

Insight

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The Present State of
Coronary Computed
Tomography Angiography:
A Process in Evolution

Biomarkers in
heart failure

**BASICS REGARDING
NATRIURETIC
PEPTIDES (NPs)**

**DIAGNOSTIC UTILITY
OF NPs**

**PROGNOSTIC UTILITY
OF NPs**

**INPATIENT
MANAGEMENT OF AHF**

**OUTPATIENT
MANAGEMENT OF CHF**

**CAVEATS: RENAL
FUNCTION, BODY MASS
INDEX, 'GREY ZONE' NP VALUES**

TROPONIN

**NEW BIOMARKERS
FOR HEART FAILURE**

Cardiology News

The Present State of Coronary Computed Tomography Angiography: A Process in Evolution

In the past 5 years since the introduction of 64-detector row cardiac computed tomography angiography (CCTA), there has been an exponential growth in the quantity of scientific evidence to support the feasibility of its use in the clinical evaluation of individuals with suspected coronary artery disease (CAD). Since then, there has been considerable debate as to where CCTA precisely fits in the algorithm of evaluation of individuals with suspected CAD. Proponents of CCTA contend that the quality and scope of the available evidence to date support the replacement of conventional methods of CAD evaluation by CCTA, whereas critics assert that clinical use of CCTA is not yet adequately proven and should be

restricted, if used at all. Coincident with the scientific debate underlying the clinical utility of CCTA, there has developed a perception by many that the rate of growth in cardiac imaging is disproportionately high and unsustainable. In this respect, all noninvasive imaging modalities and, in particular, more newly introduced ones, have undergone a higher level of scrutiny for demonstration of clinical and economic effectiveness. We herein describe the latest available published evidence supporting the potential clinical and cost efficiency of CCTA, drawing attention not only to the significance but also the limitations of such studies.

The diagnostic accuracy of CCTA has already been definitively established. By well-performed prospective, multicenter studies, CCTA is an accurate diagnostic modality with superior diagnostic accuracy to detect and exclude

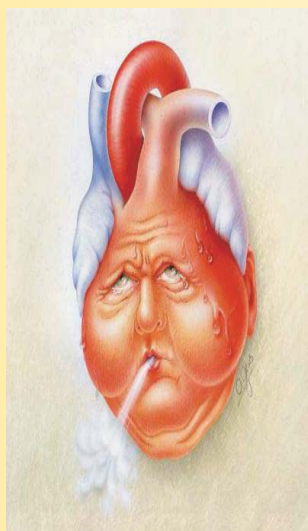
anatomically obstructive CAD. The exclusion of CAD seems to offer immediate clinical usefulness and is likely to reduce the need for subsequent resource utilization. However, improvements are still necessary to reduce overestimation of CAD severity. Nevertheless, the ability of CCTA, beyond conventional methods of CAD evaluation, to predict patient-centered outcomes and to invoke appropriate medical or invasive treatment and do so safely and in a cost-effective manner has yet to be determined. The future of CCTA will lie in the answers to these questions, which will depend on the type of high-quality evidence typically only derived from large, well-designed, randomized, controlled trials.

Reference : James K. Min, Leslee J. Shaw, Daniel S. Berman, *J Am Coll Cardiol.* 2010;55(10):957-965.

Table : CCTA- Related Issue and Pro and Con Argument

CCTA Diagnostic Test Characteristic	Pro	Con
Diagnosis of obstructive CAD	CCTA possesses a high NPV for identification of individuals in whom no further testing is warranted.	CCTA possesses high rates of false positive findings, which will lead to unnecessary catheterization and revascularization.
Anatomic diagnosis of CAD	Most individuals undergoing imaging do not have significant CAD and, thus, a test with high NPV is most useful.	Ischemia-guided management is more proven than anatomy-guided management.
Detection of subclinical atherosclerosis	CCTA diagnoses individuals with subclinical atherosclerosis, which offers the opportunity to initiate primary prevention of future CAD events.	Most individuals diagnosed by CCTA with subclinical atherosclerosis should already be receiving medical therapy. Further CCTA diagnosis may simply represent lead-time bias for which no intervention is necessary or useful.
Prognosis	CCTA plaque characterization for prognostic risk assessment is as effective and is synergistic to stress imaging findings.	Functional stress testing with or without imaging is robust for risk stratification.
Resource utilization	CCTA can act as an effective gatekeeper to cardiac catheterization, thereby reducing costs.	CCTA will simply serve as an add-on test rather than as a stand-alone test, thereby increasing costs.
Safety	CCTA exposes a patient to less radiation than other tests, including nuclear stress testing and invasive angiography.	CCTA exposes a patient to excessive radiation.

CAD = coronary artery disease; CCTA = cardiac computed tomography angiography; NPV = negative predictive value.





Biomarkers in heart failure

Cardiovascular disease has emerged as one of the most prominent causes of morbidity and mortality among adult populations. As medical advances have enabled more patients to survive postmyocardial insult, the prevalence of congestive heart failure (CHF) has exploded. It is now estimated that 5 million people in the USA live with CHF, and that approximately 550,000 new cases are diagnosed each year. Hospitalisations for heart failure have increased dramatically from 402,000 in 1979 to 1,101,000 in 2004 (National Hospital Discharge Survey), and the cost of CHF is now estimated at US\$56 billion a year, 70% of which is due to hospitalisation. Among a variety of proposed heart failure treatment modalities, cardiac biomarkers have emerged as powerful adjuncts to standardised clinical care in the diagnosis, prognosis, and treatment of acute heart failure (AHF).

Basics regarding natriuretic peptides (NPs)

B-type natriuretic peptide (BNP) is first synthesised in the myocytes as a 132 amino acid intracellular precursor known as preproBNP. During decompensation, volume overload and high pulmonary capillary wedge pressure cause the ventricle walls to stretch, triggering the cleavage and release of preproBNP as the biologically active 32 amino acid hormone BNP and its inactive N-terminal fragment (NT-proBNP). Once released, BNP has pronounced natriuretic, diuretic, and vasodilating properties, working to dramatically reduce volume overload and hypertension in patients. BNP is then believed to be removed quickly from circulation (half-life of 22 min) by both NP receptor endocytosis and endopeptidase enzymatic degradation. In contrast, NT-proBNP is suspected to be cleared from the plasma largely by renal excretion, and thus has slower fluctuations in circulating concentrations as well as a notably longer half-life of 60-120 min. In general, BNP and NT-proBNP values are reasonably correlated, and either can be used in patient care settings as long as their respective absolute values and cut points are not used interchangeably.

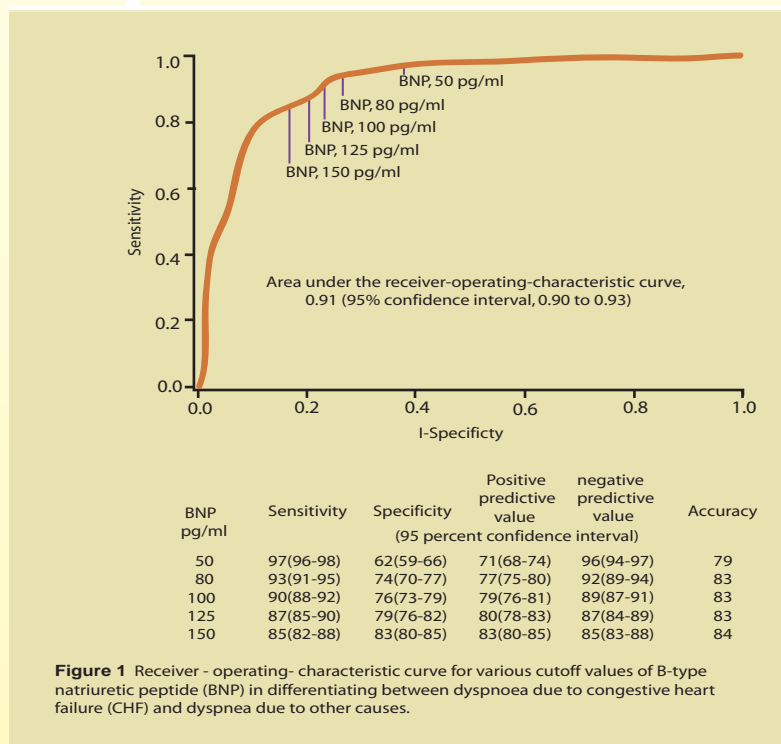
Diagnostic utility of NPs

In the Breathing Not Properly Multinational Study, BNP values from 1586 patients presenting with dyspnoea to the emergency department (ED) were found to be more accurate in diagnosing heart failure than clinical examination alone (area under the curve (AUC) 0.91) (figure-1). A BNP cut point of 100 pg/ml was 90% sensitive and 76% specific for

diagnosing heart failure. The ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study randomised 599 dyspnoeic ED patients to NT-proBNP measurements to examine the marker's clinical diagnostic utility in the setting of heart failure. Based on their results, the study investigators proposed an age independent NT-proBNP cut point of 300 pg/ml to 'rule out' AHF, introducing a measure in which patients might be screened before further costly examinations. However, since concentrations of NPs are known to increase with age, the investigators determined that a single NT-proBNP cut point would be inappropriate for the diagnosis of AHF in differing age groups, and thus proposed two different reference ranges for patients <50 years or ≥ 50 years of age (cut points 450 pg/ml and 900 pg/ml, respectively). These NT-proBNP cut points, when used alongside clinical assessment, were diagnostically superior to clinical judgement or NT-proBNP alone (AUC 0.94 vs 0.90, respectively). These studies typify the success of incorporating NP measurements into the standard armamentarium of diagnosing heart failure in patients presenting with dyspnoea.

Prognostic utility of NPs

The prognostic potential of BNP was examined in the multicentre Rapid Emergency Department Heart Failure Outpatient Trail (REDHOT) study, and showed that BNP





values were very strong predictors of 90 day outcomes. Among the 464 patients enrolled, the patients admitted with BNP concentrations >200 pg/ml had a much higher event rate of 29% when compared to that of patients admitted with BNP concentrations ≤ 200 pg/ml (9%) (table1). Investigators observed a pronounced disparity between the ED physicians' perception of CHF severity and the severity determined by BNP concentrations, and thus concluded that regular BNP assessment should be incorporated into standard clinical care to aid physicians in deciding who to admit from the ED.

In the International Collaborative of NT-proBNP (ICON) Study, 1256 subjects recruited from multiple medical centres worldwide were examined for the prognostic potential of NT-proBNP in the setting of AHF. Heart failure patients with pronounced elevations in NT-proBNP concentrations had a more than fivefold increase mortality risk by 76 days, leading investigators to propose the NT-proBNP cut point of 5180 pg/ml for predicting 76 day mortality in patients with AHF.

Inpatient management of AHF

As the prevalence of heart failure continues to rise, clinicians have looked increasingly towards NP as an objective index of heart failure severity and treatment adequacy. There are several reasons for this. First, BNP and NT-proBNP circulating concentrations correlate strongly with left ventricular end-diastolic wall stress, thus providing a surrogate measurement of severity of a patient's heart failure, irrespective of clinical symptoms. Secondly, baseline NP values offer significant prognostic information, with follow-up NP measurement offering perhaps even more significance, as patients with the greatest fall in plasma NP concentrations have been shown to have the most favourable outcomes. Third, validated automated and point-of-care assays are widely available, making NP measurement quick and convenient for both patient and physician. Fourth, NP assays cost an average of US\$20 per test, and can be used to carefully screen and monitor patients, thereby substantially reducing the costs of heart failure related hospitalisations and procedures. Finally, NP values have been shown to fall across diuretic, angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor

blocker (ARB), β-blocker, spironolactone, and nesiritide induced cardiac improvements, suggesting that NP guidance may prove extremely effective in determining the method and adequacy of heart failure treatment. In the same way that blood pressure is used to guide hypertension management and cholesterol values for hypercholesterolaemia, NP values, as surrogate for left ventricular function and pulmonary capillary wedge pressure, may be used to guide the complex pharmacotherapy of CHF. A patient's circulating NP concentrations may be thought to consist of two components: a 'dry' baseline component, as well as a 'wet' component, in which NP concentrations are acutely raised during decompensation due to the increased mechanical pressure and stretching of the ventricles. While empirical targets have been suggested for both BNP and NT-proBNP to optimise diagnosis and prognosis, 'dry' NP concentrations are known to vary appreciably between individuals due to clinical confounders such as gender, age, body mass index (BMI), and renal function; thus, universal cut points may not always be appropriate. In practice, a patient's 'dry' NP value and NP changes during decompensation, treatment, and post-treatment may provide the most useful information in making clinical decisions. In support of these assertions, Bayés-Genís et al showed that in 100 heart failure patients monitored with NT-proBNP over 7 days of hospitalisation, those with an NT-proBNP drop of ≥50% had the highest survival rates, while those with a ≤15% drop were most likely to have future complications. Notably, the NT-proBNP percentage change post-treatment was superior to initial NT-proBNP values in the prognostication of patients. Additionally, Bettencourt et al showed in 50 decompensated heart failure patients that an initial NT-proBNP concentration of >6779 ng/l was highly predictive of readmission and death; however, a post-treatment NT-proBNP >4137 ng/l was even more predictive of future cardiac events, with an 8% increase in odds ratio for every 1000 ng/l above the cut point (p<0.0001). When comparing patients with >30% or <30% decrease in NT-proBNP concentrations, those with the greatest decrease had superior outcomes. The investigators also showed that patients discharged with a BNP concentration <250 pg/ml had a very strong prognosis for eventfree survival, while failure of BNP values to decline

over hospitalisation was a very strong predictor of death and/or readmission. These findings present important implications for the reduction of hospital stay duration, rates of readmission, and direct costs of heart failure events. The B-type natriuretic peptide for Acute Shortness of breath Evaluation (BASEL) study randomised 425 patients to BNP guided treatment and found that the use of BNP values decreased both hospital admissions (75% vs 85%) and intensive care unit admissions

Table 1 Percentages of various outcomes for admitted patients divided into groups based on a BNP cut point of 200 pg/ml.

Admitted patients	BNP <200 pg/ml (n=43)	BNP >200 pg/ml (n=364)	p Value
NYHA functional class III and IV	66%	70%	0.598
Combined event rate	9%	29%	0.006
Mortality	2%	9%	0.142

Combined events include cardiac related admissions or visits, or all cause mortality.
BNP, B-type natriuretic peptide; NYHA, New York Heart Association.



(15% vs 24%). Patients also had a decreased time to discharge (8 days vs 11 days) without any increase in rehospitalisations. Perhaps most notably, BNP guided treatment led to a total cost reduction of 26%, which could represent hundreds of millions in savings if applied nationwide. Even this is an underestimation, as BNP values probably account for a number of corrected diagnoses. Another potential reduction of cost was noted in the REDHOT study in which 11% of the 464 patients enrolled were admitted with BNP values <200 pg/ml (clinical cut point associated with lower mortality). In 2001, there were 680,106 hospital admissions, with an average cost of \$5414.68 per patient, meaning that if BNP values could have reduced admissions by that same 11%, an estimated \$500 million in unnecessary healthcare costs could have been saved. In light of these findings, Mohammed and colleagues have proposed an algorithm for BNP or NT-proBNP guided management of AHF patients: NP baseline values should be obtained upon presentation for patient diagnosis, triage, and in-hospital prognosis. The patient should be treated via proven therapeutic modalities, and after treatment a followup NP value should be obtained before patient discharge in order to determine adequacy of treatment and long term prognosis. For the best outcomes, the investigators proposed the empirical targets of a $\geq 30\%$ decrease in NP concentrations over the duration of the hospitalisation, with a discharge BNP target of <350 ng/l and/or NT-proBNP target of <4000 ng/l.

Outpatient management of CHF

As in hospitalised patients, NPs can be easily used in outpatient settings to monitor patients and dramatically reduce their risk of new cardiac events and death. In the STARS-BNP study (Systolic Heart Failure Treatment Supported by BNP), 220 heart failure patients (New York Heart Association (NYHA) functional class II-IV) were randomised to BNP guided treatment with a BNP target <100 ng/l. At 3 months, the BNP cohort was seen twice as often for scheduled follow-up with more changes to their heart failure medications (134 vs 66, $p<0.05$), and ended with higher achieved doses of ACE inhibitors and β -blockers. However, they were also found to be less likely to decompensate, and through the median 15 months of follow-up, patients in the BNP cohort had far fewer heart failure related readmissions and/or deaths (25% vs 52%, $p<0.001$). Troughton et al observed similar reductions in heart failure decompensations, hospitalisations, and mortality events (19 vs 54, $p = 0.02$) when they randomised 69 heart failure patients to NTproBNP guided treatment (target <1700 ng/l). In the STARBRITE study (Strategies for Tailoring Advanced Heart Failure Regimens in the

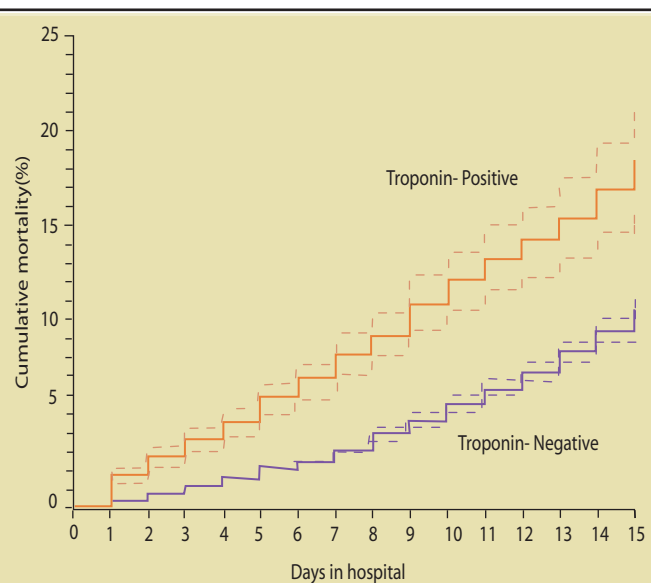


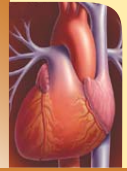
Figure 2 Mortality according to number of days in the hospital and troponin status at presentation, $P < 0.001$ by the log rank test. Dashed lines show 95% confidence intervals.

Outpatient Setting: Brain Natriuretic Peptide Versus the Clinical Congestion Score), investigators assessed the value of individualised BNP targets during short term follow-up. The investigators found that while the number of days survived out of hospital did not change, ACE inhibitor and β -blocker use was optimised, while diuretics were less likely to be increased. These studies suggest that individualised NP targets may help optimise the use of proven therapeutic medications and may also decrease adverse events over time.

Caveats: renal function, body mass index, 'grey zone' NP values

Renal impairment

Clinicians have often noted a high coincidence rate of CHF and chronic kidney disease (CKD), an observation that has become widely known as the 'cardio-renal interaction'. Though the mechanisms and effects of such an interaction are not yet fully understood, notably higher NP concentrations have been reported in heart failure patients also suffering from CKD. In a secondary analysis of the PRIDE study, previously discussed, the 599 dyspnoeic patients were also evaluated for interaction between NT-proBNP values and CKD. Renal insufficiency was closely related to risk factors for CHF, and those with CKD had a higher prevalence of CHF (all $p<0.003$). NT-proBNP values and glomerular filtration rate (GFR) were found to be inversely and independently related ($p<0.001$), and accordingly, worsening renal function was associated with cardiac abnormalities found on echocardiography. While



NT-proBNP cut points of >450 pg/ml and >900 pg/ml produced a 85% sensitivity and 88% specificity for diagnosing acute CHF in age stratified patients with normal renal function (GFR ≥ 60 ml/min/1.73 m²), in patients with impaired renal function (GFR <60 ml/min/1.73 m²), a higher NT-proBNP cut point of 1200 pg/ml was still able to effectively maximise sensitivity and specificity of heart failure diagnosis at 89% and 72%, respectively. Therefore, these results suggest that in the case of CHF and CKD coincidence, classic NP guided algorithms may still be appropriate, though cut points need to be readjusted for renal function. In comparison to other clinical factors, NT-proBNP was found to be the strongest independent predictor of mortality (hazard ratio (HR) 1.57; $p = 0.0004$), even in the presence of impaired renal function, leading investigators to confirm the auspicious role of NT-proBNP in heart failure prognosis, irrespective of renal function. In an analysis from the Breathing Not Properly Multinational Study, McCullough et al reported a similar interaction between BNP and GFR. Investigators have proposed various explanations for the heightened NP values observed in patients with CKD. Some stipulate that the higher prevalence of concomitant cardiac abnormalities in CKD patients cause the ventricles to release more NPs into the bloodstream. Others argue that circulating NP concentrations are elevated due to the reduced clearance capacity of injured nephrons.

Obesity

Obesity is a known risk factor for cardiovascular disease. Though it is well established that NP values are notably lower in obese heart failure patients than in non-obese patients, the implications of these lowered concentrations is not yet well understood. In a study to examine interaction between BNP values and obesity, Mehra et al divided 318 CHF patients into three BMI cohorts: lean, overweight, and obese (BMI <25 kg/m², 25-29 kg/m², and ≥ 30 kg/m², respectively). BNP values trended downwards across all three groups ($p < 0.01$), and were significantly lower in obese patients versus non-obese patients ($p = 0.0007$), though there was no significance found when comparing the lean and overweight cohorts. Interestingly, despite the distinct disparity in BNP values across BMI groups, the event rate among both obese (25%) and non-obese (29%) patients remained constant through 1 year. This finding has been supported in other studies, and has become widely recognised as 'the obesity paradox'. From the data, it appears that obese heart failure patients, even with higher risks and prevalence for cardiovascular disease

and heart failure, have equal and/or better survival rates than non-obese patients. The explanation for these improved outcomes is not yet clear; however, recent studies suggest that the suppression of NP response and the early manifestation of heart failure in obese patients may be accounted for, in part, by increased BNP clearance by natriuretic clearance receptors in adipose tissue, as well as a documented, intimate relationship between NPs and lipolysis. One thousand three hundred and sixty-nine patients from the Breathing Not Properly Multinational Study were similarly evaluated for BNP and BMI interaction. BNP values were found to be suppressed in obese patients, with a mean BNP concentration of 516.7 ± 505.9 pg/ml in patients with BMI <20 kg/m², and of 176.3 ± 270.5 pg/ml in those with BMI ≥ 40 kg/m², representing an almost threefold difference across the two BMI extremes. A univariate correlation was found between BMI and log BNP; however, in multivariate analysis adjusted for sex, GFR, race, CHF severity, and abnormal S3 sounds, no independent correlation between BNP and BMI was found. Thus, the investigators concluded that much of the inverse relationship between BNP and BMI might, in fact, be due to these clinical confounders and not to any specific obesity-NP interaction.

Grey zone

In most dyspnoeic patient populations, investigators have not been able to identify a single cut point to empirically rule in or rule out every patient with heart failure. This observation is in keeping with clinically guided, often non-specific, algorithms in which binary 'black or white' diagnoses are customarily inappropriate. It appears, then,

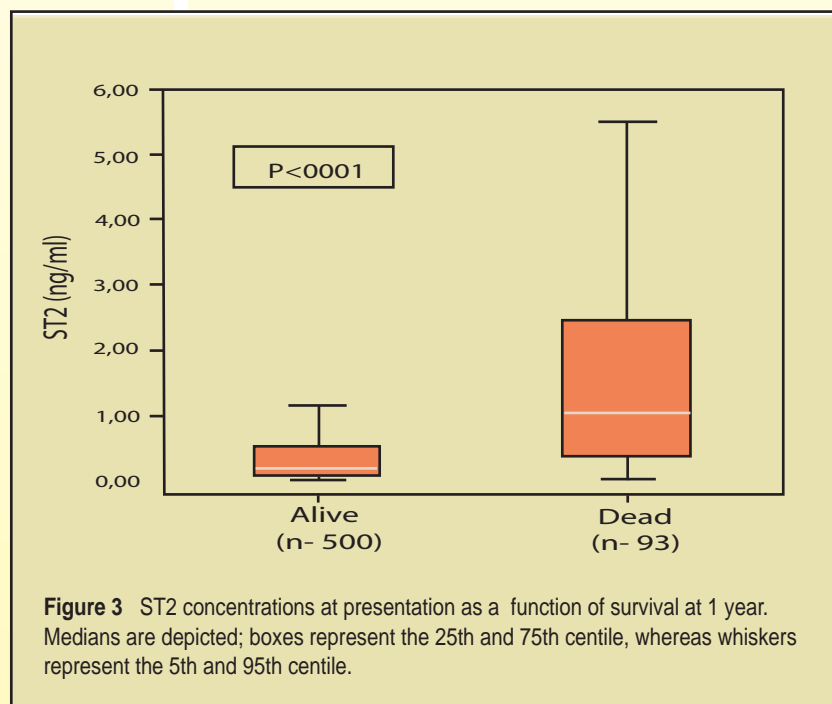


Figure 3 ST2 concentrations at presentation as a function of survival at 1 year. Medians are depicted; boxes represent the 25th and 75th centile, whereas whiskers represent the 5th and 95th centile.



that two cut-off points are necessary to screen patients adequately and reduce costs: one to effectively rule out heart failure in mildly dyspnoeic patients and eliminate unneeded hospitalisations, and another to rule in diagnosis and trigger prompt, appropriate treatment. The problem arises, then, necessarily in the 'grey zone' between these two cut points in which NP concentrations cannot be utilised as summarily to guide management decisions. Van Kimmenade et al studied 215 patients with intermediate NT-proBNP concentrations, approximately half of whom were diagnosed with heart failure. Irrespective of their final diagnosis, subjects with 'grey zone' NT-proBNP values were found to

have intermediate mortality rates between the high mortality rates of patients with heart failure and diagnostically high NT-proBNP concentrations, and the low mortality rates of those without heart failure and NT-proBNP concentrations <300 ng/l. Additionally, investigators found that adding specific clinical information to intermediate NT-proBNP values increased diagnostic accuracy, suggesting that a grey zone NT-proBNP value is still useful, and should signal further clinical examination. In the REDHOT study, investigators documented similar findings in the 153 patients presenting with BNP concentrations ranging from 100-500 pg/ml. While there was no difference in the perceived NYHA class ($p = 0.32$) or admission rate ($p = 0.76$) of these patients, they were found to have fewer events than their non-grey zone counterparts through 90 days (19.2% vs 32.9%, $p = 0.002$). Investigators thus concluded that irrespective of their clinical symptoms, patients with grey zone BNP values have a better prognosis than those in the non-grey zone composite. These two studies show that though a grey zone NP value is often not as revealing in heart failure diagnosis, it should not be considered entirely uninformative. Rather, an NP value that falls within an intermediate range should be a signal for further clinical examination, and may still aid in patient prognosis.

Troponin

The cardiac troponins, troponin I (cTnI) and troponin T (cTnT), are proteins located in the myocytes that are responsible for the regulation of cardiac muscle contraction. Often used interchangeably in a qualitative fashion (ie, 'positive' or 'negative'), 'positive' troponin values have long been associated with myocardial necrosis, and have also been shown to be excellent diagnostic and prognostic biomarkers in acute coronary syndromes. However, to date, very few studies have addressed the role of troponins in

Biomarkers in heart failure: key points 1

- ▶ 5 million people in the USA live with CHF. Approximately 550,000 new cases are diagnosed each year.
- ▶ During CHF decompensation, volume overload causes the ventricle walls to stretch, triggering the cleavage and release of BNP and its inactive N-terminal fragment (NT-proBNP).
- ▶ BNP has pronounced natriuretic, diuretic, and vasodilating properties, working to dramatically reduce volume overload and hypertension in patients.
- ▶ BNP and NT-proBNP concentrations contribute significantly to the clinical examination in diagnosing dyspnoeic patients in the ED, as well as in predicting short and long term outcomes for CHF patients.
- ▶ NP values are useful in monitoring outpatients and titrating medications, thus reducing the risk of future cardiac events and greatly reducing heart failure related costs.
- ▶ In several clinical scenarios, the interpretation of NP value is more complex, such as in heart failure patients with CKD, obesity, or intermediate NP concentrations.

patients with heart failure. In a watershed study conducted by Peacock et al, the investigators examined 67,924 acutely decompensated heart failure (ADHF) patients admitted with known troponin values to explore the relationship between elevated troponin concentrations and adverse events in patients hospitalised for ADHF. Patients who were positive for troponin (predefined as cTnI $\geq 1.0 \mu\text{g/l}$ or cTnT $\geq 0.1 \mu\text{g/l}$) had a higher rate of in-hospital mortality than troponin negative patients (8.0% vs 2.7%, $p < 0.001$), independent of other predictive variables. Analysis in the study indicated that in-hospital mortality within 1 day after admission was higher for troponin-positive than for troponin-negative patients (figure 2). This disproportionately high mortality rate, along with the longer hospitalisations and increased cardiac procedures associated with the positive troponin cohort in this study, suggest that troponin measurement should play a vital role in the early risk assessment and triage of patients presenting to the ED with ADHF.

ST2: Novel biomarker for patients with heart failure

Recent interest has arisen in the prognostic capability of the novel interleukin-1 receptor family member ST2 in patients suspected of having heart failure. In a state of acute myocardial stretch, the ST2 gene is notably upregulated, and elevated serum concentrations have been reported in patients with heart failure. Januzzi et al measured ST2 concentrations in 593 dyspnoeic patients presenting to the ED and found that though NT-proBNP was superior to ST2 in diagnosing ADHF, there was a very strong relationship between ST2 concentrations and 1 year mortality (HR 5.6, $p < 0.001$). The median concentrations of ST2 were significantly higher among heart failure patients than non-heart failure patients, and in those who died than in survivors (1.03 ng/ml vs 0.18 ng/ml; $p < 0.001$) (figure-3). Elevation of the ST2 marker was associated with the



highest rate of death in patients with ADHF, and investigators suggested that a multi-marker approach using both ST2 and NT-proBNP might be the most effective approach in determining prognosis of ADHF patients.

Mid-region biomarkers

As the limitations of BNP and NT-proBNP become more clear, investigators have begun to look at midregion biomarkers as alternatives outside the classic BNP/NT-proBNP dominated paradigm. Mid-region A-type NP (MR-proANP) and mid-region adrenomedullin (MR-proADM) have generated the most attention as potential new markers for several reasons. Both MR-proANP and MR-proADM are derived from precursor active peptides (ANP and ADM) which are released into circulation in response to cardiovascular fluid imbalance, as seen in BNP and NT-proBNP. These mid-regional markers can be easily measured by standard sandwich immunoassay technology and are much more stable than their active peptide counterparts, thus rendering them incredibly well suited for clinical settings as surrogate markers for their respective mature hormones. The Biomarkers in Assessment of Congestive Heart Failure (BACH) multinational study closely examined the diagnostic and prognostic capability of these two markers in comparison to BNP and NT-proBNP among 1636 presenting to the ED with shortness of breath. When comparing a MR-proANP cut point of 120 pmol/l to a BNP cut point of 100 pg/ml in diagnosing heart failure, MR-proANP sensitivity, specificity, and accuracy all fell within the non-inferiority margin of 10% ($p < 0.0001$), showing that MR-proANP was non-inferior to BNP as a diagnostic tool for heart failure (figure-3). Additionally, the study investigators concluded that MR-proANP added significantly to the diagnostic performance of BNP (especially in the presence of clinical confounders), and that using MR-proANP in conjunction with clinical assessment further reduced physician diagnosis indecision by 29%. With prognosis, the BACH study found that MR-proADM was superior to both BNP and NT-proBNP in predicting 90 day mortality in dyspnoeic patients presenting to the ED and diagnosed with heart failure. MR-proADM added significantly to the prognostic utility of both BNP and NT-proBNP, and was particularly strong in predicting 30 day survival, as indicated by the area under the receiver operating curves (AUC) of MR-proADM (0.739), BNP (0.555), and NT-proBNP (0.641). These findings led the BACH investigators to conclude that MR-proADM values can add significantly to existing prognostic biomarkers and help identify patients who should receive higher priority in the ED.

Biomarkers in heart failure: key points 2

- ▶ In the future, investigators will look increasingly towards multi-marker strategies.
- ▶ Cardiac troponin measurements have proven extremely useful in the early risk assessment and triage of patients presenting to the ED with ADHF.
- ▶ ST2 has generated much interest as a very strong prognostic marker for death in the setting of ADHF.
- ▶ The mid-region biomarkers, MR-proANP and MR-proADM, add significantly to the diagnostic and prognostic performance of BNP, and their stability renders them very well suited for clinical settings.
- ▶ GDF-15 is upregulated in the cardiac myocytes in response to mechanical stretch, and is under investigation as a prognostic marker.

New biomarkers for heart failure

The biomarker horizon continues to expand as investigators tirelessly look to improve heart failure recognition and treatment. Of late, both galectin-3 and growth differentiation factor 15 have generated some interest, and have proven themselves worthy of further exploration. Galectin-3 is a protein produced by activated cardiac macrophages during an inflammatory response. As inflammatory mechanisms have been identified as potential facilitators of heart failure progression, galectin-3 has been described in the literature as a potential biomarker for patients with heart failure. In a multi-marker analysis of 599 dyspnoeic patients presenting to the ED, van Kimmernade et al showed that serum galectin-3 concentrations were significantly elevated in patients with heart failure in comparison to those without, and that galectin-3 had a greater AUC of 0.74 ($p = 0.0001$) than NT-proBNP in predicting 60 day mortality. Galectin-3 added significantly to NT-proBNP's prognostic capability, and thus provides encouraging support for the future development of multi-marker heart failure algorithms. Growth differentiation factor, (GDF)-15 has also recently emerged as a potential new biomarker for heart failure. A member of the transforming growth factor- β cytokine superfamily, GDF-15 expression is upregulated in the cardiac myocytes in response to mechanical stretch, and promotes antiapoptotic, antihypertrophic, and anti-remodelling effects on the injured heart. Kempf et al recently analysed 455 CHF patients with known GDF-15 concentrations, and showed that increasing values of GDF-15 translated to higher mortality risk in patients with heart failure. According to the study, after adjustments for known clinical variables and established prognostic biomarkers, GDF-15 remained an independent predictor of mortality (HR 2.26, $p < 0.001$) and added important prognostic information to various patient subgroups, including those defined by age, BMI, heart failure aetiology, NYHA functional class, and left ventricular ejection fraction. These results suggest that GDF-15 may add prognostic information beyond that of current methods, and thus merits further exploration.

Reference: Heart 2010 96 : 314-320



Cardiology News

Clopidogrel Without PCI Curbs Mortality in MI With Heart Failure

Clopidogrel seems to improve survival in patients with acute myocardial infarction (MI) and heart failure who don't undergo percutaneous coronary intervention (PCI). The matched cohort with heart failure consisted of 5050 patients overall, with a mean follow-up of 1.5 years. The group without heart failure included 6092 patients followed for a mean of 2.1 years. Patients with heart failure had a mortality rate of 28.1% with clopidogrel versus 32.2% without it (hazard ratio, 0.86). Patients without heart failure, however, had a mortality rate of roughly 9.5% regardless of whether or not they received clopidogrel. The researchers conclude that clopidogrel is underused, and increased awareness of the benefit of clopidogrel in such high-risk patients can have considerable clinical impact.

J Am Coll Cardiol 2010;55:1300-1307.

Stem Cells Contaminated by RBCs are Less Effective in Coronary Repair

When patients with acute myocardial infarction receive intracoronary infusions of bone marrow-derived progenitor cells (BMCs), red blood cell contamination of the BMC preparation will make it less effective. The investigators note that BMC-treated patients had significantly better left ventricular ejection fraction (LVEF) recovery at 4 months than placebo patients. But they also found that red cells in the final cell product were significantly correlated with reductions in BMC viability, colony-forming unit capacity, and invasion capacity - and ultimately, with reduced recovery of LVEF. Platelet contamination did not have the same impact. To confirm their suspicion that the red blood cells were affecting the functionality of the BMCs, the researchers incubated them in vitro. Indeed, the red blood cells dose-dependently reduced the viability and functional activity of the BMCs, and they also impaired the therapeutic benefit of the BMCs in mice.

J Am Coll Cardiol 2010;55:1385-1394.

Replacing Fat With Complex Carbs May Not Adversely Affect Lipid Profile

Replacing 7% to 8% of fat intake with complex carbohydrates for 6 years is not associated with clinically adverse effects on triglyceride levels, high-density lipoprotein (HDL) cholesterol levels, or lipoprotein subclasses in postmenopausal women. The Women's Health Initiative Dietary Modification Trial tested the effects on chronic disease of a dietary pattern lower in fat and higher in vegetables, fruit, and grains. The objective was to evaluate the effects of dietary carbohydrate changes on lipids and lipoprotein composition. Diabetic white women with higher triglyceride concentrations may have greater increases in triglycerides. Limitations of this study include relatively small numbers of women for whom lipoprotein data were available, reliance on self-report for determination of food intake, lack of data before 1 year of intervention, and confounding of analyses of individual nutrients. Thus, this diet, combined with increased activity, may be used by persons choosing to restrict calories by reducing fat intake to achieve weight loss. Because therapies that lower LDL [low-density lipoprotein] cholesterol and non-HDL cholesterol reduce CVD [cardiovascular] risk, dietary interventions should focus on strategies that affect these 2 lipid variables.

Am J Clin Nutr. 2010;91:829-830, 860-874.

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Editorial Note

Dear Doctor,

We are happy to present the 17th issue of "Insight Heart". It is a small endeavor to provide you compiled & updated information on cardiovascular diseases and its management. This issue is focused on "**Biomarkers in heart failure**". We will appreciate your thoughtful comments.

Thanks and regards.