23-2.48) and 2.74 (95% CI, 1.85-3.62), respectively (Figure 2). The risk of developing unfavorable clinical events increased significantly with each increasing quartile of baseline NT-proBNP concentration. No considerable heterogeneity among the six available studies was found (data not shown).

Four studies reported HR (and 95% CIs) by the median value of NT-proBNP, per 1-SD increase of log NT-proBNP or per 1000 pg/mL increase of NT-proBNP, and the overall effect was pooled roughly. Under the random-effects model, the result showed that poor prognosis risk of patients with elevated NT-proBNP was also increased (HR 1.58; 95% CI, 1.16-2.01; Figure 3). There was a significant heterogeneity among the four available studies ($I^2 = 83\%$; $P < .001$), which could be partly explained by different cutpoints of NT-proBNP concentration. We did not perform further subanalysis because there were only four studies and the cutpoints varied greatly among included studies.

Discussion

Our present meta-analysis has quantitatively assessed the association between NT-proBNP and poor prognosis risk in nine cohort studies consisting of 16,516 stable CAD patients. Five more studies were added to this meta-analysis on the basis of the previous meta-analysis published by Di Angelantonio and colleagues.[3] The previous study included 40 studies and divided them into three groups, including *general populations*, *populations defined by having elevated CVD risk factors*, and *populations with manifest stable CVD*. However,

TABLE 1

Characteristics of Nine Prospective Trials Included in the Meta-analysis

Study	Country	N	Patients	Outcomes	Follow-up (y)	Reported HRs	Adjustments
Harutyunyan MJ et al[9]	Denmark	4372	Stable patients with history of PCI or CABG	All-cause mortality	2.6	According median of NT-proBNP	Sex, age, smoking habits, hypertension, diabetes, previous MI, treatment
Ndrepepa G et al[10]	Germany	1552	Stable patients with history of PCI	All-cause death	3.6	Per 1000 pg/mL of NT-proBNP	Age, sex, diabetes, BMI, smoking, NYHA class, CRP, LVEF
Omland T et al[11]	United States, Canada, Italy	3761	Stable patients with history of PCI or CABG	Cardiovascular death	4.8	Per 1-SD of log NT-proBNP	Randomization status
März W et al[12]	Germany	1641	Stable patients with history of PCI	All-cause death	5.5	2nd, 3rd, and 4th quartile vs 1st quartile	Age, sex, diabetes, BMI, smoking, hypertension, dyslipidemia, GFR, previous MI, treatment, revascularization at baseline, LVEF, CRP
Bibbins-Domingo K et al[13]	United States	987	Stable patients with history of MI or PCI or angiographic evidence of CAD	All-cause death	3.7	4th quartile vs 1st quartile per 1-SD of log NT-proBNP	Age, sex, diabetes, smoking, BP, cholesterol, Ccr, LVEF, troponin T, NYHA class
Rothenbacher D et al[14]	Germany	1206	Stable patients with angiographic evidence of CAD	Cardiovascular events	4	2nd, 3rd, and 4th quartile vs 1st quartile	Age, sex, smoking, diabetes, treatment, cholesterol, CRP, LVEF
Ndrepepa G et al[15]	Germany	1059	Stable patients with history of PCI	All-cause death	3.6	2nd, 3rd, and 4th quartile vs 1st quartile	Randomization status
Kragelund C et al[16]	Denmark	1034	Stable patients with angiographic evidence of CAD	All-cause death	9.2	2nd, 3rd, and 4th quartile vs 1st quartile	Age, sex, family history, MI, and PCI history, CCS class, hypertension, diabetes, heart failure, smoking, BMI, Ccr, lipid, LVEF, severity of CAD at angiography
Schnabel R et al[17]	Germany	507	Stable patients with angiographic evidence of CAD	Cardiovascular events	2	2nd, 3rd, and 4th quartile vs 1st quartile	BMI, hypertension, diabetes, smoking, HDL, treatment, extent of vessel disease, hs-CRP, LVEF

BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; Ccr, continuous creatinine clearance; CCS, Canadian Cardiovascular Society; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SD, standard deviation.

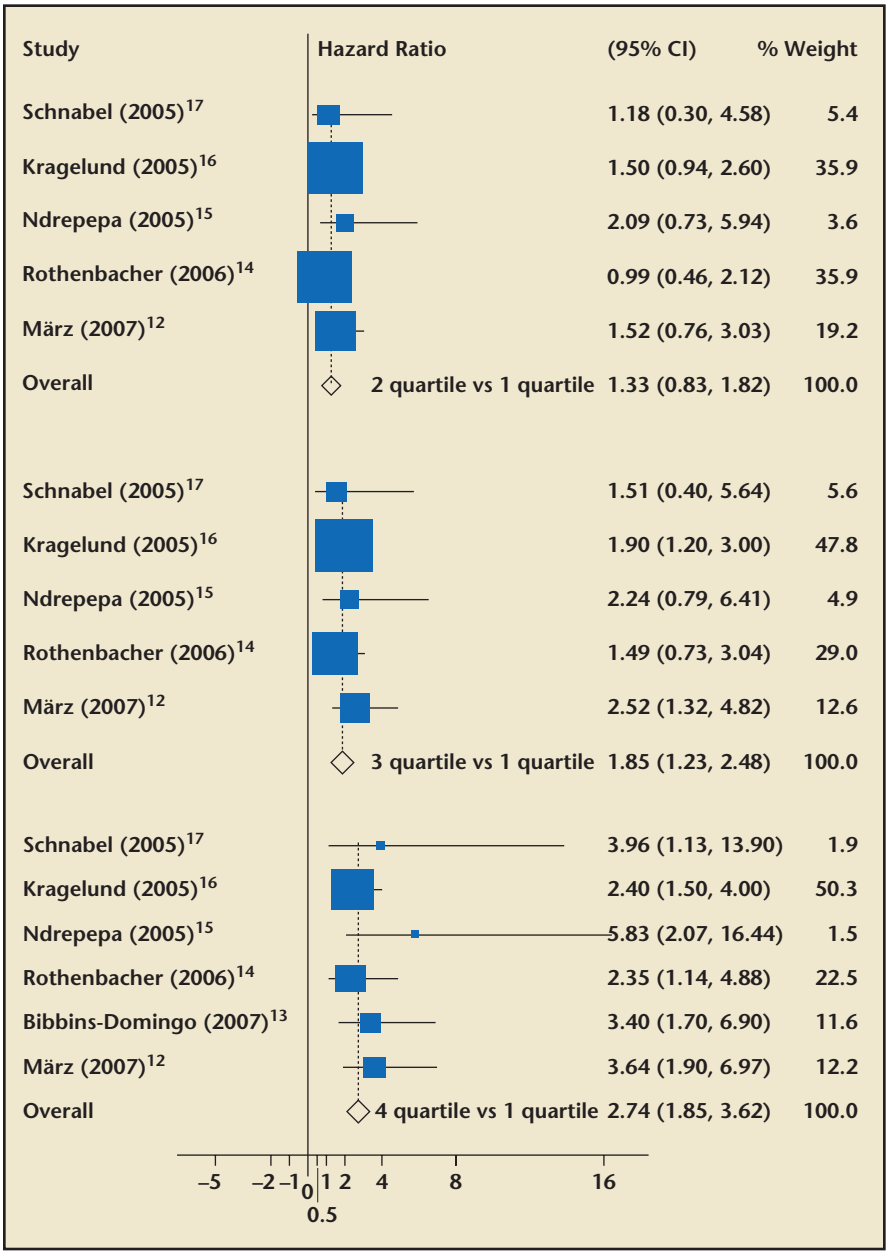

Figure 2. Forest plot of poor prognosis risk by quartiles of NT-proBNP among patients with stable coronary artery disease. The size of the marker for the point estimate (*diamond*) is proportional to the sample size for each study. Horizontal lines show 95% confidence intervals. A fixed model was used. CI, confidence interval; NT-proBNP, N-terminal prohormone B-type natriuretic peptide.

in the group with manifest stable CVD, the authors included patients diagnosed with stroke, transient ischemic attack, non–ST-segment elevation acute coronary syndrome, peripheral arterial disease, unstable angina pectoris, and suspected CAD. Thus, we excluded those studies with nonstable CAD patients and added some other studies omitted by the previous study.

The overall results showed that there was an almost threefold increase in poor prognosis risk for those in the top quartile of baseline NT-proBNP concentration compared with those in the bottom quartile. A subgroup analysis also showed that the risk slightly but significantly increases with the elevation of NT-proBNP, whether grouped by the median concentration, per 1 SD increase of log NT-proBNP, or per 1000 pg/mL increase of NT-proBNP. It should be noted that the HRs used in this meta-analysis were all calculated by the most adjusted factors. Therefore, our conclusion was quite reliable and supported the hypothesis that baseline NT-proBNP is independently associated with the long-term prognosis of stable CAD patients.

Although most of the included studies grouped the population according the median or quartiles of NT-proBNP, the specific NT-proBNP levels varied greatly among different studies. Thus, it was impossible to give a cutpoint and declare that patients above the cutpoint were at high risk and those below the cutpoint were at low risk.

NT-proBNP Expression and Myocardial Ischemia

It has been documented that BNP is synthesized and released mainly from the cardiac ventricles in response to increased ventricular stretch and wall tension. Several studies have demonstrated that acute myocardial ischemia can also stimulate release of BNP. Goetze and colleagues[18] found a remarkable elevation of plasma BNP and proBNP concentrations in patients with CAD but without concomitant left ventricular dysfunction. The same researchers also made a surgical reduction of the blood flow to an area of the anterior ventricular wall in pigs. The tissue content of BNP messenger RNA was found to increase 3.5-fold; they concluded that acute hypoxia can stimulate cardiac BNP expression.[19] Their findings were confirmed by a subsequent study in patients with CAD.[20] Studies about percutaneous coronary angiography also found that BNP values transiently increased during balloon inflation and fell after reperfusion.[21,22] Furthermore, expression of BNP was not only

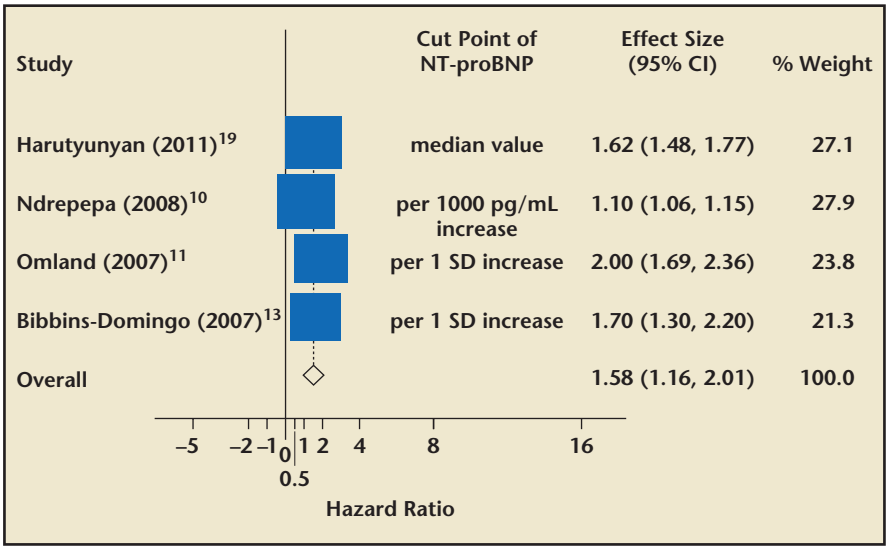

Figure 3. Forest plot of poor prognosis risk by the median value of NT-proBNP, per 1-SD increase of logNT-proBNP or per 1000 pg/mL increase of NT-proBNP among patients with stable coronary artery disease. A random model was used. CI, confidence interval; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; SD, standard deviation.

found to increase in response to acute myocardial ischemia, but also in response to potential myocardial ischemia. A previous study investigated the BNP concentration in patients with type 2 diabetes and ischemic heart disease with no history of cardiac failure and it demonstrated that BNP was elevated in patients with silent ischemia diagnosed with exercise testing.[23]

NT-proBNP in Stable CAD Patients

NT-proBNP has been demonstrated to be independently associated with the severity of coronary artery lesions in patients with both acute coronary syndromes[24] and stable CAD.[10,15,16] However, increasing evidence has shown that BNP expression can be stimulated by aging, hypertension,[25] atrial fibrillation,[26] and chronic kidney dysfunction,[27] which might explain why elevated NT-proBNP is correlated with poor prognosis in CAD patients. The reported HRs of all studies included in this meta-analysis, however, were fully adjusted by many other factors, including age, sex, diabetes, smoking, blood pressure, cholesterol, continuous creatinine clearance, left ventricular ejection fraction, and New York Heart Association class, so we can conclude that the independent association between NT-proBNP and long-term prognosis of patients with stable CAD might be explained by myocardial ischemia, which is caused by coronary lesions.

Limitations

Although the present analysis involves nine studies and 16,516 individuals, the conclusion should be carefully interpreted because of several limitations. First, a huge variation of follow-up duration might generate a significant heterogeneity among included studies. It seems impossible to avoid the variation of follow-up duration because the included studies were all cohort designed and the reported HRs were calculated at different follow-up duration. Second, we did not perform the meta-regression, sensitivity analysis, and funnel plot to investigate potential publication bias because of the relatively small number of included studies. Third, the interested endpoint of the present meta-analysis was a composite of all-cause mortality and cardiovascular mortality and events because the included studies reported disorganized adverse events. Thus, significant heterogeneity might be generated and, meanwhile, it was hard to decide what specific events were more likely with an elevated NT-proBNP.

NT-proBNP has been demonstrated to be independently associated with the severity of coronary artery lesions in patients with both acute coronary syndromes and stable CAD.

Conclusions

Available prospective studies indicate strong independent associations between the circulating concentration of NT-proBNP and long-term prognosis in the population with stable CAD. ■

The authors report no real or apparent conflicts of interest.

References

1. Dickstein K, Cohen-Solal A, Filippatos G, et al; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J.* 2008;29:2388-2442.
2. Goetze JP, Christoffersen C, Perko M, et al. Increased cardiac BNP expression associated with myocardial ischemia. *FASEB J.* 2003;17:1105-1107.
3. Di Angelantonio E, Chowdhury R, Sarwar N, et al. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. *Circulation.* 2009;120:2177-2187.
4. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557-560.
5. Mayer O Jr, Simon J, Plásková M, et al. N-terminal pro B-type natriuretic peptide as prognostic marker for mortality in coronary patients without clinically manifest heart failure. *Eur J Epidemiol.* 2009;24:363-368.
6. Richards M, Nicholls MG, Espiner EA, et al. Comparison of B-type natriuretic peptides for

assessment of cardiac function and prognosis in stable ischemic heart disease. *J Am Coll Cardiol*. 2006;47: 52-60.
7. Dai DF, Hwang JJ, Lin JL, et al. Joint effects of N-terminal pro-B-type-natriuretic peptide and C-reactive protein vs angiographic severity in predicting major adverse cardiovascular events and clinical restenosis after coronary angioplasty in patients with stable coronary artery disease. *Circ J*. 2008;72:1316-1323.
8. Ndrepepa G, Kastrati A, Braun S, et al. N-terminal probrain natriuretic peptide and C-reactive protein in stable coronary heart disease. *Am J Med*. 2006;119: 355.e1-e8.
9. Harutyunyan MJ, Mathiasen AB, Winkel P, et al; CLARICOR Trial Group. High-sensitivity C-reactive protein and N-terminal pro-B-type natriuretic peptide in patients with stable coronary artery disease: a prognostic study within the CLARICOR trial. *Scand J Clin Lab Invest*. 2011;71:52-62.
10. Ndrepepa G, Braun S, Mehilli J, et al. Accuracy of N-terminal probrain natriuretic peptide to predict mortality or detect acute ischemia in patients with coronary artery disease. *Cardiology*. 2008;109: 249-257.
11. Omland T, Sabatine MS, Jablonski KA, et al; PEACE Investigators. Prognostic value of B-Type natriuretic peptides in patients with stable coronary artery disease: the PEACE Trial. *J Am Coll Cardiol*. 2007;50: 205-214.
12. März W, Tiran B, Seelhorst U, et al; LURIC Study Team. N-terminal pro-B-type natriuretic peptide predicts total and cardiovascular mortality in individuals with or without stable coronary artery disease: the Ludwigshafen Risk and Cardiovascular Health Study. *Clin Chem*. 2007;53: 1075-1083.
13. Bibbins-Domingo K, Gupta R, Na B, et al. N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP), cardiovascular events, and mortality in patients with stable coronary heart disease. *JAMA*. 2007;297:169-176.
14. Rothenbacher D, Koenig W, Brenner H. Comparison of N-terminal pro-B-natriuretic peptide, C-reactive protein, and creatinine clearance for prognosis in patients with known coronary heart disease. *Arch Intern Med*. 2006;166:2455-2460.
15. Ndrepepa G, Braun S, Niemöller K, et al. Prognostic value of N-terminal pro-brain natriuretic peptide in patients with chronic stable angina. *Circulation*. 2005;112:2102-2107.
16. Kragelund C, Grønning B, Køber L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med*. 2005;352:666-675.
17. Schnabel R, Rupprecht HJ, Lackner KJ, et al; AtheroGene Investigators. Analysis of N-terminal-pro-brain natriuretic peptide and C-reactive protein for risk stratification in stable and unstable coronary artery disease: results from the AtheroGene study. *Eur Heart J*. 2005;26:241-249.
18. Goetze JP, Christoffersen C, Perko M, et al. Increased cardiac BNP expression associated with myocardial ischemia. *FASEB J*. 2003;17:1105-1107.
19. Goetze JP, Gore A, Møller CH, et al. Acute myocardial hypoxia increases BNP gene expression. *FASEB J*. 2004;18:1928-1930.
20. Pascual-Figal DA, Antolinos MJ, Bayes-Genis A, et al. B-type natriuretic peptide release in the coronary effluent after acute transient ischaemia in humans. *Heart*. 2007;93:1077-1080.
21. Goetze JP, Yongzhong W, Rehfeld JF, et al. Coronary angiography transiently increases plasma pro-B-type natriuretic peptide. *Eur Heart J*. 2004;25:759-764.
22. Tateishi J, Masutani M, Ohyanagi M, Iwasaki T. Transient increase in plasma brain (B-type) natriuretic peptide after percutaneous transluminal coronary angioplasty. *Clin Cardiol*. 2000;23:776-780.
23. Rana BS, Davies JI, Band MM, et al. B-type natriuretic peptide can detect silent myocardial ischaemia in asymptomatic type 2 diabetes. *Heart*. 2006;92:916-920.
24. Sadanandan S, Cannon CP, Chekuri K, et al. Association of elevated B-type natriuretic peptide levels with angiographic findings among patients with unstable angina and non-ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2004;44:564-568.
25. Partanen N, Husso M, Vuolteenaho O, et al. N-terminal pro-atrial natriuretic peptide reflects cardiac remodelling in stage 1 hypertension. *J Hum Hypertens*. 2011;25:746-751.
26. Marsiliani D, Buccelletti F, Carroccia A, et al. Natriuretic peptides and atrial fibrillation. *Eur Rev Med Pharmacol Sci*. 2010;14:855-860.
27. Khalifeh N, Haider D, Hörl WH. Natriuretic peptides in chronic kidney disease and during renal replacement therapy: an update. *J Investig Med*. 2009;57:33-39.

MAIN POINTS

- Measurement of circulating levels of N-terminal prohormone B-type natriuretic peptide (NT-proBNP) has been recommended in the diagnosis and prognosis of patients with heart failure.
- B-type natriuretic peptide (BNP) is synthesized and released mainly from the cardiac ventricles in response to increased ventricular stretch and wall tension. Furthermore, expression of BNP was not only found to increase in response to acute myocardial ischemia, but also in response to potential myocardial ischemia.
- Increasing evidence has shown that BNP expression can be stimulated by aging, hypertension, atrial fibrillation, and chronic kidney dysfunction, which might explain why elevated NT-proBNP is correlated with poor prognosis in patients with coronary artery disease.
- Overall results showed that there was an almost threefold increase in poor prognosis risk for those in the top quartile of baseline NT-proBNP concentration compared with those in the bottom quartile.