An Evidence-Based Algorithm for the Use of B-Type Natriuretic Testing in Acute Coronary Syndromes

Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA,[1] W. Frank Peacock, MD, FACEP,[2] Brian O'Neil, MD, FACEP,[3] James A. de Lemos, MD, FACC,[4] Norman E. Lepor, MD, FACC, FAHA, FSCAI,[5] Robert Berkowitz, MD, PhD, FACC[6]

[1]Department of Medicine, Divisions of Cardiology, Nutrition, and Preventive Medicine, William Beaumont Hospital, Royal Oak, MI; [2]Department of Emergency Medicine, The Cleveland Clinic, Cleveland, OH; [3]Department of Emergency Medicine, Wayne State University School of Medicine, Detroit, MI; [4]Donald W. Reynolds Cardiovascular Research Center, UT Southwestern Medical Center, Dallas, TX; [5]Cedars Sinai Medical Center, Los Angeles, CA; [6]Heart Failure Program, Hackensack University Medical Center, Hackensack, NJ

Measurable B-type natriuretic peptides (BNPs), which are largely produced by the left ventricle, include BNP and N-terminal prohormone BNP (NT-proBNP). These proteins are released by cardiomyocytes in response to wall tension and neurohumoral signals, and are established tools in the diagnosis and prognosis of heart failure (HF). We identified 32 articles for entry into evidence tables that presented original data on BNP and/or NT-proBNP in more than 100 patients with acute coronary syndromes (ACS) presenting with chest discomfort with or without dyspnea. Natriuretic peptide (NP) elevation was associated with older age, female sex, hypertension, diabetes, prior HF, prior ischemic heart disease, and reduced renal function. Clinical correlates of elevated blood NP levels included left main or 3-vessel coronary disease, lipid-rich plaques with large necrotic cores in proximal locations, large zones of myocardial ischemia or infarction, no-reflow and impaired perfusion after percutaneous intervention, reduced left ventricular ejection fraction, higher Killip classification, and the development of cardiogenic shock. All studies indicated that after adjustment for baseline predictors and clinical risk scores, elevated NP concentrations were independently predictive of the development of HF and all-cause mortality. In contrast, studies did not consistently demonstrate that NPs were predictive of myocardial infarction and rehospitalization for ACS. In addition to baseline measurement, there is consensus that repeat testing at 4 to 12 weeks and 6 to 12 months in follow-up is helpful in the anticipation of late cardiac sequelae and may assist in assessing prognosis and guiding management.
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Key words: B-type natriuretic peptide • N-terminal pro-B-type natriuretic peptide • Acute coronary syndrome • Acute myocardial infarction • Diagnosis • Complications • Prognosis • Systematic review • Hospitalization • Mortality

It has been recognized and shown that tests for B-type natriuretic peptide (BNP) and for the amino terminal fragment N-terminal prohormone BNP (NT-proBNP) are accurate and useful markers of heart failure (HF). These tests have been shown to improve physicians' ability to diagnose HF in acutely ill, symptomatic patients when there is uncertainty in the diagnosis.[1] Indeed, the

accuracy of clinical assessment of HF by history, physical examination, and conventional testing alone has been fallible, particularly in women, the elderly, the obese, and in those with renal insufficiency.[2] BNP and NT-proBNP have been shown to be sensitive and accurate markers of HF and have been shown to be superior for predicting HF relative to other markers of cardiac dysfunction.[2]

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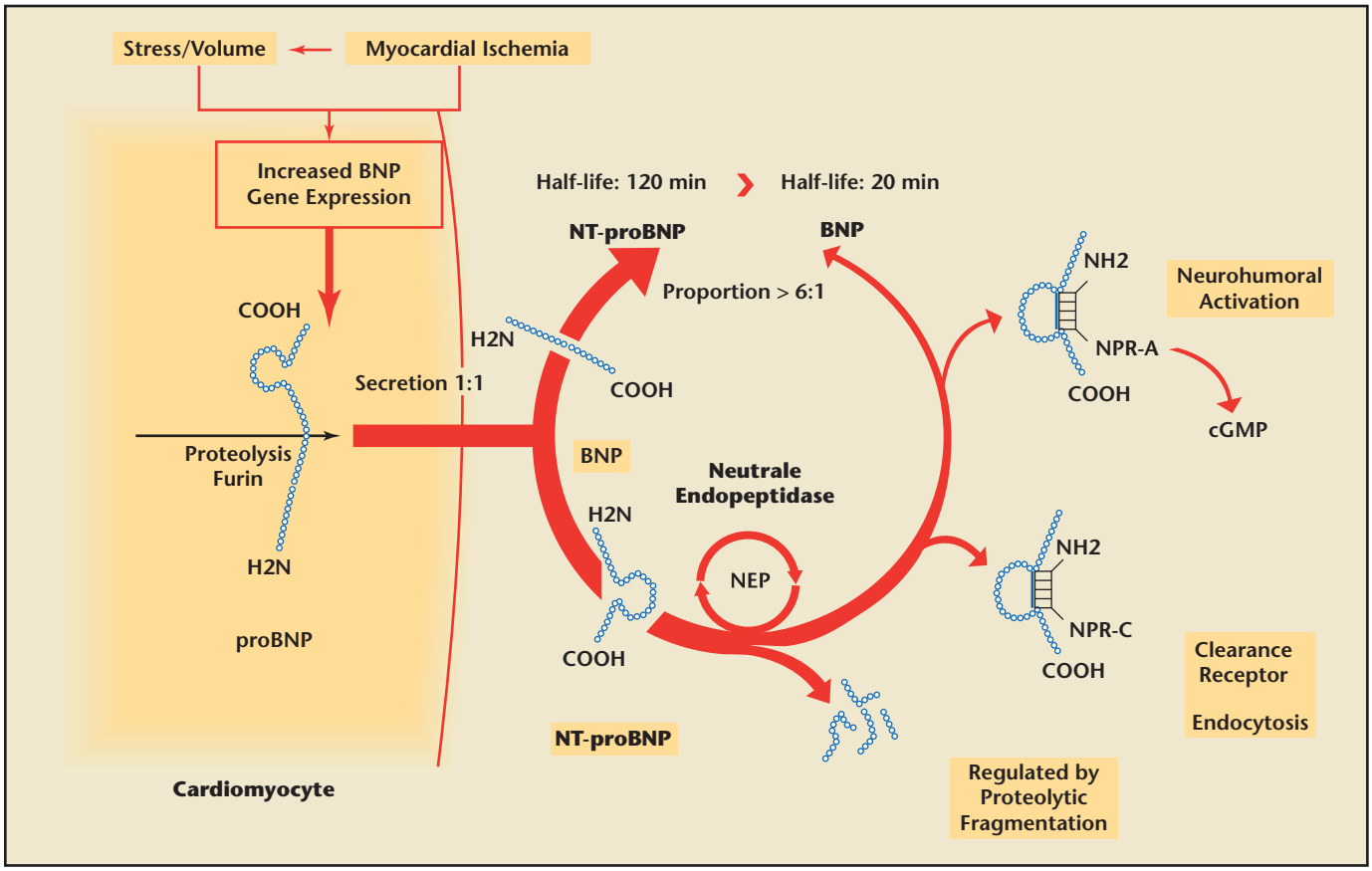
The gene for BNP is located on chromosome 1 and can be rapidly activated in response to signal transduction from the myocyte cell wall.[3] After protein synthesis, BNP is cleaved from the precursor molecule, proBNP, by the enzyme corin, into the active BNP hormone and the inactive NT-proBNP fragment. Biologically active BNP is released from cardiomyocytes in response to wall tension, which, according to the law of Laplace, is determined by the pressure within and the radius of the chamber. Because the left ventricle has the greatest mass of all the cardiac chambers, natriuretic peptides (NPs) largely reflect the dynamic wall tension experienced by the left ventricle that occurs with ischemia, pressure and volume overload, and neurohumoral activation in acute coronary syndromes (ACS). In HF, levels of these markers relate to the severity of symptoms and cardiac dysfunction (Figure 1).[4] All assays for BNP and NT-proBNP recognize epitopes on the parent peptide proBNP; thus, in the setting of acute decompensated HF and possibly ACS, it is believed that levels of these proteins reflect both immature and mature peptide products.[5] In addition, fragment peptides are known to be in the circulation of patients with HF (BNP3-32 and BNP6-32) and glycosylation of both BNP and

Figure 1. *Synthesis and neurohormonal activation of BNP and NT-proBNP in ACS patients. ACS, acute coronary syndromes; BNP, B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; NEP, neutral endopeptidase; NPR-A, natriuretic peptide receptor-A; NT-proBNP, N-terminal prohormone BNP. Reproduced from* Heart, *Weber M and Hamm C, Vol. 92, pp. 843-849, 2006, with permission from BMJ Publishing Group Ltd.*[25]



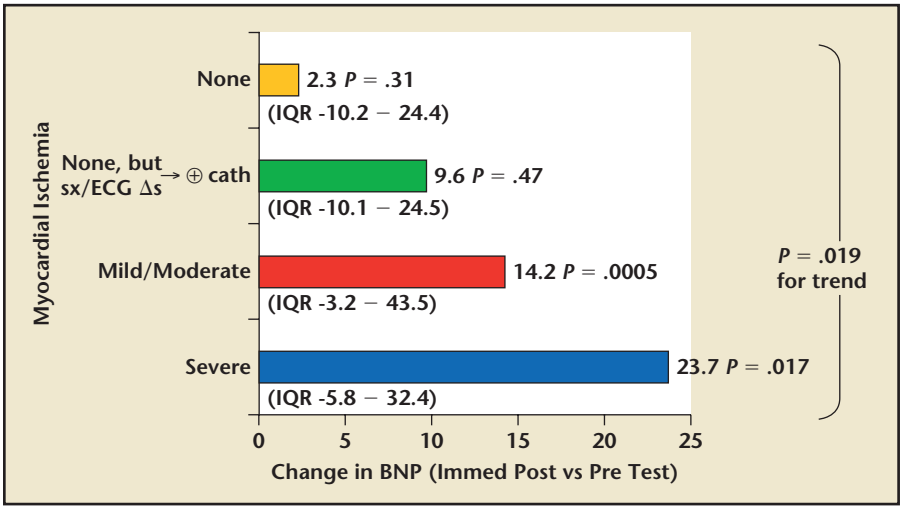


Figure 2. *Demonstration of cardiac ischemia triggering the release of BNP in patients with coronary disease and ischemia detected by stress testing. Cath, cardiac catheterization; BNP, B-type natriuretic peptide; ECG, electrocardiographic; immed, immediately, IQR, interquartile range; sx, symptoms. Reproduced from* Journal of the American College of Cardiology, *Vol. 44, Sabatine MS et al, "Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia," pp. 1988-1995, Copyright 2004, with permission from Elsevier.*[7]

NT-proBNP can occur as with many proteins to a variable degree depending on levels of glycemia and circulatory durations of the peptides.[6] Blood concentrations of BNP and NT-proBNP rise quickly in the setting of decompensation and have sustained elevation provided increased wall tension and neurohumoral activation remain present. It has been shown in the setting of reversible, transient ischemia that BNP will rise within 7 minutes of stress testing and remain elevated at 4 hours (Figure 2).[7] Thus, it is reasonable to consider NP testing in the setting of sustained, spontaneous episodes of ischemia otherwise termed ACS.

There are some differences that may affect the interpretations of these 2 markers in different patient populations. For example, BNP has a shorter half-life than NT-proBNP because the 2 peptides are cleared by different mechanisms. Thus, levels of NT-proBNP are higher than those of BNP despite being produced at a theoretical 1:1 ratio. Whereas the predominant pathway for clearance of NT-proBNP is by renal excretion, BNP appears to have multiple clearance pathways, including NP clearance receptors in the kidney and peripheral tissues, as well as degradation by plasma neutral endopeptidase (vasculature), meprin A (kidneys), and neprilysin (brain).[8] Thus, BNP levels are less affected by renal dysfunction alone than are levels of NT-proBNP.[3] However, levels of both peptides can be elevated in the setting of chronic kidney disease and loss of renal mass, and this may give a misleading suggestion of cardiac decompensation. In addition, the literature has consistently shown that a high body mass index is related to lower levels of BNP and NT-proBNP, presumably due to excess clearance by degradative enzymes in adipose tissue or lean tissue compartments.[9] Supporting this hypothesis, it has recently been shown that dietary and surgical weight loss of adipose and lean tissue results in a rise in BNP.[10] Finally, it is possible that NPs have lipolytic properties, and thus, higher levels can be associated with lower levels of adiposity because of direct effects on adipocytes.[11]

Previous Recommendations

A meta-analysis of 5 studies by Galvani and colleagues in 2004 demonstrated that elevation of either BNP or NT-proBNP had a pooled odds ratio (OR) for all-cause mortality of 3.38 and 4.31 over the short and longer term, respectively.[12] In 2007, based on 13 studies from 1996 to 2004 (n = 15,655), the National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Practice Guidelines gave a class IIa recommendation: "Measurement of brain-type (B-type) natriuretic peptide (BNP) or N-terminal prohormone BNP (NT-proBNP) may be useful, in addition to a cardiac troponin (Tn), for risk assessment in patients with a clinical syndrome consistent with ACS.[13] The benefits of therapy based on this strategy remain uncertain (Level of Evidence: A)." Furthermore, the NACB put forth a class IIb recommendation as follows: "A multimarker strategy that includes measurement of 2 or more pathobiologically diverse biomarkers in addition to a cardiac Tn may aid in enhancing risk stratification in patients with a clinical syndrome consistent with ACS. BNP and high-sensitivity C-reactive protein (CRP) are the biomarkers best studied using this approach. The benefits of therapy based on this strategy remain uncertain (Level of Evidence: C)." In agreement with these statements, the most recent (2007) American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of non–ST-segment elevation (NSTE) ACS cited the use of NP management as a class IIb indication: "Measurement of B-type natriuretic peptide (BNP) or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS. (Level of Evidence: B)."[14] These recommendations have been supported from subsequent studies demonstrating that risk scores such

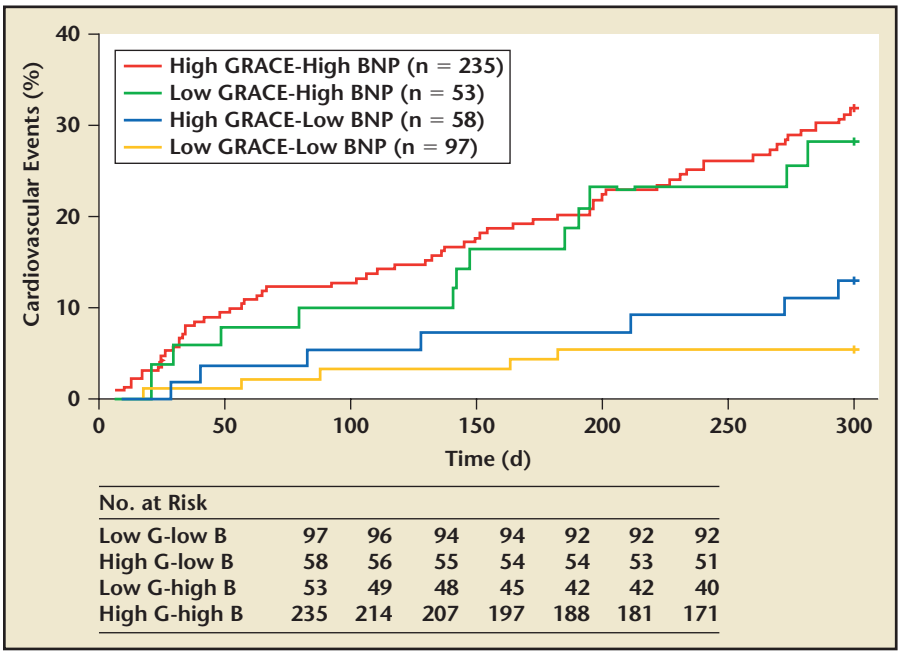


Figure 3. *Combination of BNP and GRACE risk scores in the prediction of cardiovascular events after acute coronary syndromes. BNP, B-type natriuretic peptide; GRACE, Global Registry of Acute Coronary Events. Reproduced from* Heart, *Ang DS et al, Vol. 95, pp. 1836-1842, 2009, with permission from BMJ Publishing Group Ltd.*[15]

as GRACE (Global Registry of Acute Coronary Events), can be bolstered with the knowledge of BNP in the prediction of cardiovascular events after ACS, as shown in Figure 3.[15] Neither of these guidelines had sufficient evidence to make statements about the clinicopathologic correlates of elevated NP levels, nor did they make recommendations about subsequent testing in the outpatient arena.

Methods

We performed a literature review using the NACB and ACC/AHA guidelines mentioned above as a base of key studies, and identified 32 articles that reported on > 100 ACS subjects and were focused primarily on the study of BNP (n = 12) for NT-proBNP (n = 15) and both peptides (n = 2) in either unstable angina, NSTE myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI). Data were abstracted and entered into evidence Tables 1 and 2, as shown. Smaller studies were included and cited in the text to support key concepts and important inferences.

Unstable Angina and NSTEMI

In unstable angina and NSTEMI, BNP and NT-proBNP levels have been shown to have similar prognostic value. Cameron and colleagues[16] measured both peptides in patients presenting to the emergency department with a variety of cardiovascular problems. Despite the level of NT-proBNP being quantitatively higher than BNP, they were closely correlated ($r = 0.89$, $P < .0001$) across subgroups of patients with coronary artery disease, hypertension, hypercholesterolemia, and diabetes, all of which can influence vascular function and potentially left ventricular wall tension. The higher level of NT-pro BNP (median of 185 ng/mL compared with 15 ng/mL for BNP) might be explained by its prolonged half-life and greater reliance on glomerular filtration function for elimination.[3]

Substudies of clinical trials with protocol-driven care (Orbofiban in Patients with Unstable Coronary Syndromes-Thrombolysis In Myocardial Infarction 16 [OPUS-TIMI 16], Treat Angina with Aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18 [TACTICS-TIMI 18], Fragmin and fast Revascularization during InStability in Coronary artery disease [FRISC II], Invasive versus Conservative Treatment in Unstable coronary Syndromes [ICTUS], Global Use of Strategies To Open Occluded Coronary Arteries IV [GUSTO IV], Platelet Receptor Inhibition in Ischemic Syndrome Management [PRISM], Aggrastat to Zocor [AtoZ], and Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes-Thrombolysis In Myocardial Infarction 36 [MERLIN-TIMI 36])[17-24] have evaluated the prognostic value of BNP or NT-proBNP in patients presenting with NSTE-ACS.[25] In all studies, elevated values of BNP and NT-proBNP have consistently been found in approximately 25% to 50% of subjects recruited. Furthermore, both markers were highly predictive for an adverse outcome independent of other biomarkers, especially Tn and CRP. However, it must be emphasized that BNP and NT-proBNP were predictive

In STEMI patients, markedly elevated BNP levels predicted LAD and multivessel disease, reduced ejection fraction, diastolic dysfunction, and hemodynamic compromise including cardiogenic shock and the need for intra-aortic balloon counterpulsation early during hospitalization.

Table 1
Summary of Data From Studies With ≥ 100 ACS Subjects Measuring BNP

Study	Assay	Sample Time	Level of Interest (pg/mL)	Clinical Correlates	Late Outcomes
Omland T et al.[18] Cooperative New Scandinavian Enalapril Survival Study AMI = 131	BNP	72 h	>114 pg/mL (> 33 pmol/L) (4th quartile) 25%	Correlated with reduced LVEF	45% mortality at 4 y
Richards AM et al.[29] N = 121	BNP	2-4 d and 3-5 mo	≥104 pg/mL (≥ 30 pmol/L) Median	Correlated with lower LVEF, higher LV end-systolic volumes early and late; also correlated with NT-proBNP, ANP, cGMP, NT-proANP, ADM, and NE	RR = 5.9 for death, RR = 5.5 for HF at 2 y
de Lemos JA et al.[19] OPUS-TIMI-18 N = 2525 STEMI = 825 NSTEMI = 565 UA = 1133	BNP	40 h	> 80 pg/mL 50% > 137.8 pg/mL (4th quartile) 25%	Associated with older age, female sex, white race, hypertension, HF, vascular disease, higher Killip class, CK-MB and Cr	Higher 30-d and 10-mo MI, HF, and death; adjusted OR = 5.6 for mortality at 10 mo for BNP > 137.8 pg/mL
Crilley and Farrer[39] STEMI = 133	BNP	3-7 d then 2 mo	> 456 pg/mL	Associated with worsened wall motion index and increased LV volumes (> 456 pg/mL)	BNP higher in patients who died by 1 y (675 vs 365 pg/mL)
Richards AM et al.[30] AMI = 666	BNP	24-96 h	> 104 pg/mL (> 30 pmol/L) Median 50%	Not reported	BNP higher in those incurring death, HF, MI, or new ACS; death at 3 y, all analyses indicated BNP (analyzed both as a continuous variable and in binary fashion, ie, above vs below median levels); performed similarly to NT-proBNP (see NT-proBNP results)
Morrow DA et al.[23] TACTICS-TIMI 18 N = 1676 N = 276 with angiographic data[40]	BNP	Study entry	> 80 pg/mL 19.1%	Associated with older age, female sex, and prior HF, diabetes, ST depression, multivessel disease	Death = 8.4%, death or HF = 16.3% at 6 mo; BNP not predictive of MI or rehospitalization for ACS; invasive strategy not favored in BNP > 80 pg/mL without elevated cTnI
Mega JL et al.[31] ENTIRE TIMI-23 STEMI = 438	BNP	< 6 h	> 80 pg/mL 10.5%	64.1% impaired flow, 53.8% poor perfusion, 95.8% no ST resolution	Death at 30 d = 17.4%
Grabowski M et al.[32,41] STEMI = 126	BNP	7.3 h	> 100 pg/mL ≥ 331 pg/mL	TIMI flow < 3 in 27% after PCI, OR = 3.4; no-reflow in 23.1%, OR = 6.2	Death at 42 d = 14.3%, adjusted OR = 16.3 for BNP > 100; if TIMI risk score ≥ 4 and ≥ 331, 50% mortality

(*continued*)

Table 1 (Continued)

Study	Assay	Sample Time	Level of Interest (pg/mL)	Clinical Correlates	Late Outcomes
Morrow DA et al.[42] AtoZ Trial NSTEMI = 4496	BNP	Hospital discharge, 4, 12 mo	> 80 pg/mL	Declining BNP conferred lower risk of death, MI, or HF	Associated with death or new HF when measured at discharge (21%) adjusted HR, 2.5; at 4 mo, 19%, adjusted HR, 3.9; and at 12 mo 11% adjusted HR, 4.7; death or new HF at 2 y
Kuklinska AM et al.[43] STEMI = 86	BNP	3.7 h	> 99.2 pg/mL	Sensitivity = 93.3%, AUC = 0.950 for prediction composite endpoint	Death, stroke, recurrent ischemic events at 7 mo, OR=732.2
Brown AM et al.[44] Chest pain = 426	BNP	ED presentation and 90 min	> 51 pg/mL	BNP added to myoglobin, CK-MB, and cTnI increased sensitivity for AMI from 87.2%-97.4%	30-d all-cause mortality, AMI, or revascularization at 30 d, BNP increased sensitivity from 71.2%-88.5%
Jeong YH et al.[45] STEMI = 207	BNP	4.7 h	> 80 pg/mL 27.5%	Higher TIMI risk, greater delay to PCI, no difference in-hospital death and MI	Death, MI, HF, at 1 y 15.8% not significantly different from 10.7%
Brügger-Andersen T et al.[46] Risk in the Acute Coronary Syndrome Suspected ACS = 828	BNP	Admit	> 310 pg/mL	Prior HF 57.5%	Death at 30 d, HR = 9.4, death at 2 y, HR = 5.1 cardiac death or MI at 30 d, HR = 1.7, at 2 y HR = 2.3
Ang DS et al.[15,47,48] STEMI = 120 NSTEMI = 236 UA = 93	BNP	Admission 7-wk post	> 80 pg/mL	STEMI BNP = 9210 NSTE-ACS = 134 pg/mL; 50% had persistently elevated BNP > 80 pg/mL; BNP additive to TIMI risk score, GRACE risk score	Death at 10 mo 10%; readmission with ACS, HF, all-cause mortality 26.7% at 10 mo, RR = 4.2; change in BNP at 7 wk predictive of future events
Morrow DA et al.[24] MERLIN-TIMI 36 NSTE-ACS = 4543	BNP	Admission	> 80 pg/mL 42.6%	Antianginal ranolazine associated with reduced composite in those with BNP > 80 pg/mL	Composite 26.4% vs 20.4%, cardiovascular death 8.0% vs 2.1%, and MI 10.6% vs 5.8% at 1 y

AtoZ, Aggrastat to Zocor; ACS, acute coronary syndromes; ADM, adrenomedullin, AMI, acute myocardial infarction; ANP, atrial natriuretic peptide; AUC, area under receiver operating characteristic curve; BNP, B-type natriuretic peptide; CK-MB, creatine kinase-myocardial band; cGMP, cyclic guanosine monophosphate; Cr, creatinine; cTnI, cardiac troponin-I; ED, emergency department; ENTIRE, Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion strategy in ST-elevation myocardial infarction; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; HR, hazard ratio; ICU, intensive care unit; IVUS, intravascular ultrasound; LM, left main; LVEF, left ventricular ejection fraction; MERLIN, Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes; NE, norepinephrine, NSTEMI, non–ST-segment myocardial infarction; NT-proANP, N-terminal prohormone ANP; NT-proBNP, N-terminal prohormone BNP; OR, odds ratio; PCI, percutaneous coronary intervention; RR, relative risk; STEMI, ST-segment elevation myocardial infarction; TACTICS, Treat Angina with Aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy; TIMI, Thrombolysis in Myocardial Infarction Study Group; UA, unstable angina.

Table 2
Summary of Data From Studies With ≥ 100 ACS Subjects Measuring NT-proBNP

Study	Assay	Sample Time	Level of Interest	Clinical Correlates	Late Outcomes
Richards AM et al.[29] N = 121	NT-proBNP	2-4 d and 3-5 mo	≥ 1353 pg/mL (≥ 160 pmol/L)	Correlated with lower LVEF, higher LV end-systolic volumes early and late; also correlated with BNP, ANP, cGMP, NT-proANP, ADM, and NE	RR = 19.7 for death, RR = 5.5 for HF at 2 y
Omland T et al.[26] STEMI = 204 NSTEMI = 220 UA = 185	NT-proBNP	72 h	> 4609 pg/mL (> 545 pmol/L) Median 50%	Associated with older age, lower LVEF, NT-proBNP higher STEMI > NSTEMI > UA	Mortality at 51 mo, adjusted RR = 2.6
Jernberg T et al.[21] N = 755 NSTEMI = 407 Other = 368	NT-proBNP	Admit and 6 h	> 400 pg/mL Median 50% > 1654 pg/mL 4th quartile 25%	Associated with older age, female sex, diabetes, HTN, HF, Cr; increased from admit to 6 h in NT-proBNP AMI	Death at 40 mo, RR = 10.7 (median), RR = 26.6 (4th quartile)
Richards AM et al.[30] N = 666	NT-proBNP	24-96 h	> 1370 pg/mL (> 162 pmol/L) Median 50%	Not reported	Death at 3 y, adjusted RR = 6.6; death or HF, RR = 2.7; reinfarction RR = 3.5
Jernberg T et al.[17] Lindahl B et al.[36] FRISC II NSTE-ACS = 2019	NT-proBNP	39 h, 2 d, 6 wk, 3 mo, 6 mo	≥ 906 pg/mL (men) ≥ 1345 pg/mL (women) 3rd tertile	Associated with older age, prior MI, prior HF, ST depression, cTnT, lower LVEF, LM, or 3-vessel disease, median levels declined from previous time points	Death at 2 y, adjusted OR = 3.8, 3.1 for the invasive and conservative groups, respectively
James SK et al.[49] GUSTO-IV NSTE-ACS = 6809	NT-proBNP	9.5 h	> 1869 pg/mL (4th quartile) 25%	Correlated with age, serum Cr, time from symptom onset	Survival curve shows significant early to 1-y mortality (27.1%)
Zeller M et al.[50] NSTEMI = 101	NT-proBNP	2 d	136 pg/mL Median 50%	Independently associated with older age, HTN, LVEF < 50%, PURSUIT risk score	In-hospital death, recurrent MI, or HF occurred in 27% with median NT-proBNP of 184 pg/mL
Galvani M et al.[51] ANMCO N = 1756 STEMI = 615 NSTE-ACS = 1138	NT-proBNP	3 h	≥ 1358 pg/mL (4th quartile) 25%	Associated with older age, female sex, diabetes, HTN, smoking, HF, Cr, cTnT, CK-MB, increasing Killip class	Mortality 15% at 30 d, adjusted RR = 3.9
Heeschen C et al.[22] PRISM NSTE-ACS = 1791	NT-proBNP	Admit, 48, 72 h	> 250 pg/mL 49.6%	Associated with older age, ST depression, T-wave inversion, prior HF, elevated cTnT; rising serial levels associated with refractory ischemia	Death or nonfatal MI at 30 d, adjusted OR = 2.68, 17.2% event rate for persistently elevated levels
Bazzino O et al.[52] PACS Group NSTEMI = 257 UA = 1226	NT-proBNP	3.2 h	> 586 pg/mL 39.5%	Associated with older age, female sex, prior MI, prior revascularization, lower CrCl, CK-MB, cTnI, cTnT; NT-proBNP added to TIMI risks, and ACC/AHA risk classifications	Death at 30 d, OR = 1.7; death OR = 1.4, death or MI, OR = 1.7, at 180 d, respectively; NT-proBNP not predictive of MI alone
Kim H et al.[53] STEMI = 56 NSTEMI = 98 UA = 61	NT-proBNP	Admit	> 500 pg/mL	Correlated with lower LVEF	Sensitivity 87.5% for death, MI, HF, rehospitalization at 1 y

(*continued*)

Table 2
(Continued)

Study	Assay	Sample Time	Level of Interest	Clinical Correlates	Late Outcomes
Kavsak et al.[54,55] STEMI = 22 NSTEMI = 20 UA = 174	NT-proBNP	2.0 and 9.0 h	> 183 pg/mL Median for 2nd time point 50%	Rise from 2.0-9.0 was not predictive of outcomes	Adjusted HR for mortality at 6 mo, 2 y, and 8 y: 3.5, 3.9, 3.2
Hong YJ et al.[56] STEMI = 20 NSTEMI = 51 UA = 85	NT-proBNP	Before PCI time not reported	≥ 200 pg/mL 37.2%	Higher rates of vulnerable plaque by IVUS-virtual histology, no-reflow, OR = 4.4	Not reported
Windhausen F et al.[20] ICTUS NSTE-ACS = 1141	NT-proBNP	Admit	≥ 1170 ng/L (men) ≥ 2150 ng/L (women (4th quartile) 25%	Associated with older age, prior MI, HTN, reduced CrCl, LM and multivessel disease	Adjusted death HR = 5.0, MI and rehospitalization for ACS not significant at 1 y
Weber M et al.[27] STEMI = 490 NSTE-ACS = 2124	NT-proBNP	Admit	> 474 pg/mL	The predictive value associated with NT-proBNP > 474 pg/mL, demonstrated consistently in various subgroups such as age < 65 and > 65 y, male and female sex, diagnosis of STEMI or NSTE-ACS, TIMI risk score, time from onset of symptoms < 6 h and > 6 h, and diabetes mellitus	Adjusted HR for death at 6 mo: 5.0, derivation validation methods
Sarullo FM et al.[57] STEMI = 130 with LVEF > 45%	NT-proBNP	Admit and 96-120 h later	415 pg/mL (time 1) 1005 pg/mL (time 2) (mean of 3rd tertiles)	Associated with older age and lower LVEF	OR = 8.7 for residual ischemia (present in 75% of 3rd tertile) on stress nuclear testing at 30 d
Kwon TG et al.[58] KAMIR STEMI = 1052	NT-proBNP	Admit	> 991 pg/mL 31.3%	Associated with older age, female sex, smoking, prior HF, ischemic heart disease, higher Killip class, lower EF, LM, multivessel disease longer ICU stay	Cardiogenic shock requiring IABP developed in 12.5%, in-hospital death, adjusted OR = 3.7

ACC/AHA, American Heart Association, American College of Cardiology; ACS, acute coronary syndromes; ADM, adrenomedullin, AMI, acute myocardial infarction; ANMCO, Associazione Nazionale Medici Cardiologi Ospedalieri; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; CK-MB, creatine kinase-myocardial band; Cr, creatinine; CrCl, creatinine clearance; cTnI, cardiac troponin I; cTnT, cardiac troponin T; FRISC, Fragmin and fast Revascularization during InStability in Coronary artery disease; GUSTO, Global Use of Strategies To Open Occluded Coronary Arteries; HF, heart failure; HTN, hypertension; HR, hazard ratio; IABP, intra-aortic balloon counterpulsation; ICU, intensive care unit; ICTUS, Invasive versus Conservative Treatment in Unstable coronary Syndromes; IVUS, intravascular ultrasound; KAMIR, Korean Acute Myocardial Infarction Registry; LM, left main; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NE, norepinephrine; NT-proANP, N-terminal prohormone ANP; NT-proBNP, N-terminal prohormone BNP; NSTEMI, non-ST-segment myocardial infarction; OR, odds ratio; PACS, Prognosis in Acute Coronary Syndromes; PCI, percutaneous coronary intervention; PRISM, Platelet Receptor Inhibition in Ischemic Syndrome Management; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; RR, relative risk; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction Study Group; UA, unstable angina.

for short-term mortality and HF but not consistently for recurrent ischemic events, including myocardial infarction (MI) and rehospitalization for ACS, especially when matched for age and sex.[26]

In OPUS-TIMI-18, de Lemos and associates[19] studied the value of BNP in patients with unstable angina and NSTEMI and showed that a single measurement of BNP obtained within 40 hours of the onset of ischemic symptoms can be used for risk stratification in ACS. In the same study, it was shown that BNP can be elevated, even in the absence of MI. Patients exceeding the threshold of 80 pg/mL, approximating the level of neurohormonal activation in HF (100 pg/mL), had an increased risk of 10-month mortality (OR = 5.8) compared with patients with BNP < 80 pg/mL. Other authors found the same threshold as useful to identify patients at risk for HF and death at 6 months after ACS.[23] The combined Bad Nauheim ACS registry and the Prognosis in Acute Coronary Syndromes (PACS) cohort used by Weber and colleagues[27] also clearly demonstrated that in the absence of elevated cardiac Tn T (cTnT), NT-proBNP > 474 pg/mL was independently predictive of mortality at 6 months. The NT-proBNP level range obtained on admission associated with risk of death in ACS in other studies is between 136 and 4609 pg/mL (Table 2). Thus, it is clear that both BNP and NT-proBNP have prognostic value for mortality over the entire spectrum of ACS, including those without confirmed acute MI by Tn elevation.

BNP and NT-proBNP also add incremental prognostic information to other biomarkers, including Tn I and T and CRP, in patients with NSTEMI. Sabatine and associates[28] demonstrated that patients with 1, 2, or 3 elevated biomarkers had, respectively, 2.1-, 3.1-, and 3.7-fold increases in the risk of death, MI, and congestive HF at 6 months. Thus, the concept that the simultaneous elevation of multiple markers of myocardial injury and/or dysfunction is associated with escalating risk of death is supported by this study.

In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Thrombolysis In Myocardial Infarction 36 Trial (MERLIN-TIMI 36), BNP was elevated > 80 pg/mL at baseline in 1935 of 4543 patients (43%) and was associated with higher rates of recurrent ischemia, MI, and cardiovascular death.[24] In addition, treatment with ranolazine, an anti-ischemia agent that has its effect by inhibiting the late sodium channel in ischemic cardiomyocytes, was associated with a lower rate of composite endpoint events over the next year in those with BNP > 80 pg/mL. Thus, these data support a treatment interaction with BNP being an indicator, perhaps, of a greater ischemic burden related to multivessel disease in patients with NSTE-ACS.

STEMI

In 2 observational studies from a single-center in New Zealand, Richards and colleagues[29,30] demonstrated that BNP and NT-proBNP were highly correlated in a mixed population of NSTEMI and STEMI (r = 0.95), and also strongly related to other NPs (atrial natriuretic peptide [ANP], NT-proANP), as well as the second messenger cyclic guanosine monophosphate (cGMP), adrenomedullin, and norepinephrine. In STEMI, Mega and associates[31] demonstrated in the Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion strategy in ST-elevation myocardial infarction-Thrombolysis In Myocardial Infarction (ENTIRE-TIMI 23) study that a BNP level of more than 80 pg/mL at initial presentation identified patients at a 7-fold higher risk of death. In the same study, increased concentration of BNP at initial presentation of patients with STEMI was associated with impaired reperfusion and fibrinolysis. This has been supported by Grabowski and coworkers,[32] who demonstrated in 126 consecutive patients with STEMI that a BNP > 100 pg/mL (median) was associated with the following: TIMI grade < 3 after percutaneous coronary intervention (PCI) (OR = 3.4, P = .02), the no-reflow phenomenon (OR = 6.2, P = .007), and death (OR = 16.3, P = .03), after adjusting for other variables.

Pathophysiologic Correlates

In STEMI patients, BNP level has been associated with underlying severity of coronary artery disease and degree of ischemic myocardium. Palazzuoli and coauthors[33] studied 88 patients with NSTEMI and preserved ejection fraction, and found that BNP levels were significantly higher in patients with 3-vessel disease compared with patients with 2- or 1-vessel disease. Patients with left anterior descending artery (LAD) stenosis had higher BNP levels compared with patients with stenoses in other vessels. This concept of the association between BNP and ischemia-related increase in wall tension is supported by studies showing that there is an increase in BNP level after exercise myocardial perfusion testing with significant

BNP and NT-proBNP also add incremental prognostic information to other biomarkers, including Tn I and T and CRP, in patients with NSTEMI.

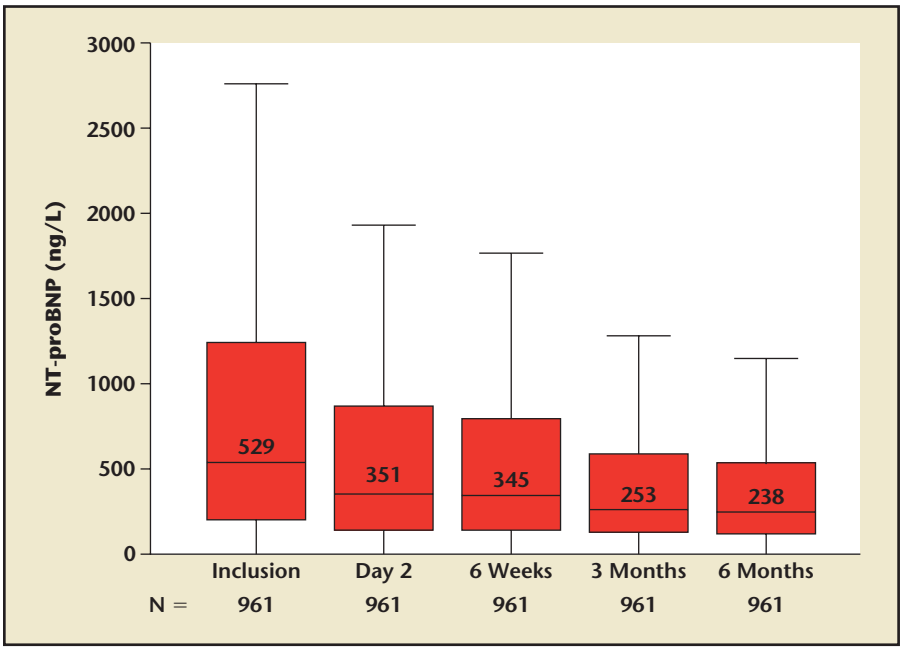


Figure 4. *Serial changes in N-terminal prohormone B-type natriuretic peptide (NT-proBNP) after acute myocardial infarction. Reproduced from* Journal of the American College of Cardiology, *Vol. 45, Lindahl B et al, "Serial analyses of N-terminal pro-B-type natriuretic peptide in patients with non-ST-segment elevation acute coronary syndromes: a Fragmin and fast Revascularisation during In Stability in Coronary artery disease (FRISC)-II substudy," pp. 533-541, Copyright 2005, with permission from Elsevier.*[36]

ischemia and after transient ischemia induced by PCI.[34]

In a retrospective study reported by Neyou and colleagues,[35] 91 patients admitted with STEMI, with BNP levels obtained within 24 hours of admission, markedly elevated BNP levels (median, 25th percentile and 75th percentile of the BNP value were 366, 142, and 1011 pg/mL, respectively) predicted LAD and multivessel disease, reduced ejection fraction, diastolic dysfunction, and hemodynamic compromise including cardiogenic shock and the need for intra-aortic balloon counterpulsation early during hospitalization. In the same study, despite prompt angiography and primary PCI, substantial elevations of BNP was a prognostic marker of in-hospital mortality due to cardiovascular causes after STEMI. These data suggest that BNP level might predict not only the infarct size but also may portend cardiogenic shock in patients with STEMI.

Serial Measurement

Several studies have made serial measurements of BNP or NT-proBNP during the index hospitalization and approximately 6 to 8 weeks and then 6 to 12 months in follow-up. Lindahl and colleagues[36] demonstrated that NT-proBNP steadily declines each day after hospital admission for ACS, as shown in Figure 4. Jernberg and associates[21] studied 755 patients with an ACS and observed no difference in the predictive value as indicated by the area under the receiver operating characteristic curve for NT-proBNP on admission and after 6 hours. In a substudy of the PRISM trial, Heeschen and coworkers[22] demonstrated an incremental prognostic value of serial NT-proBNP assessment on admission and a later measurement at 72 hours. In the FRISC II trial, serial NT-proBNP values were evaluated during the acute and the chronic phase of ACS and the predictive value of NT-proBNP measured 3 and 6 months after hospitalization was a better predictor of 2-year mortality than early NT-proBNP determination at admission or at 48 hours after the acute event. In this study, NT-proBNP levels declined from a median of 529 at the index event, to 238 pg/mL at 6 months.[36] These data suggest that measurement on admission, and perhaps at 1 or 2 time periods after hospital discharge, may be a reasonable strategy to optimize prognosis (Figure 5).

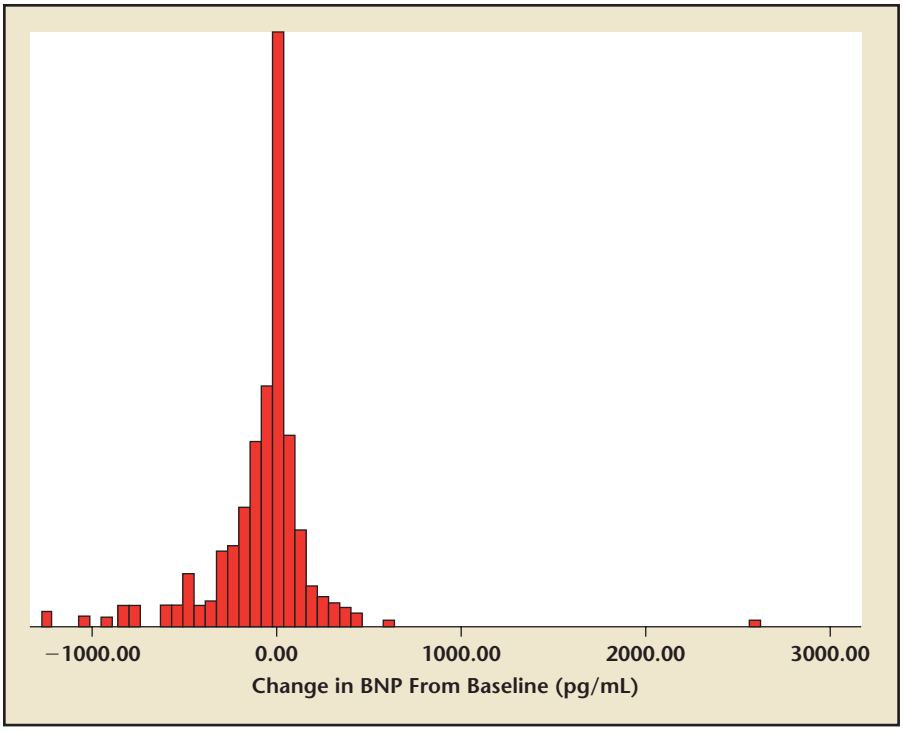
Management Implications

The therapeutic benefits that can be derived from BNP and NT-proBNP assessment in ACS are not clear with respect to invasive versus conservative management. In the TACTICS-TIMI 18 trial no difference was observed in the effect of invasive versus conservative management when stratified by baseline levels of BNP.[23] It is important to point out that the BNP value was not known to clinicians at the time of the trial and that this was not a test of BNP-guided management. Several trials have investigated the potential utility of NT-proBNP for identifying patients who might benefit from a more intensive management strategy including the FRISC II, PRISM, and ICTUS trials.[16,17,20] In the FRISC II trial, there was a trend toward a better outcome in patients with NT-proBNP values in the highest tertile who underwent invasive management. However, only in combination with elevated interleukin-6 concentrations did NT-proBNP values in the third tertile confer a statistically significant treatment benefit from early invasive therapy.[17] When considering NT-proBNP alone followed over time in FRISC II, researchers found no significant difference between patients randomized to an invasive versus a noninvasive strategy in baseline

levels, rate of change, or 6-month levels.[36] In the substudy of the PRISM trial, Heeschen and colleagues[22] analyzed the effect of glycoprotein IIb/IIIa inhibition with tirofiban with respect to NT-proBNP values. Even though patients with high NT-proBNP values had a lower event rate with tirofiban treatment compared with placebo at 48 hours, there was no significant interaction between NT-proBNP values and the clinical benefit of tirofiban treatment at 30 days. Likewise, in the ICTUS trial, an early invasive strategy provided no mortality reduction, irrespective of NT-proBNP at baseline.[20] Unlike the studies in ACS, in HF populations, there is a body of literature supporting the use of BNP/NT-proBNP guidance in the management of left ventricular dysfunction, resulting in more effective use of medications and a reduction in hospitalization and death.[37] These data can be extrapolated to the ACS patient who develops signs or symptoms of HF or has a low left ventricular ejection fraction (LVEF) measured during the index event, therefore providing support for the performance of serial measurements after discharge as an aid in medical management (Figure 6). Strategies based on the identification of left ventricular dysfunction include the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, β-adrenergic blockers, aldosterone receptor antagonists, and later in the course, implantable cardioverter defibrillators and cardiac resynchronization therapy.[14]

Unlike the studies in ACS, in HF populations, there is a body of literature supporting the use of BNP/NT-proBNP guidance in the management of left ventricular dysfunction, resulting in more effective use of medications and a reduction in hospitalization and death.

Figure 5. *Histogram of the change in B-type natriuretic peptide (BNP) from baseline to 7 weeks in follow-up in acute coronary syndromes. Reproduced with permission from Ang DS et al, 2009,* Clinical Science, *Vol 117, pp 41-48. © the Biochemical Society.*[48]

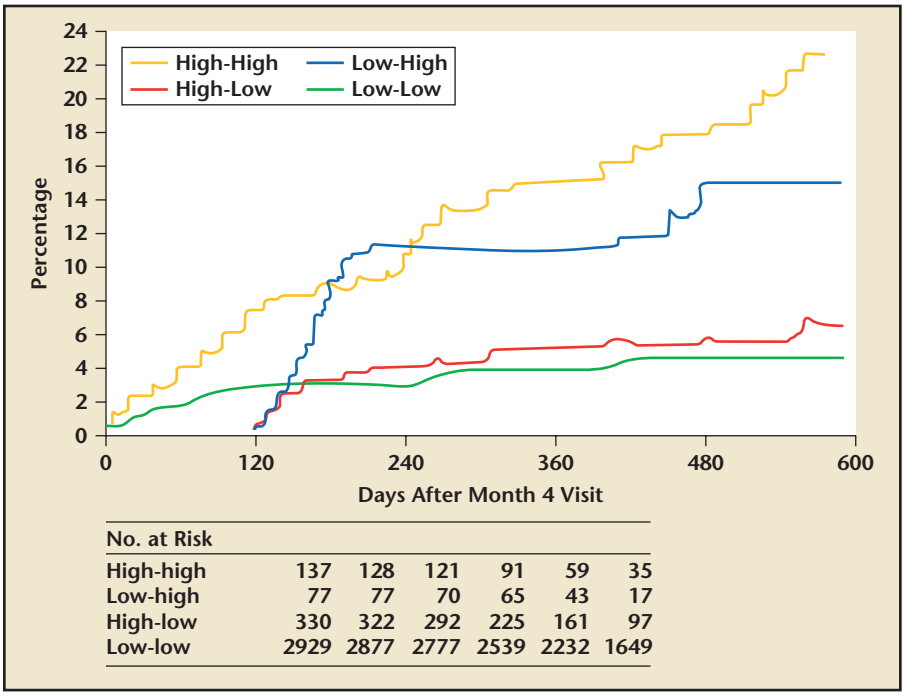


Threshold Values

Overall, BNP and NT-proBNP have a comparable prognostic value in stable angina, unstable angina, NSTEMI, and STEMI, as assessed by many studies using the area under the receiver operating characteristic curve.[3] The threshold value of BNP is lower and more consistent than of NT-proBNP, most likely secondary to the different half-life and mode of elimination of the peptides. Because NT-proBNP is more greatly influenced by age-related declines in glomerular filtration rate and by intrinsic kidney disease, the overall threshold values and the variability in those levels is greater than that of BNP. As indicated in Table 1, the threshold values of interest reported for BNP and NT-proBNP range from 80 to 310 pg/mL and 136 to 4609 pg/mL, respectively (Tables 1 and 2). Studies of NT-proBNP testing in HF have suggested different cutoff values depending on renal filtration function.[38] Because there is no true biologic threshold for either BNP or NT-proBNP in vitro, we proposed a teachable paradigm for routine NP testing that allows consideration of both peptides in clinical practice.

Algorithm for NP Testing in Suspected ACS

Figure 7 presents a risk stratification approach combining history, electrocardiography, biomarkers of myocardial injury (cardiac troponin-I, cTnT, creatine kinase-myocardial band, myoglobin), and NP testing. Very



No. at Risk						
High-high	137	128	121	91	59	35
Low-high	77	77	70	65	43	17
High-low	330	322	292	225	161	97
Low-low	2929	2877	2777	2539	2232	1649

Figure 6. *Risk of death or new or worsening heart failure according to baseline B-type natriuretic peptide (BNP) and convalescent values at 4 months after acute coronary syndromes. CHF, congestive heart failure. Reprinted with permission from Morrow DA et al.*[42]

low-risk patients in whom acute MI has been ruled out and have normal BNP/NT-proBNP levels may be considered for discharge to home after noninvasive imaging is performed acutely or planned as an outpatient. For patients with either electrocardiographic or biomarker findings of ACS anticipated clinical correlates of short- and long-term outcomes are shown with NP level elevation. Consideration for serial inpatient testing (day 3 or at discharge) and follow-up outpatient measurement at 4 to 12 weeks and 6 to 12 months is reasonable, based on the studies listed in Table 1. Decisions concerning treatment should be driven by the clinical scenario; however, NP levels indicative of very high risk, and patients in cardiogenic shock, may prompt more intensive management with attempts at early revascularization and a readiness for hemodynamic support. In addition, patients with the development of low LVEF or HF benefit from the use of ACE inhibitors, angiotensin receptor blockers, aldosterone receptor blockers, and β-blockers that are indicated for HF. After 3 months, it is reasonable to consider prophylactic implantable cardio defibrillator and cardiac resynchronization therapy according to recent guidelines. It should be emphasized that the NP level alone should not be a trigger for pharmacologic or mechanical therapy; however, it may be used to assist the clinician when considered with other diagnostic information such as echocardiography, angiography, and stress imaging.

Conclusions

Testing for BNP or NT-proBNP has a significant impact on patient care and outcome in high-risk groups and in patients with suspected ACS. The development of automated assays testing for these markers of risk is a valuable tool for physicians. Consequently, nearly all hospitals now have the capability to test for NPs. Prompt and appropriate use of therapeutic interventions can have a positive impact on patient quality of life. Accurate markers of risk, such as BNP and NT-proBNP, are valuable for the assessment and monitoring of ACS patients in the emergency department, during the hospital stay, and at the time of outpatient follow-up. We propose an evidence-based algorithm for the incorporation of these tests in routine clinical evaluation of ACS and believe its use will enhance understanding of risk, expectation of complications, and facilitation of acute and convalescent management. ■

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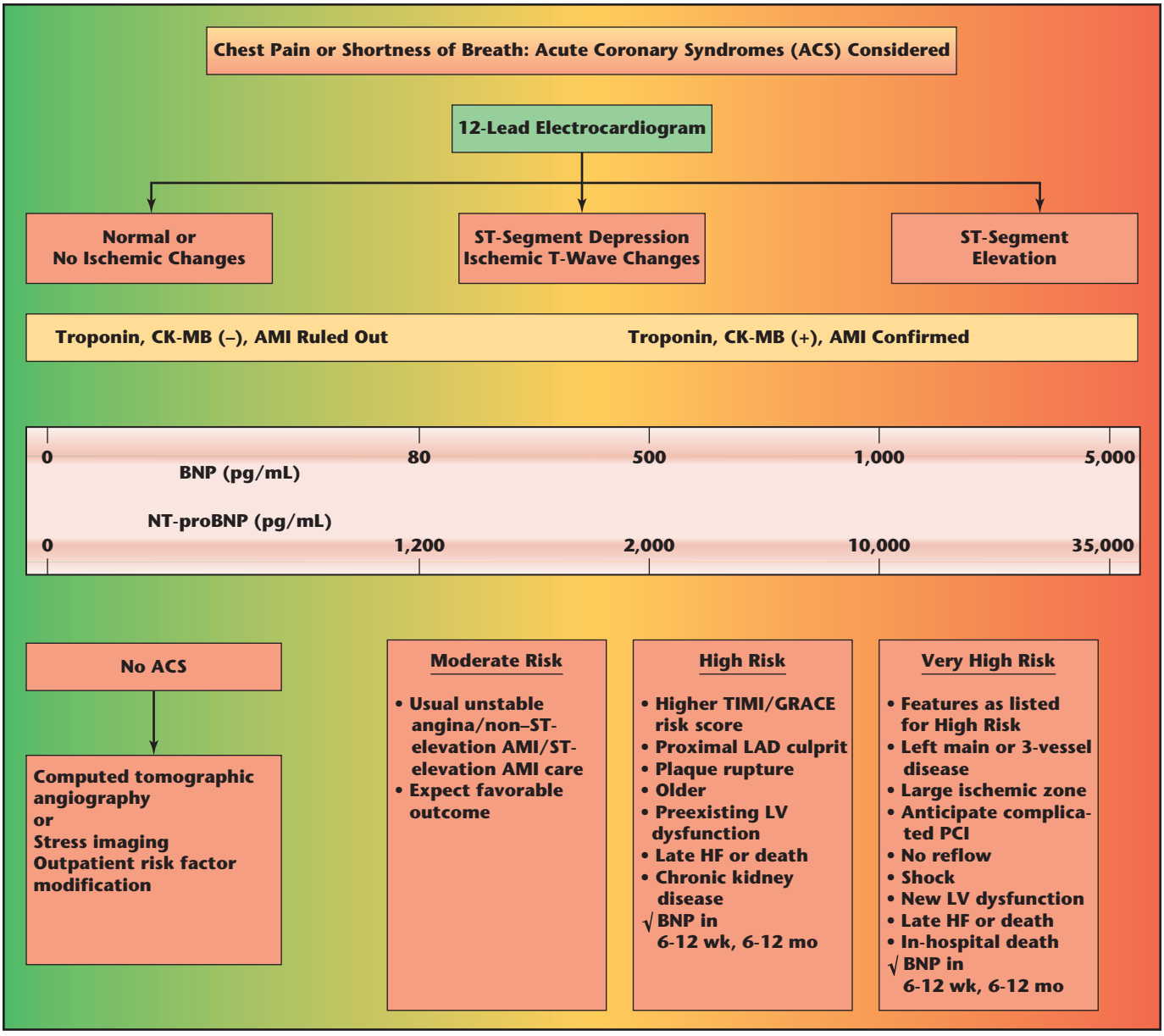

Figure 7. *Evidence-based algorithm for the measurement and clinical use of BNP and NT-proBNP in NSTE-ACS. It may serve as an approximate nomogram to anticipate outcomes according to clinical findings by lining up various features of each case. AMI, acute myocardial infarction; BNP, B-type natriuretic peptide; CK-MB, creatine kinase-myocardial band; HF, heart failure; GRACE, Global Registry of Acute Coronary Events; LAD, left anterior descending artery; LV, left ventricular; NT-proBNP, N-terminal prohormone BNP; PCI, percutaneous coronary intervention; Prox, proximal; TIMI, thrombolysis in myocardial infarction.*

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Main Points

- Measurable B-type natriuretic peptides (BNPs), largely produced by the left ventricle, include BNP and N-terminal prohormone BNP (NT-proBNP). These proteins are released by cardiomyocytes in response to wall tension and neurohumoral signals, and are established tools in the diagnosis and prognosis of heart failure (HF) in acutely ill patients.
- Natriuretic peptide (NP) elevation is associated with older age, female sex, hypertension, diabetes, prior HF, prior ischemic heart disease, and reduced renal function.
- Numerous studies support the evidence that threshold values of interest reported for BNP and NT-proBNP range from 80 to 310 pg/mL and 136 to 4609 pg/mL.
- NP levels alone should not be a trigger for pharmacologic or mechanical therapy; however, they may be used to assist the clinician in consideration with other diagnostic information such as echocardiography, angiography, and stress imaging.
- In addition to baseline measurement, there is consensus that repeat testing at 4 to 12 weeks and 6 to 12 months in follow-up is helpful in the anticipation of late cardiac sequelae and may assist in assessing prognosis and guiding management.
- An evidence-based algorithm for the incorporation of these tests in routine clinical evaluation of ACS is presented here; we believe its use will enhance understanding of risk, expectation of complications, and facilitation of acute and convalescent management.

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