Japanese-Western Consensus Meeting on Biomarkers

Executive Summary

Alan S. Maisel,1 MD, Kazuwa Nakao,2 MD, Piotr Ponikowski,3 MD, W. Frank Peacock,4 MD, Michihiro Yoshimura,5 MD, Toru Suzuki,6 MD, Takayoshi Tsutamoto,7 MD, Gerasimos S. Filippatos,8 MD, Yoshihiro Saito,9 MD, Yoshihiro Seino,10 MD, Naoto Minamino,11 PhD, Yasunobu Hirata,12 MD, Masashi Mukoyama,13 MD, Toshio Nishikimi,14 MD, and Ryozo Naga15 MD

On November 21, 2009, biomarker leaders from Europe and America met with leading biomarker and cardiologists of Japan to discuss and come to consensus on state-of-the-art natriuretic peptide research. Natriuretic peptides, brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP), have revolutionized the way we look at patients presenting with dyspnea. While not considered stand-alone tests, natriuretic peptide (NP) testing clearly adds value to the workup and follow-up of patients. In order to use NP levels correctly, physicians need to be aware of the molecular biology of the peptides, appropriate cutoffs in various conditions, and important caveats for using natriuretic peptide levels. These were all discussed at the meeting. Additionally, natriuretic peptide testing as portrayed in guidelines from the participating countries were compared and contrasted. When describing BNP values in Japan and in the United States in parallel, each BNP value was calculated by using the correlation data of Fischet al.11

State-of-the-art BNP research: Brain natriuretic peptide (BNP) first isolated from the porcine brain is a cardiac hormone secreted mainly from the ventricle of the heart. Human BNP consists of 32 amino acids, and its molecular size differs from those of other species. The primary structure of BNP also shows marked species difference as shown in Figure 1, indicating that the specificity of the antibody used for the assay system should be carefully considered. Metabolic clearance of natriuretic peptide family, atrial natriuretic peptide (ANP), BNP and C-type natriuretic peptide (CNP) comprises two systems, neutral endopeptidase-mediated degradation and clearance receptor-mediated internalization. The rank order in affinity for human clearance receptor is ANP > CNP > BNP, indicating that the half life of BNP in the bloodstream is longer than those of ANP and CNP. In striking contrast with molecular forms of ANP in plasma and the heart, the molecular forms of BNP consist of proBNP and BNP in humans as well as in rats. Table I shows a comparison of BNP and ANP in various aspects. Although a recent paper reported that BNP does not circulate in patients with heart failure, which indicates proBNP functions as a circulating form of BNP-like immunoreactivity in human plasma, this misleading result can be explained by the very poor recovery of BNP-32 extraction and peptidase digestion of BNP-32. The posttranslational processing of proBNP is more advanced in the central nervous system. The modification by O-glycosylation of the N-terminal part of proBNP, which interferes with the processing of proBNP, makes precise analysis of molecular forms of circulating BNP-like and N-terminal proBNP-like immunoreactivities very difficult for clinical biomarkers. Since the functional molecule of BNP is BNP-32, and BNP-32 is not modified by O-glycosylation and other modifications, BNP-32 should be measured as a biomarker for heart failure (HF), like insulin for diabetes mellitus as shown in Table II.

Complex BNP species in human plasma: BNP is a clinically useful diagnostic marker for pathophysiological conditions of heart disease, including HF, ventricular remodeling, and pulmonary hypertension.2-3 BNP-32 (active form), proBNP (proBNP[1-108], weakly active form), and NT-proBNP (proBNP[1-76], inactive form) circulate in the plasma of healthy subjects in contrast with atrial natriuretic peptide (ANP) (Figure 2). Although plasma levels of these BNP species increase in HF patients, recent studies have revealed that the plasma proBNP level shows a higher elevation than that of BNP-32.4,5 In the plasma of HF patients, furthermore, proBNP is O-glycosylated in the NT-proBNP region, and O-glycosylated (Glyco-) proBNP with weak activity circulates along with Glyco-NT-proBNP and other known BNP species (Figures 2 and 3).6-7 Commercially available BNP assay kits, such as from Shionogi and Abbott, utilize antibodies directed against a ring or a C-terminal portion of BNP-32, which cross-react with proBNP to comparable or lesser extents.8,9 Glyco-NT-proBNP is less reactive in NT-proBNP assay kits, such as from Roche, and is underestimated as indicated by recovery of its immunoreactiv-
Collectively, plasma immunoreactive (IR-) BNP species are more complex than thought, and the output from diagnostic kits is a summation of products of the concentration and cross-reactivity of each BNP species shown in Figure 3.

HF may regulate the molecular composition of BNP species in plasma. The proBNP/BNP-32 (high molecular mass IR-BNP/low molecular mass IR-BNP) ratios estimated by gel filtration HPLC were reported to distribute widely depending on the status of HF. This ratio is notably higher in HF patients caused by ventricular overload than atrial overload as well as in those with decompensated HF, and it decreases after treatment. Based on the higher proBNP/BNP-32 ratio in ventricle than in the atrium, the relative contribution of BNP secreted from the ventricle and the atrium is deduced to be a major factor regulating the proBNP/BNP-32 ratio in plasma.

Another key regulator of the proBNP/BNP-32 ratio is a converting enzyme (CE). Furin is a most promising candidate for the proBNP-CE, and converts it into BNP-32 and NT-proBNP. Even in healthy subjects, proBNP, BNP-32 and NT-proBNP are present in plasma. In the case of ANP, α-ANP and NT-proANP are main species in plasma of normal subjects, while pro-ANP and β-ANP appear in plasma of HF patients. ProANP is specifically cleaved by corin when secreted from cardiac atrium. Although proBNP-CE in cardiac atrium and ventricle remains unidentified, furin is recognized as a most promising candidate.

<table>
<thead>
<tr>
<th>Structure</th>
<th>BNP</th>
<th>ANP</th>
</tr>
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<tbody>
<tr>
<td>Storage Form</td>
<td>BNP-γ-BNP (ProBNP)</td>
<td>γ-ANP (ProANP)</td>
</tr>
<tr>
<td>Circulating Form</td>
<td>BNP-γ-BNP (ProBNP)</td>
<td>α-ANP</td>
</tr>
<tr>
<td>Site of Production</td>
<td>Ventricle &gt; Atrium</td>
<td>Atrium &gt; Ventricle</td>
</tr>
<tr>
<td>Secretagogue</td>
<td>Ventricular Load</td>
<td>Atrial Load</td>
</tr>
<tr>
<td>Plasma Level (normal)</td>
<td>6.4 fmol/mL</td>
<td>0.9 fmol/mL</td>
</tr>
<tr>
<td>Increase (Heart Failure)</td>
<td>X 1000</td>
<td>X 100</td>
</tr>
<tr>
<td>Induction</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Metabolic Clearance</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Receptor Selectivity</td>
<td>Long-Acting</td>
<td>Short-Acting</td>
</tr>
<tr>
<td>ANP-A Receptor</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>ANP-B Receptor</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clearance Receptor</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
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Table II. What is the Functional Molecule?

<table>
<thead>
<tr>
<th>Diabetes Mellitus</th>
<th>Heart Failure</th>
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<tbody>
<tr>
<td>Insulin</td>
<td>BNP</td>
</tr>
<tr>
<td>C-peptide</td>
<td>N-Terminal pro BNP</td>
</tr>
<tr>
<td>Proinsulin</td>
<td>ProBNP</td>
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</table>

BNP is a cardiac hormone secreted mainly from human ventricle.
2) Precise measurements of individual BNP species in plasma.
Currently used BNP and NT-BNP assay kits have not been developed for measurements of individual molecules in complex BNP species in plasma, and include ambiguity in the reported values. To make these kits more reliable, the cross-reactivity of each BNP species in the assay kit should be evaluated with quantitated standard peptides of completely confirmed structures. Combination of the well characterized assay kits and several antibodies being developed, such as an antibody against a hinge region (proBNP[74-79]) of proBNP, will pave the way for measurements of individual BNP species in plasma. The data thus obtained will provide insights into the relation between the complexity of plasma BNP species and heart disease.

BNP in the emergency department and ICU:
1) Positioning of BNP measurement in the emergency room (ER) and intensive care unit (ICU).
BNP is an extremely valuable tool for diagnosing cardiac failure in various clinical settings. BNP values are useful for the following: the early diagnosis of HF in health screening, as well as for determining the differential diagnosis, severity, therapeutic effects and prognosis of patients with HF.

A rapid assay has recently become available that has further expanded the applicability of BNP, particularly in the emergency room (ER) and intensive care unit (ICU).

a) BNP reference values. The values of BNP increase when cardiac function decreases (Figure 4). However, the type of changes in BNP values depends on the underlying heart disease. For example, values of ANP increase in mitral stenosis, which exerts stress on the atrium but not on the ventricle, whereas those of BNP increase only mildly. Also, BNP values obviously change with time from the onset of acute myocardial infarction (Figure 5).

Issues regarding BNP reference values must be discussed because they change depending on the rationale for the measurement. The BNP value of healthy Japanese individuals is ≤ 18.4 pg/mL (approximately 20 pg/mL). For early detection of cardiac dysfunction in health screenings, a reference value can be set at about 40 pg/mL. However, the reference value needs to be substantially increased for applications in the ER where many patients are critically ill. When considering the relationship with prognosis, a value of about 200 pg/mL is appropriate (Figure 6). An important issue is that ≤ 200 pg/mL does not mean the absence of HF; it merely indicates that HF is mild, and such reference values must not be misinterpreted.

BNP values are slightly affected by extracardiac factors. For example, BNP values tend to slightly increase in the elderly or in patients with renal failure, but tend to slightly decrease in obese individuals.

These facts taken together indicate that BNP values reflect not only the severity of HF, but also the type of underlying disease, the severity of renal dysfunction, and the effects of age and obesity.
b) In the ER. Rapid BNP assays are useful when patients transported to the ER have suspected HF. Combining chest X-ray images with standard blood test findings and BNP values renders a differential diagnosis of HF a relatively simple matter. The severity of HF when complicated by pneumonia was previously difficult to determine when BNP could not be measured. However, the introduction of the rapid BNP assay allows easier diagnosis of HF. Therefore, BNP can play a major role in the differential diagnosis and severity assessment of HF in the ER.
c) In the ICU. Measuring BNP values is also strongly recommended for patients in the ICU, particularly for understanding

![Figure 4](https://example.com/figure4.png)


![Figure 5](https://example.com/figure5.png)

**Figure 5.** Time course of plasma levels of ANP and BNP in patients with AMI. Morita E, Yoshimura M, et al. Circulation 1993.

![Figure 6](https://example.com/figure6.png)

**Figure 6.** High survival rate in patients with low BNP value in acute myocardial infarction. BNP was measured after about 4 weeks after the onset of AMI. Suzuki S, Yoshimura M, et al. Circulation 2004.
the course of HF. It is important to know the chronological changes in BNP values after admission. Since therapy can lower BNP values relatively quickly, they should be measured every few days. However, BNP is not currently measured at this frequency because of its cost, but active BNP measurement is desirable in the future. Several clinical studies have clarified that persistently high BNP values are associated with a poor prognosis, and this can be improved by planning therapy based on BNP values. However, further investigations are warranted. Overall, BNP values are useful for assessing therapeutic effects and the prognosis of patients with HF in the ICU.

2) Interpretation of BNP Levels in Acute Care. When initially confronted with a symptomatic suspected HF patient, the physician has three tasks; namely to make an appropriate diagnosis, effect prompt treatment, and provide a disposition. Each task must be accomplished rapidly and accurately if optimal outcomes are to be realized, as erroneous diagnosis and treatment delays are associated with adverse outcomes.

While rapid treatment may be required to save the life of the patient, diagnostic accuracy is critical as dire consequences result from inappropriate treatment. In one study of 499 patients transferred by ambulance and ultimately found to suffer HF, the probability of survival was 251% (95% CI 137-455, \(P < 0.01\)) higher if treatment was performed before transfer, rather than delayed an average of 36 minutes until hospital arrival. Conversely, mortality increased by 350% (\(P < 0.05\)) when non-HF dyspnea was treated with HF therapy instead of bronchodilators. Ultimately, there is a clear premium on diagnostic accuracy.

Unfortunately, the most rapidly available tools for diagnosis, namely the history and physical condition, are grossly inaccurate, as demonstrated in Table III. Even a finding such as the S3, which has excellent specificity, has such poor sensitivity that its value is minimized in a large portion of the HF population.

Natriuretic peptides (NPs) represent a rapid and accurate test to assist in the evaluation of patients presenting with acute dyspnea. In the Breathing Not Properly trial of > 1,500 patients presenting to an emergency department with undifferentiated dyspnea, the physician’s diagnostic accuracy by clinical judgment was only 74%, but improved to 81.6% when the results of BNP testing were considered.

Beyond accuracy, speed of treatment is also critical. In a study of hospitalized HF patients receiving vasoactive treatment, patients receiving early therapy (mean, 1.1 hours) had a mortality of 4.3% compared to 10.9% (\(P < 0.0001\)) in those who received delayed (mean, 22 hours) therapy. The need for rapid diagnosis and treatment is further supported by analyses of 14,900 patients stratified by BNP and time to loop diuretic quartiles. In this study, the greatest mortality was seen in those patients with the highest BNP levels and longest delay in treatment (Figure 7).

Finally, BNP levels are directly associated with mortality. In an analysis of over 45,000 patients, higher levels were reflective of greater acute mortality risk. The lowest inpatient mortality of 1.9% was seen when the BNP was < 430 pg/mL, and increased to 6% in patients with a BNP > of 1,730 pg/mL (\(P < 0.0001\)). As a mortality rate of 6% exceeds the contemporary mortality rate of myocardial infarction, this knowledge may help the physician to decide whether a patient is an ICU candidate as compared to requiring regular hospitalization.

3) Consensus statements. In patients presenting to their physicians with dyspnea, doctors should check the clinical history, perform a physical examination, chest X-ray and ECG, along with laboratory measurements that include BNP.

When using cut-off values in patients with acute dyspnea, apply two values: one to “rule out” (<100 pg/mL in the United States, <65 pg/mL in Japan) and one to “rule in” HF (>400 pg/mL in the United States, >254 pg/mL in Japan). The intermediate or grey zone (100-400 pg/mL in the United States, 65-254 pg/mL in Japan) area requires extra physician attention and ancillary testing. For early detection of cardiac dysfunction in health screenings, the reference value can be set at about 40 pg/mL in Japan and 66 pg/mL in the United States. However, the reference value needs to be substantially increased for applications in the ER where many patients are critically ill. When considering the relationship with prognosis, a value of about 200 pg/mL in Japan and 318 pg/mL in the United States is appropriate.

Clinical acumen and further testing are often necessary to make a correct final diagnosis. Even in patients with a high probability of diagnosis, the BNP level gives important information concerning risk stratification. This is especially important since there is a discrepancy in the perceived severity of CHF and BNP levels.

Caveats in using NP levels: Natriuretic peptides, including BNP and NT-proBNP, have emerged over the years as invaluable tools both for the diagnostic approach and the prognostic assessment of patients with HF. However, there are several caveats related to NPs. Several conditions may lead either to false positive or to false negative results. Causes for NP elevation other than acute HF (HF) include a previous history of HF,

<table>
<thead>
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<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
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<tbody>
<tr>
<td>History of HF</td>
<td>62</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>56</td>
<td>53</td>
<td>54</td>
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<tr>
<td>Orthopnea</td>
<td>47</td>
<td>88</td>
<td>72</td>
</tr>
<tr>
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<td>S₃</td>
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<td>JVD</td>
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<td>94</td>
<td>72</td>
</tr>
<tr>
<td>Edema</td>
<td>67</td>
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<td>68</td>
</tr>
</tbody>
</table>

Figure 7. Mortality versus quartiles of diuretic time and BNP level.
advanced age, renal dysfunction, acute coronary syndrome, pulmonary disease, pulmonary embolism, high-output states such as sepsis, cirrhosis or hyperthyroidism and atrial fibrillation. Pathogenetic mechanisms related with higher than expected levels of NP include myocardial wall stress from ventricular dysfunction, hyxerpolemia, hypertension, reduced renal clearance, subclinical ischemia, myocardial remodeling and fibrosis and maladaptive neurohormonal stimulation. On the other hand, NP levels may be lower than expected in the case of obesity, flash pulmonary edema, HF originating upstream to the left ventricle, as in the case of acute mitral regurgitation or mitral stenosis, cardiac tamponade and constrictive pericarditis. As outlined in the recent HF guidelines, there is a considerable grey zone for the BNP and NT-proBNP values ranging between 100 and 400 pg/mL and 400 and 2,000 pg/mL, respectively. Grey-zone values may result from the involvement of the right ventricle in cases with pulmonary disease, including chronic obstructive lung disease with cor pulmonale or pulmonary hypertension, right ventricular failure from long-standing left ventricular failure or right ventricular disease (infarction, valvular disease) and pulmonary embolism. Grey-zone values require a more detailed clinical and laboratory assessment, while knowledge of baseline NP levels would be of great help. In any case, NP should be interpreted as continuous variables. When using BNP in patients with acute dyspnea, two values should be applied: one to “rule out” HF (≤ 100 pg/mL) and one to “rule in” HF (> 400 pg/mL). When using NT-proBNP, instead, one rule-out value (≤ 300 pg/mL) and three different rule-in values based on age should be applied. In the case of renal dysfunction, given its frequent coexistence with heart disease, high NP levels should not be ignored, but the applied cut-offs for detecting HF may need to be raised when eGFR falls below 60 mL/minute. In contrast, in obese patients lower cut-off values need to be used and a rule-out BMP value of 50 pg/mL should be applied in patients with BMI (body mass index) > 35.

Consensus statements.

a) Grey zone. The grey zone (100-400 pg/mL in the United States, 65-254 pg/mL in Japan, for BNP, or 400 to 2,000 for NT-proBNP) represents 25% of dyspneic patients, 75% of whom will have CHF as the ultimate diagnosis. The presence of concomitant pulmonary disease is present in many of these patients.

The overall prognosis for dyspneic patients with BNP levels in the grey zone is good and may help risk stratify patients for admission or discharge.

For BNP levels of 100-400 pg/mL in the United States, 65-254 pg/mL in Japan, the following must be considered:

- Stable underlying dysfunction
- Right ventricular failure from pulmonary hypertension
- Acute pulmonary embolism
- Renal failure (SCR usually > 2.5 mg/dL)
- Patients may present with HF with healthy BNP levels or with below expected levels. This can occur in the following situations:
  - Flash pulmonary edema (< 1-2 hours)
  - HF up-stream from the left ventricle (ie, acute mitral regurgitation from papillary muscle rupture)
  - Obese patients (BMI > 35 kg/m²)

b) Renal dysfunction. Modest alterations in BNP levels occur with renal insufficiency (eGFR below 60 mL/minute), with a likely recalibration of the cutoff value to approximately 200 pg/mL in the United States and 128 pg/mL in Japan for patients presenting with dyspnea in the ED.

As HF is the cause of dyspnea in patients with renal dysfunction, BNP can be of great value in diagnosing acute HF in patients with renal insufficiency.

c) Obesity. Since obese patients (BMI > 35 kg/m²) express lower levels of BNP for any given severity of HF, caution should be exercised in interpreting BNP levels in such patients.

In patients presenting with acute dyspnea, obese patients (BMI > 35) should have a rule out value of 50 pg/mL in the United States and 33 pg/mL in Japan. Most obese patients with acute HF will, however, have BNP levels over 100 pg/mL in the United States and 65 pg/mL in Japan.

There seems to be a linear relationship between BMI and BNP. Patients who are obese or very obese should have their BNP multiplied by 2.0-3.0 to obtain a BNP level of similar severity with those of healthy weight.

BNP levels are still highly prognostic in obese patients.

Cost-effectiveness of BNP testing: The use of plasma BNP levels, in combination with other clinical information, provides information that seems to be helpful in the diagnosis, prognosis, and management of HF as well as screening for left ventricular dysfunction. However, there are very few data on the cost-effectiveness of BNP testing. The BASEL study is an important study in patients with acute HF. A prospective, randomized, controlled study of 452 patients who presented to the emergency department with acute dyspnea: 225 patients were randomly assigned to a diagnostic strategy involving the measurement of BNP levels with the use of a rapid bedside assay, and 227 were assessed in a standard manner. In the BASEL study, final diagnosis of HF was about 50%. Time to the initiation of the appropriate therapy was about 30 minutes, which is significantly shorter in the BNP group compared to in the control group. The mean total cost of treatment was significantly lower in the BNP group than in the control group. The BASEL study indicated that rapid-BNP testing in the management of acute HF reduced the total cost of treatment by 26% (P = 0.0006).

To compare the cost-effectiveness of BNP and echocardiography for predicting outcome in patients with CHF at discharge, 116 patients hospitalized with CHF underwent simultaneous BNP and Doppler echocardiographic examinations once ready for discharge. In this study, in patients admitted to hospitals with CHF, predischarge BNP was more cost-effective than comprehensive Doppler echocardiographic examination for the prediction of future cardiac death or rehospitalization for CHF (P < 0.001).

In the United States, less than $50,000 per Quality Adjusted Life of Years (QALY) is evaluated as cost-effective. Screening populations with 1% prevalence of reduced EF (mean at age 60) with BNP followed by echocardiography seem to be cost-effective. In Europe, less than $60,000 per QALY is evaluated as cost-effective. In Japan, consensus has not been reached as to the limit of cost-effectiveness. There is no data regarding the prevalence of low ejection fractions in the general population in Japan, but there is likely a lower prevalence compared to the United States and Europe. Further studies are needed to assess the cost-effectiveness of BNP testing for establishing international guidelines on the management of HF.
Rationale of BNP-guide management for in-patients/out-patients with HF: BNP is a cardiac hormone secreted mainly from the ventricle, and its expression is augmented by ventricular wall stretch. The plasma BNP level is elevated in accordance with the severity of HF. With the biological characteristics of BNP expression, BNP is widely used as a biomarker to diagnose HF and predict its prognosis. Now BNP is recognized as the most faithful surrogate marker for hard endpoints in clinical trials in HF. Recent studies have reported that HF therapy guided by BNP-relating peptide improves outcomes compared with conventional therapy. However, the investigators have not reached consensus on the target value of the plasma BNP or N-terminal proBNP (NT-proBNP) in the management of HF.

1) Circulating BNP is elevated with the activation of the ventricular renin-angiotensin system (RAS). In HF, the systemic and local RAS as well as the sympathetic nervous system are activated to maintain blood supply to vital organs and to maintain cardiac performance by changing loading conditions in the acute phase and by remodeling the ventricle in the chronic phase. RAS activation is a compensatory mechanism, but RAS is over-activated probably because of genetic programming, and consequently leads to a vicious cycle of HF in humans. Nowadays, inhibition of over-activated RAS by an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker is essential in the treatment of HF. From the clinical point of view, how do physicians recognize whether the inhibition of the systemic and local RAS is sufficient?

In the case of the systemic RAS, renin is the rate-limiting enzyme for its activation, and plasma renin activity and the plasma concentration of end product, aldosterone, indicate its activation (Figure 8). However, these plasma markers do not indicate the activation of the cardiac RAS. In the ventricular tissues, activation of cardiac local RAS up-regulates BNP gene expression in cardiomyocytes directly or indirectly, that is, through endothelin released from cardiac fibroblasts. Thus, elevation of plasma BNP levels indicates the activation of cardiac RAS, because BNP is exclusively synthesized in the heart (Figure 8). In other words, elevation of plasma BNP level suggests that the dosage of RAS blockers is not sufficient to block over-activated RAS in the heart.

2) Representative case of HF treated with RAS blockers (Figure 9). A 40-year old male patient with acute decompensated heart failure (ADHF) due to dilated cardiomyopathy was admitted to our hospital because of severe dyspnea and severely reduced cardiac performance. He had a plasma BNP level of 1,070 pg/mL and aldosterone of 2,160 pg/mL without RAS blocking agents. Echocardiography revealed diffuse severe hypokinesis with an ejection fraction of 16%. Medical treatment consisting of 75 mg of alacepril and 40 mg of furosemide was begun, but alacepril was changed to 50 mg of losartan because of adverse effects on liver function. As shown in Figure 9, the treatment with ARB promptly decreased plasma aldosterone concentration but did not affect plasma BNP levels. The addition of carvedilol at a dose of 2.5 mg was not tolerated. At that time, chest X-rays and echocardiogram indicated left- and right-sided heart failure, with prerenal failure with serum creatinine of 6.7 mg/dL. Finally, 2.5 mg of enalapril was added to the regimen and the dose was increased to 5 mg, and carvedilol was initiated, followed by reduction of the plasma BNP level below the level of 100 pg/mL. Keeping the plasma BNP level below 100 pg/mL for more than 6 months brought reverse remodeling of the ventricle and the patient’s symptoms were improved.

Before the addition of enalapril, the plasma aldosterone level was decreased from over 2,000 pg/mL to around 200 pg/mL, but the plasma BNP level was not changed, suggesting that systemic RAS was substantially inactivated by the ARB treatment but cardiac RAS is not changed. After the addition of enalapril and carvedilol, both the plasma BNP and aldosterone concentrations were decreased to near normal ranges, and cardiac performance was restored to an ejection fraction of about 40% and cardiomegaly disappeared. This finding suggests that reverse remodeling was only achieved by sufficient inhibition of cardiac local RAS by sufficient doses of RAS blockers.

3) The lower the better. Circulating BNP level is a surrogate marker of cardiac RAS activation, indicating that physicians should try to reduce and keep the plasma BNP level as low as possible. Based on prospective studies, a plasma BNP level below 200 pg/mL may be a cutoff for better prognosis. Figure 10 shows three different trajectories of BNP release. The patient with the lowest BNP at discharge usually has the best prognosis.

4) Consensus statements. Not everyone who is clinically euvolemic is without congestion. Clinical euvolemia with a high BNP level means that in some patients congestion is still present. If BNP can be low-
ered in these patients without causing renal insufficiency or hypotension, true optovolemia may be reached.

While in a given patient the BNP level does not always correlate to wedge pressure, in a patient admitted with acute HF, a high BNP level (generally over 600 pg/mL in the United States, 378 pg/mL in Japan) and high filling pressures secondary to volume overload, a treatment-induced decrease in wedge pressure will almost always be associated with a rapid drop in BNP levels as long as the patient is maintaining adequate urine output (> 30 mL/hour).

At least three BNP levels should be measured during hospitalization: admission and at discharge when optovolemic. Further levels might be drawn in an attempt to support clinical improvement or lack thereof.

While a drop in BNP level of 30% is important, it is not the magnitude of the drop as much as it is the final BNP level that relates to optovolemic status and prognosis. **Outpatient titration:** The correlation between the drop in BNP level and the patient’s improvement in symptoms (and subsequent outcome) during hospitalization suggests that BNP-guided “tailored therapy” in an outpatient setting might be effective. Since NP levels reflect end-diastolic wall stress, which is elevated by both increased filling pressures and by LV dilation, measuring serial levels over time may provide a way, in conjunction with our clinical acumen, to monitor the effects of drug therapy on LV remodeling.

In a pilot study of 69 patients with HF and LV dysfunction who were randomized to receive therapy guided by natriuretic peptide levels or standard care, BNP-guided treatment, targeting a BNP level < 200 pg/mL, significantly reduced total cardiovascular events, and delayed time to first event.33 The STARS-BNP trial, which used a target BNP < 100 pg/mL, also showed a reduction in HF deaths and hospitalizations for HF when BNP levels were used to tailor outpatient therapy.

Perhaps BNP-guided therapy is successful simply because it serves as a reminder to physicians to give evidence-based treatment. But in the STARS trial most patients were already on adequate doses of guideline-derived therapy. Hence it may be that BNP levels offer further information that can help decide whether to up-titrate therapy or perhaps even withhold further therapy.

Other drugs for HF appear to decrease BNP levels. It appears that ACE inhibitors, angiotensin receptor blocker agents, spironolactone, and perhaps beta blockers drive BNP levels down, although it is unclear whether this is a true marker of clinical improvement. In the Valsartan Heart Failure Trial (Val-HeFT), changes in BNP over time induced by pharmacologic therapy were shown for the first time to correlate with morbidity and mortality.32 Patients with the greatest percentage decrease in BNP and norepinephrine (NE) from baseline had the lowest morbidity and mortality, whereas patients with the greatest percentage increase in BNP and NE were at greatest risk. The authors found BNP to be more predictive of morbidity and mortality than NE, or, in a separate analysis, than aldosterone.

**Consensus statements.** NP levels drawn early after discharge may confirm the adequacy of outpatient therapy. Early rises in NP levels following hospital discharge are often a manifestation of inadequate diuretic therapy.

There is considerable day-to-day variation in BNP levels. A 50% increase in BNP levels over baseline in the appropriate clinical setting often represents decompensation, especially with weight gain and either edema or dyspnea.

Treatment with ACE inhibitors, beta-blockers and, angiotensin receptor blockers and aldosterone antagonists result in decreases in optovolemic BNP levels over the long term.

Randomized controlled trials using NP-guided therapy have demonstrated a significant reduction in the primary combined endpoint of death and re-hospitalization in patients less than 76 years of age.

**BNP in general screening:**

1) **The main issue.** HF is a progressive disease that is clearly recognized to benefit from early diagnosis and therapeutic intervention. Thus, recognition during the asymptomatic stages can lead to early initiation of treatment with expectations of improved survival and quality-of-life. Asymptomatic LV dysfunction is thought to be present in approximately 3% - 5% of the general population. The issue at present is that despite the fact that BNP is widely recognized to be the ‘gold standard’ biomarker for detection of left ventricular dysfunction and of cardiac dysfunction overall, a cut-off level or clinical decision limit that will allow for accurate detection of patients that are still in asymptomatic stages that will benefit from early recognition and treatment are still lacking or have not reached a consensus.

2) **What the current guidelines show (Table IV).** The Japanese JCS Guidelines (2005/2006) state that the cut-off value of BNP for screening LV dysfunction remains unclear. However, the guidelines recognize that BNP has high negative predictive value for CHF. The ACC/AHA Guidelines (2009) state that BNP represents a potential tool for screening LV dysfunction. The ESC Guidelines (2008) do not make a specific statement on this issue.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>JCS</td>
<td>The cut-off value of BNP for screening LV dysfunction remains unclear. However, BNP has high negative predictive value for CHF.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACC/AHA</td>
<td>BNP represents a potential tool for screening LV dysfunction.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESC</td>
<td>No description</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 3) New data supporting stronger indications (Table V). Although initially the normal cut-off value of 18.4 pg/mL was used as both the normal cut-off as well as the clinical decision limit, it was recognized early on that approximately 15% of seemingly healthy asymptomatic subjects show levels that exceed this level. Subsequent studies conducted to determine a cut-off for asymptomatic patients with heart disease show that in general that a clinical decision limit ranging from 40 pg/mL to 80 pg/mL might be applicable (see Table V showing various clinical decision limits as determined through various studies). However, these studies have also outlined that age, sex and body mass (obesity) are complicating factors that affect BNP levels and how to take these factors into account still remains an issue.

### 4) Consensus points. BNP is clearly recognized to be beneficial for detecting cardiac dysfunction including from still asymptomatic stages.

However, establishing a definitive cut-off level to allow reasonable discrimination of patients is still an ongoing subject of discussion.

### BNP and diastolic dysfunction:

#### 1) The main issue. Diastolic dysfunction is recognized to be a cause of HF. In fact, diastolic dysfunction may be present in almost one-half of patients with HF. In the presence of preserved or systolic function, this type of HF is referred to as HF with preserved/norormal ejection fraction (HF-NEF). As HF is recognized to be present in approximately 10% of elderly people and is a leading global medical problem, recognition is of the utmost importance. Diastolic dysfunction is often associated with hypertension and increased myocardial wall thickness (stiffness), but at present, optimal therapeutic interventions are still not clear. It is noteworthy that HF-NEF patients represent a rather heterogeneous population. To better improve care and attention to this condition, recognition remains prerequisite but this remains a challenge as echocardiographic measures are still the only reliable method of detection. BNP is clearly recognized to be elevated in diastolic dysfunction, but how it can be used remains unclear.


#### 4) Consensus statements. In patients presenting with acute HF with preserved-LV function, BNP levels are elevated, although usually not as high as in patients with systolic dysfunction (800 pg/mL versus 400 pg/mL in the United States, 506 pg/mL versus 254 pg/mL in Japan).

BNP should not be used by itself to differentiate systolic from diastolic dysfunction in the emergency department.

In patients with normal systolic function, elevated BNP levels along with diastolic filling abnormalities might help to reinforce the diagnosis of diastolic dysfunction.

In the future, drug-trials for treating patients with diastolic dysfunction might include BNP levels as entrance criteria and as endpoints for treatment success.

BNP concentrations above age-adjusted cut-off points may identify elderly patients with diastolic dysfunction.

### BNP measurement in the guidelines (Japan, Europe, and USA):

#### 1) The main issue. BNP is clearly recognized to be beneficial for diagnosing and treating HF in not only the Japanese Guidelines (JCS) but also those of the United States (ACC/AHA) and Europe (ESC). However, there are different recommendations for the use of BNP on the global scale, and harmonization between international societies is still in the discussion phase.

#### 2) What the current guidelines show

a) Heart failure (Table VII). The JCS published two guidelines on HF, namely Guidelines for Treatment of Chronic Heart Failure (CHF) in 2005 and Guidelines for Treatment of Acute Heart Failure in 2006 by different committees and members. In the JCS Guidelines of CHF, BNP was classified as Class I

### Table V. Summary of Studies on LVD and BNP Cut-off Values in the General Population

<table>
<thead>
<tr>
<th>Number (n)</th>
<th>Cohort</th>
<th>BNP (pg/mL)</th>
<th>Criteria</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Ref.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>249</td>
<td>General</td>
<td>18.4</td>
<td>LVD</td>
<td>-</td>
<td>-</td>
<td>(1)</td>
<td>In patients with normal systolic function, elevated BNP levels and diastolic filling abnormalities might help to reinforce the diagnosis of diastolic dysfunction.</td>
</tr>
<tr>
<td>1252</td>
<td>General</td>
<td>17.9</td>
<td>LVSD</td>
<td>77</td>
<td>87</td>
<td>(2)</td>
<td>ACC/AHA</td>
</tr>
<tr>
<td>155</td>
<td>70-84 years</td>
<td>64.7</td>
<td>LVSD</td>
<td>92</td>
<td>65</td>
<td>(3)</td>
<td>BNP in association with echocardiographic filling patterns can improve diagnostic accuracy.</td>
</tr>
<tr>
<td>480</td>
<td>Men</td>
<td>47.0</td>
<td>LVD + α'</td>
<td>69</td>
<td>91</td>
<td>(4)</td>
<td>ESC</td>
</tr>
<tr>
<td>173</td>
<td>Men &gt; 65 years</td>
<td>47.0</td>
<td>LVD + α'</td>
<td>89</td>
<td>84</td>
<td>(4)</td>
<td>BNP and NT-proBNP rise in response to myocardial wall stress. Usually, lower levels are observed in patients with preserved LV systolic function.</td>
</tr>
<tr>
<td>248</td>
<td>Men risk (+)</td>
<td>46.0</td>
<td>LVD + α'</td>
<td>76</td>
<td>88</td>
<td>(4)</td>
<td>BNP and NT-proBNP rise in response to myocardial wall stress. Usually, lower levels are observed in patients with preserved LV systolic function.</td>
</tr>
<tr>
<td>513</td>
<td>Women</td>
<td>85.0</td>
<td>LVD + α'</td>
<td>50</td>
<td>95</td>
<td>(4)</td>
<td>BNP and NT-proBNP rise in response to myocardial wall stress. Usually, lower levels are observed in patients with preserved LV systolic function.</td>
</tr>
<tr>
<td>205</td>
<td>Women &gt; 65 years</td>
<td>85.0</td>
<td>LVD + α'</td>
<td>75</td>
<td>90</td>
<td>(4)</td>
<td>BNP and NT-proBNP rise in response to myocardial wall stress. Usually, lower levels are observed in patients with preserved LV systolic function.</td>
</tr>
<tr>
<td>244</td>
<td>Women risk (+)</td>
<td>84.0</td>
<td>LVD + α'</td>
<td>75</td>
<td>92</td>
<td>(4)</td>
<td>BNP and NT-proBNP rise in response to myocardial wall stress. Usually, lower levels are observed in patients with preserved LV systolic function.</td>
</tr>
<tr>
<td>4527</td>
<td>Men</td>
<td>32.3</td>
<td>CHF</td>
<td>83</td>
<td>77</td>
<td>(5)</td>
<td>BNP and NT-proBNP rise in response to myocardial wall stress. Usually, lower levels are observed in patients with preserved LV systolic function.</td>
</tr>
<tr>
<td>8939</td>
<td>Women</td>
<td>62.4</td>
<td>CHF</td>
<td>64</td>
<td>94</td>
<td>(5)</td>
<td>BNP and NT-proBNP rise in response to myocardial wall stress. Usually, lower levels are observed in patients with preserved LV systolic function.</td>
</tr>
</tbody>
</table>

1 indicates VHD, HCM, HHD, IHD and AF. 2 indicates HTN and/or DM. Ref. (1) indicates Jpn Heart J 2000; (2), Lancet 1998; (3), BMJ 2000; (4), J Card Fail 2005; and (5), Int J Cardiol 2009.

### Table VI. Description of BNP and HFNEF in JCS, ACC/AHA and ESC Guidelines

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCS</td>
</tr>
<tr>
<td>2005/2006</td>
</tr>
<tr>
<td>ACC/AHA</td>
</tr>
<tr>
<td>2009</td>
</tr>
<tr>
<td>ESC</td>
</tr>
<tr>
<td>2008</td>
</tr>
</tbody>
</table>

In patients with normal systolic function, elevated BNP levels and diastolic filling abnormalities might help to reinforce the diagnosis of diastolic dysfunction. The ACC/AHA Guidelines (2009) state that BNP in association with echocardiographic filling patterns can improve diagnostic accuracy. The ESC Guidelines (2008) state that BNP and NT-proBNP rise in response to myocardial wall stress, and that lower levels are usually observed in patients with preserved LV systolic function.

#### 3) New data supporting stronger indications. The data at present show that BNP is clearly elevated in HF-NEF but to lesser values than in systolic function. However, BNP cannot discriminate between the two conditions. Furthermore, recent studies have shown that factors that affect diastolic function and myocardial stiffness such as increased wall thickness, presence of hypertension and atrial fibrillation as well as ischemia are factors that need to be accounted for.

#### 4) Consensus statements. In patients presenting with acute HF with preserved-LV function, BNP levels are elevated, although usually not as high as in patients with systolic dysfunction (800 pg/mL versus 400 pg/mL in the United States, 506 pg/mL versus 254 pg/mL in Japan).

BNP should not be used by itself to differentiate systolic from diastolic dysfunction in the emergency department.

In patients with normal systolic function, elevated BNP levels along with diastolic filling abnormalities might help to reinforce the diagnosis of diastolic dysfunction.

In the future, drug-trials for treating patients with diastolic dysfunction might include BNP levels as entrance criteria and as endpoints for treatment success.

BNP concentrations above age-adjusted cut-off points may identify elderly patients with diastolic dysfunction.
in the diagnosis of CHF. However, the JCS Guidelines of Acute HF state that BNP measurements are not always necessary on the basis that the significance of BNP is unclear under this condition because BNP levels are higher than several hundred pg/mL in patients with acute HF. However, it was noted that BNP is useful for monitoring and in the diagnosis of patients with preserved systolic function (diastolic dysfunction).

- CLASS I (For diagnosis of CHF)
  
  The efficacy of measurements of BNP in the diagnosis of CHF has been reported. Plasma concentrations of ANP and BNP correspond to hemodynamics. BNP reflects better end-diastolic pressure of LV than ANP, and therefore BNP is superior to ANP for the diagnosis of CHF, especially in the diagnosis of 1) the presence, 2) severity, and 3) prognosis of CHF.

- Not available (For diagnosis of acute HF)
  
  BNP measurements are not always necessary. The significance of BNP is unclear because BNP levels are higher than several hundred pg/mL in patients with acute HF.

- CLASS II (For therapy of CHF)
  
  Measurements of serum concentration of BNP are useful for predicting the efficacy of beta-blocker therapy. However, no agreement regarding the optimal value has been obtained.

In general, the ACC/AHA and ESC Guidelines recognize the usefulness of BNP in the diagnosis of HF regardless of being in chronic or acute phases. The ACC/AHA Guidelines describe the significance of BNP in the diagnosis of HF as Class IIa. Moreover, in the ACC/AHA Guidelines, BNP measurement was upgraded to Class I in hospitalized patients with CHF in 2009. The ESC Guidelines state that plasma concentrations of natriuretic peptides are useful biomarkers in the diagnosis of HF (Class I).

b) STEMI. For BNP in STEMI, the JCS Guidelines (2008) state that BNP is a class IIa recommendation, and that BNP reflects infarction size and is a predictor of adverse cardiac events.

c) In ACS/NSTEMI. The JCS Guidelines (2008) do not have a recommendation for BNP although they state that higher levels of plasma BNP may indicate poor prognosis in ACS patients.

For pulmonary hypertension, the JCS Guidelines (2007) do not have a recommendation for BNP although they state that higher or increased levels of BNP may be associated with increased mortality rates in patients with PPH.

For perioperative cardiovascular evaluation and management for noncardiac surgery, the JCS Guidelines (2008) do not have a recommendation for BNP although they state that BNP may predict cardiac morbidity and mortality after major surgery.

For valvular heart disease, the JCS Guidelines (2008) do not have a recommendation for BNP although they state that BNP may predict symptom-free survival and postoperative outcome in severe aortic stenosis.

4) Consensus statements. BNP is recognized to be beneficial for diagnosing and treating HF in addition to various heart conditions not only in the Japanese guidelines (JCS) but also those of the United States (ACC/AHA) and Europe (ESC). Harmonization and consensus between countries is an outstanding issue.

Role of BNP in acute coronary syndrome (diagnosis of the role of TnT, H-FABP and BNP in acute myocardial infarction):

1) Cardiac biomarkers for acute coronary syndrome. At present, three groups of cardiac biomarkers are applied for detection of myocardial damage and the early diagnosis of ACS as shown in Figure 11. Earlier investigation revealed that measurements of cardiac troponin T detected the presence of minor myocardial damage in patients with unstable angina. CK and CKMB were not significantly elevated, and those with minor myocardial damage showed higher risk for cardiac events (acute myocardial infarction, cardiac death, or necessity of emergency coronary revascularization) in the acute phase compared with those without minor myocardial damage. Thereafter, myocardial infarction was redefined based on clinical presentation, ECG findings and the elevation of cardiac troponins instead of conventional CK or CKMB measurements.

2) H-FABP rapid panel test for earlier diagnosis of myocardial infarction. Japanese investigators developed a whole blood rapid panel test for heart-type fatty acid-binding protein (H-FABP) and demonstrated its clinical utility for early diagnosis of myocardial infarction. The diagnostic sensitivity and negative predictive value of the H-FABP test were superior compared with those in the rapid troponin T test.
3) **Profile of BNP elevation in ACS.** In patients with acute STEMI, the magnitude and plasma profile of BNP elevation are associated with the size of the infarct area and subsequent LV dysfunction. Following the STEMI, plasma levels of BNP increase rapidly and peak after approximately 12 to 24 hours. Furthermore, differences in the profiles of NT-proBNP elevation between STE-ACS and NSTE-ACS were demonstrated in 165 consecutive patients admitted to the CCU. Conventional myocardial necrosis markers, CKMB and TnT levels, on admission were significantly higher in the STE-ACS than those in NSTE-ACS. However, conversely, NT-proBNP on admission was significantly higher in the NSTE-ACS compared with the STE-ACS especially in the earlier phase. When the correlations between TnT and NT-proBNP were analyzed in STE-ACS and STE-ACS, the differences revealed augmented elevation of NT-proBNP in the NSTE-ACS patients as compared with prominent elevation of troponin T in the STE-ACS, indicating larger ischemic insult despite the smaller myocardial necrosis in NSTE-ACS as compared with STE-ACS.

**4) Timing of measurements.** Data from the FRISK trial showed that NT-proBNP levels are highest on admission, within 24 hours of onset, decreased markedly in the first 24 hours and then gradually over the following 6 months. Interestingly, the predictive ability of NT-proBNP appears to increase with time, suggesting that persistent elevation is a particularly strong marker of adverse outcome. In a study of PRISM, the addition of a second NT-proBNP value at 72 hours following the admission appeared to improve risk prediction concerning the endpoint of death or recurrent MI at 30 days. Regardless of the NT-proBNP value on admission, an NT-proBNP value > 250 pg/mL (assumable BNP > 80 pg/mL) at 72 hours indicated a marked increased risk.

*These studies clearly demonstrate that both circulating BNP and NT-pro-BNP levels obtained in the acute phase or in the subacute phase are strongly associated with short-term and long-term cardiovascular mortality, independently of conventional risk factors, extent of myocardial necrosis and of coronary artery disease, HF, and LV dysfunction. Importantly, BNP and NT-proBNP identify patients without clinical signs of HF and with preserved LV function who are at high risk for death or HF events. It is meaningful that the association between BNPs and recurrent MI is generally weak, and in most studies nonexistent after adjustment for potential confounders. BNPs are closely associated with the incidence of HF, suggesting that the ability of BNPs to predict death in ACS is mainly explained by its ability to predict HF. BNPs provide complementary prognostic information to troponins; where troponins are superior to BNPs in predicting ischemic events.*

**5) Proposed algorithm.** A proposed algorithm for measurement of BNPs in NSTE-ACS is shown in Figure 12. However, more clinical studies are necessary to evaluate the role of natriuretic peptides in the management of ACS.

**High sensitivity troponin in acute care:** Chest pain is common to a large number of presentations. The main concern is potential acute coronary syndrome (ACS). This possibility requires the clinician to make a determination as to the probability of its presence, and it is the sorting that represents the diagnostic challenge. One of the earliest available risk stratification tools is the ECG. Although obtained in minutes, and having excellent specificity, it is very insensitive. In fact Pope, et al reported finding an ECG diagnosis of STEMI in only 2% of suspected ACS patients.

Thus, scoring systems were created to improve risk stratification. One of the most common scoring systems is the TIMI (thrombolysis in myocardial infarction) risk score. This assigns points based on coronary artery disease risk factors, and 2 acute event markers (Figure 13). While high scores are associated with adverse outcomes, low scores do not predict safety. Furthermore, since TIMI scores do not diagnose an acute event, in the emergency department where disposition decisions are based on the presence or absence of an event, and not necessarily the underlying disease risk, scoring systems have limited utility for disposition decisions.

In current practice, serum cardiac markers are the dominant objective risk stratification tool. Contemporary troponin assays can identify the presence of myocardial necrosis within 4-6 hours of presentation. Unfortunately, in the time immediately after chest pain onset, troponin assays are commonly negative. This initial insensitivity is both a function of the underlying pathology (as it relates to the timing of troponin release from necrotic heart cells) as well the inability of many of our current troponin assays to detect very low levels of this protein. Newer troponin assays, with better lower level detection, offer the promise of earlier diagnosis.

It is important to detect low levels of troponin, as even slight increases above the 99th percentile value confer high risk for short-term adverse events. Also if detectable, lower
levels that change over time also suggest increased risk. In a study of 2,188 patients undergoing serial serum marker testing (Table VIII), very small changes in markers, never exceeding the manufacturer’s recommended cutpoint, were associated with increased 30 day adverse outcomes. A recent study of high sensitivity troponin suggests that they have improved overall diagnostic accuracy. In one study of 718 emergency department (ED) patients with suspected AMI, the performance of the hsTn far exceeded that of the current standard, with negative predictive values (NPV) in the high 90s (Figure 14). While not of sufficient exclusionary power for immediate discharge from the ED, its accuracy is a significant improvement over existing markers. A second analysis of 1,813 suspected MI patients found that a high sensitivity troponin had superior performance compared to current troponin assays, myoglobin, or CKMB (Figure 15).

Although the newer troponin offers improved accuracy, this will complicate the interpretation of results. Improvements in sensitivity are realized with concurrent decreases in specificity. Consequently, while a Tn > 99th percentile is associated with increased short-term adverse outcomes, it is not necessarily the case that the underlying pathology is MI resulting from epicardial coronary artery occlusion. Thus greater diagnostic acumen is required.

A multiple cutpoint strategy for marker interpretation may help solve this conflict. It has been suggested that patients with a troponin level between the upper limit of the reference interval and the decision limit for AMI should be labeled as having “myocardial injury.” In this fashion all troponin elevations > 99th percentile would be considered in a high risk group, requiring additional therapy and evaluation to determine the etiology of their myocardial injury, while those with levels exceeding the MI cutpoint would receive immediate MI care.

### Table VIII. If It Moves, It Is Bad

<table>
<thead>
<tr>
<th>Marker</th>
<th>Comparator</th>
<th>OR for 30 day MACE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ing Tn</td>
<td>versus stable</td>
<td>2.25</td>
<td>1.42-3.55</td>
</tr>
<tr>
<td>↑ing Tn</td>
<td></td>
<td>3.04</td>
<td>1.94-4.75</td>
</tr>
<tr>
<td>↓ing CKMB</td>
<td>versus stable</td>
<td>0.67</td>
<td>0.48-0.95</td>
</tr>
<tr>
<td>↑ing CKMB</td>
<td></td>
<td>0.96</td>
<td>0.57-1.60</td>
</tr>
</tbody>
</table>

Logistic regression models showing the odds ratios for predicting ACS. MACE indicates MI, revascularization (PCI or CABG), or positive testing (> 70% stenosis at catheterization, [+ ] MPI or non-invasive stress testing) within 30 days of index visit.

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**References**

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46. Seino Y, Ogata K, Takano T, et al. Use of a whole blood rapid panel test for heart-type fatty acid-binding protein in patients with acute chest pain: comparison with rapid troponin T and myoglobin


