

## Review Article



# Biomarkers in Acute Heart Failure: Diagnosis, Prognosis, and Treatment

Nicholas Wettersten , MD<sup>1,2</sup>

<sup>1</sup>Section of Cardiology, San Diego Veterans Affairs Health System, San Diego, CA, USA

<sup>2</sup>Division of Cardiology, University of California, San Diego, La Jolla, CA, USA

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### Correspondence to

Nicholas Wettersten, MD

Section of Cardiology, San Diego Veterans Affairs Healthcare System, Cardiology 4 West, Room 4022 (111A), 3350 La Jolla Village Drive, San Diego, CA 92161, USA.  
E-mail: nwettersten@health.ucsd.edu

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### ORCID iDs

Nicholas Wettersten 

<https://orcid.org/0000-0002-6122-1152>

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## ABSTRACT

Heart failure is a global health problem. An episode of acute heart failure (AHF) is a period of substantial morbidity and mortality with few advances in the management of an episode that have improved outcomes. The measurement of multiple biomarkers has become an integral adjunctive tool for the management of AHF. Many biomarkers are now well established in their ability to assist with diagnosis and prognostication of an AHF patient. There are also emerging biomarkers that are showing significant promise in the areas of diagnosis and prognosis. For improving the management of AHF, both established and novel biomarkers may assist in guiding medical therapy and subsequently improving outcomes. Thus, it is important to understand the different abilities and limitations of established and emerging biomarkers in AHF so that they may be correctly interpreted and integrated into clinical practice for AHF. This knowledge may improve the care of AHF patients. This review will summarize the evidence of both established and novel biomarkers for diagnosis, prognosis and management in AHF so that the treating clinician may become more comfortable incorporating these biomarkers into clinical practice in an evidence-based manner.

**Keywords:** Heart failure; Biomarkers; Diagnosis; Prognosis; Therapy

## INTRODUCTION

Heart failure (HF) poses a substantial global public health problem. It is estimated there are over 64 million individuals living with HF worldwide at a substantial cost, morbidity and mortality.<sup>1</sup> Episodes of acute heart failure (AHF) are especially vulnerable periods of increased morbidity and mortality, and there have been few therapeutic advances that improve outcomes.<sup>2-4</sup> Reasons for this lack of improvement in outcomes and care of AHF patients might be the inability to recognize the different pathophysiologic processes occurring during decompensation, failure to recognize when optimal fluid status is achieved, and difficulty in identifying which patients have a worse prognosis and need of more aggressive interventions. Biomarkers may play an important role in addressing these deficiencies and their routine incorporation into clinical practice may improve outcomes.

Biomarkers have become valuable tools to use in combination with other clinical information for the diagnosis, prognosis, and management of multiple cardiovascular diseases, especially

HF. While many biomarkers are well-established for their use in cardiovascular disease and in chronic HF management, there are some specialized and nuanced uses specific to AHF. Furthermore, multiple novel biomarkers have recently shown promising results specifically in AHF that may potentially improve patient management. This review will focus on the use of biomarkers in AHF highlighting the use of established biomarkers and the potential of novel biomarkers to improve diagnosis, prognosis, and management.

## NATRIURETIC PEPTIDES

Some of the earliest and most established biomarkers in HF, especially AHF, are the natriuretic peptides (NPs). Their discovery and clinical integration have demonstrated the substantial additive benefit biomarkers have with other clinical information to diagnose, risk-stratify and manage AHF patients. When referring to NPs, individuals are most often referring to B-type natriuretic peptide (BNP) and the N-terminal fragment of proBNP (NT-proBNP), though other NPs exist and can be measured such as atrial natriuretic peptide (ANP) and the mid-regional proANP (MR-proANP). BNP is produced and released primarily from the ventricles of the heart during periods of volume or pressure overload.<sup>5)</sup> BNP is first produced as a 134-amino acid preproBNP peptide.<sup>5)</sup> Subsequently, a 26 amino acid signaling peptide is cleaved to form the 108-amino acid proBNP molecule.<sup>5)</sup> This is then cleaved into the inactive 76-amino acid NT-proBNP and biologically active 32-amino acid C-terminal portion BNP.<sup>5)</sup> Once produced, BNP's half-life is approximately 20 minutes while NT-proBNP's half-life is 120 minutes.<sup>5)</sup> BNP is cleared both by the type-C natriuretic peptide receptor and neutral endopeptidases, like neprilysin. This latter clearance mechanism is why BNP levels are believed to rise when the neprilysin inhibitor sacubitril is used, though there is debate as to how efficient neprilysin is at degrading BNP in humans and if assay differences influence BNP detection with sacubitril.<sup>6,7)</sup> Both NT-proBNP and BNP are partially cleared by the kidneys and it was thought that NT-proBNP clearance was more significantly impacted by reduced kidney function, but a well-designed mechanistic study showed BNP and NT-proBNP have equivalent kidney clearance.<sup>8)</sup> There is no set conversion factor for equating BNP and NT-proBNP levels, thus it is preferable to only measure one form in management so serial measurements can be compared.

In 2002, the Breathing Not Properly trial demonstrated that the use of BNP substantially improved the ability to diagnose AHF in patients presenting with acute dyspnea and an unclear diagnosis of AHF.<sup>9)</sup> Soon thereafter in 2005, the Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study showed that NT-proBNP could also assist with diagnosing AHF in patients with acute dyspnea of an unknown cause.<sup>10)</sup> And though the profile and management of AHF patients have changed in the more than 15 years since NPs were first described, the diagnostic utility of NPs has recently been reaffirmed in the modern era of AHF.<sup>11)</sup> These studies in addition to others have resulted in the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) Heart Failure Guidelines giving a class I recommendation for measuring either BNP or NT-proBNP in patients with possible AHF when a diagnosis is in question based on history and exam findings.<sup>12)</sup> In this situation, the major strength of NPs is their ability to rule out AHF as low levels have a high sensitivity for excluding a diagnosis of AHF.<sup>13)</sup>

However, there are many important caveats to remember when interpreting NP levels. Elevated NP levels are less specific for confirming a diagnosis of AHF unless they are substantially elevated, and both NPs have a 'gray zone' in which sensitivity and specificity are

**Table 1.** Rule in, rule out, and gray zone for BNP and NT-proBNP

Diagnosis	BNP (pg/mL)		NT-proBNP (pg/mL)	
	Any age	<50 years	50–74 years	≥75 years
Rule out	<100	<300	<300	<300
Gray Zone	100–500	300–450	300–900	300–1,800
Rule in	>500	>450	>900	>1,800

BNP = B-type natriuretic peptide; NT-proBNP = N-terminal fragment of pro-B-type natriuretic peptide.

**Table 2.** Conditions that can cause elevated natriuretic peptides

• Acute coronary syndrome
• Atrial fibrillation
• High output
• Anemia
• Aortic Stenosis
• Acute pulmonary embolus
• Pulmonary hypertension/right heart strain
• Sepsis
• Mitral regurgitation

lower and the diagnosis of HF is less certain (**Table 1**).<sup>14)15)</sup> It is in this ‘gray zone’ that many other conditions can mimic AHF and cause a strain on the heart provoking an elevation in NPs (**Table 2**).<sup>16)</sup> There are also certain AHF states and HF-like conditions where NPs may not be elevated (**Table 3**).<sup>16)</sup> Thus, this gray zone is an area where additional biomarkers are needed to assist with diagnosis.

There are additional variables to consider when interpreting NP levels. NPs are higher in patients with heart failure with reduced ejection fraction (HFrEF) than patients with heart failure with preserved ejection fraction (HFpEF). This can sometimes make the diagnosis of HFpEF difficult or falsely rule out a diagnosis of HF because NP levels fall into the gray zone or could even be in the normal range with decompensated HFpEF.<sup>17)18)</sup> Other factors can alter NP levels causing levels to be higher including increasing age, declining kidney function and atrial fibrillation, or cause levels to be lower including obesity and black race.<sup>19)</sup> Lastly, in a patient with established HF and chronically elevated NP levels, it can be difficult to determine if new or worsening shortness of breath, fatigue or edema is from HF decompensation or another condition such as pneumonia. In general, NPs levels that are substantially higher than previous levels, such as >50% higher than levels measured when the HF patient was compensated, are consistent with worsening HF status and volume overload.<sup>13)</sup> While it is important to remember these caveats when interpreting NPs, their remarkable utility for assisting with the diagnosis of AHF in a patient where the diagnosis is still equivocal based on history and exam is unquestionable. It has now become standard of care to measure NPs in any patient presenting with acute dyspnea or other symptoms suggestive of AHF, in which the diagnosis is not certain based on history and exam, much as the electrocardiogram is essential to evaluating any patient with chest pain or equivalent symptoms to help diagnose an acute coronary syndrome (ACS).

**Table 3.** Conditions that have lower natriuretic peptides than expected

• Flash pulmonary edema
• Mitral stenosis
• Pericardial constriction
• ‘Burned out’ cardiomyopathy
• Acute mitral regurgitation
• Cardiac tamponade
• Genetic polymorphisms

Further research has shown that NP's usefulness in AHF extends beyond diagnosis and their assessment is instrumental in prognostication and potentially in managing AHF. In two large analyses, one of 48,629 patients from Acute Decompensated Heart Failure National Registry (ADHERE) and the other of 99,930 patients from the Get With The Guidelines-Heart Failure Registry (GWTG-HFR), have demonstrated unequivocally that higher admission values of NPs are associated with an increased risk of in-hospital mortality.<sup>20)21)</sup> This point is pertinent to remember when interpreting an elevated NP not just as a strong indicator that a diagnosis of AHF is likely, but also that the more elevated the level, the higher the risk of death is for that patient. While the admission value is important for initial risk stratification, discharge values are even more valuable for long-term risk stratification. Multiple studies, including one of over 7,000 patients from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, have demonstrated discharge NP levels are more prognostic for mortality and HF readmission after discharge than the admission NP level.<sup>22-24)</sup> These studies focused on BNP and evaluated different values as cut-points for risk, finding that the risk for mortality and HF readmission was lowest when BNP was less than 250–350 pg/mL at discharge. Fewer studies have evaluated NT-proBNP, but the results have been similar with discharge values better at identifying lower risk cohorts than admission values.<sup>25)26)</sup> Notably, these studies primarily looked at the percent change in NT-proBNP level from admission to discharge and found that a reduction of  $\geq 30\%$  in NT-proBNP from the admission level was associated with a lower risk of death and readmission. Similarly, a percent change ( $\geq 30\%$  reduction) in BNP from admission to discharge can also identify a lower risk cohort; although, the absolute discharge BNP value appears to be more prognostic when compared to percent reduction.<sup>22)23)27)</sup>

While most studies have explored either absolute cut-offs or percent reductions in NP levels at discharge, one study explored both absolute cut-offs and percent changes to try and determine which method was better for prognostication by analyzing NT-proBNP levels from 1,266 AHF from 7 different cohorts.<sup>28)</sup> While both absolute value cut-offs and percent changes from admission to discharge were prognostic, the authors noted that the prognostic impact of absolute cut-offs varied based on the admission value while the prognostic significance of percent changes were independent of the initial admission value, thus the authors concluded that percent change should be used.<sup>28)</sup> Of note, the authors only evaluated NT-proBNP in this study, and whether the same findings would be seen with BNP still needs to be determined. As critical as NPs are for assisting with diagnosis and initial risk stratification at admission, discharge values are even more important for determining long-term prognosis and potentially developing a future care plan based on an AHF patient's risk.

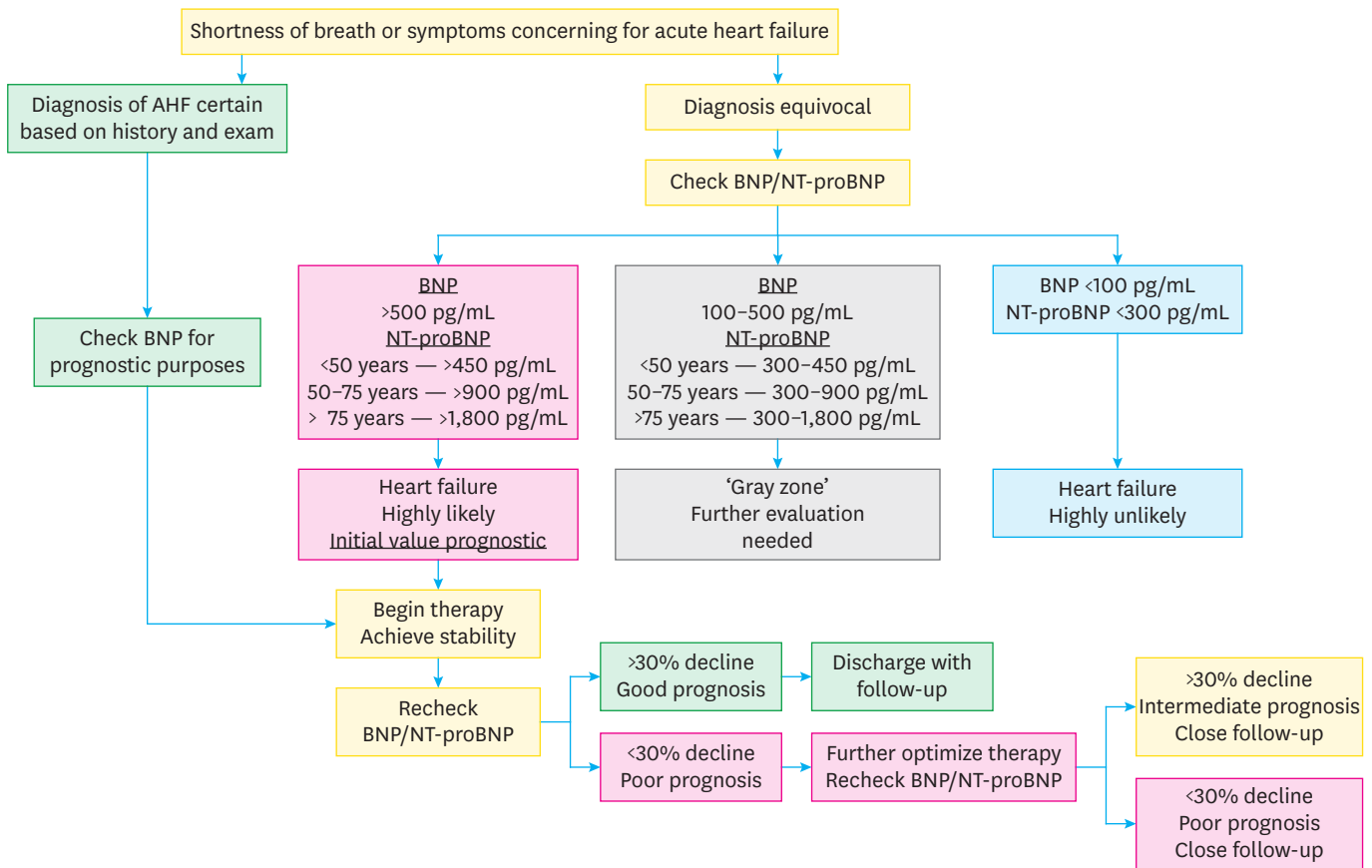
An ideal biomarker is one that can be used for diagnosis, prognosis, and management with biomarker levels changing in response to therapeutic interventions.<sup>16)</sup> In AHF, NPs clearly assist with diagnosis and prognosis, and may be able to fulfill the final role of an ideal biomarker by guiding management. Biomarker guided therapy with NPs has primarily been evaluated in an outpatient setting with mixed results. Two prior meta-analyses have generally shown improved outcomes with reduced mortality and HF hospitalization using an NP guided strategy.<sup>29)30)</sup> To more definitively answer this question, The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial was initiated in 2013 and reported in 2017.<sup>31)</sup> This trial was to enroll 1,100 patients with chronic HF and randomize them to either usual care or an NT-proBNP guided arm with the goal of achieving an NT-proBNP  $\leq 1,000$  pg/mL. The trial was stopped early though after enrolling just under 900 patients as there was no difference between groups for the primary

outcome of time to first HF hospitalization or cardiovascular mortality.<sup>31)</sup> These results were thought to potentially be an end to NP-guided therapy; however, there have been concerns with the GUIDE-IT trial design that may make its findings not as definitive. First, many HF patients enrolled seemed to have advanced HF that was refractory to medical therapy. Second, patients were treated at advanced HF centers where practitioners already focused on aggressive titration of medical therapy, thus patients in the 'usual care' arm likely did not receive the usual care actually practiced outside of advanced HF centers. Lastly, most trial patients were unable to achieve target dosing of medical therapy, thus failing to achieve a main goal of the trial. A post-hoc analysis of GUIDE-IT though did show the potential benefits of NP guided therapy. This analysis showed that the patients who successfully reached an NT-proBNP  $\leq 1,000$  pg/mL, regardless of randomization arm, had a substantially improved survival and reduced time to first HF hospitalization compared to patients unable to reach an NT-proBNP  $\leq 1,000$  pg/mL.<sup>32)</sup> Furthermore, a step-wise increase in risk for the primary outcome was seen with higher NT-proBNP levels.<sup>32)</sup> Thus, these latter findings emphasize the importance of reducing NP levels with medical therapy in HF patients. While most studies for NP-guided therapy have been in an outpatient setting, a few studies have attempted to evaluate the role of NP-guided therapy in hospitalized patients with AHF.

In a non-randomized retrospective study of 186 AHF patients, therapy was titrated with bioimpedance and BNP levels to try and achieve a BNP  $< 250$  pg/mL at discharge.<sup>33)</sup> The investigators found that AHF patients unable to reach this goal, despite further adjustments in diuretics and neurohormonal therapy, had a greater than three-fold increased risk of death or HF readmission in the 6 months following discharge.<sup>33)</sup> In a randomized trial, 271 AHF patients were randomized at the time of clinical stability prior to discharge to usual care or NT-proBNP guided therapy with the goal of intensifying therapies in patients who still had an NT-proBNP  $\geq 3,000$  pg/mL.<sup>34)</sup> With this study design though, only 63 of the 137 AHF patients in the NT-proBNP guided therapy arm and 53 of the 134 subjects in the usual care arm had an NT-proBNP  $\geq 3,000$  pg/mL.<sup>34)</sup> No differences in outcomes were found between the NT-proBNP guided arm and usual care arm at 6 months; however, overall those subjects that did have NT-proBNP decrease from a pre-discharge value  $\geq 3,000$  pg/mL to  $< 3,000$  pg/mL at discharge had improved outcomes compared to those whose NT-proBNP did not decrease.<sup>34)</sup> In a subsequent randomized study, 405 AHF patients were similarly randomized to either usual care or an NT-proBNP guided strategy with the goal of achieving a  $\geq 30\%$  reduction in the discharge NT-proBNP level from the admission value.<sup>35)</sup> Patients were enrolled at admission, but not randomized until later in the hospitalization when clinical stability had been established. The primary analysis found no difference in all-cause mortality or HF hospitalization at 6-months. However, similar to the other randomized trial, because patients were enrolled at admission and only randomized when clinical stability was established, the majority of patients had already achieved a  $\geq 30\%$  reduction in NT-proBNP at the time of randomization resulting in a smaller 'actionable' patient population. Only 71 of the original 202 patients randomized to the biomarker guided therapy arm had a  $< 30\%$  reduction in NT-proBNP and thus could actually undergo further intensive modification of therapy to see if biomarker guidance improved outcomes. Because of this reduced power, the authors performed a post-hoc analysis between the patients in the usual care arm and the 71 patients that actually underwent NT-proBNP guided therapy. They found those patients who had already achieved a  $\geq 30\%$  reduction in NT-proBNP at time of randomization did the best, while those patients with a  $< 30\%$  reduction in NT-proBNP that subsequently achieved  $\geq 30\%$  reduction with NT-proBNP guided therapy had an intermediate outcome, and patients who were unable to obtain a 30% reduction had the worse outcome.<sup>35)</sup> The authors noted the

difficulties with study design and highlighted that future studies should focus on high-risk patients with a <30% reduction in NT-proBNP at time of ‘stability’ to determine if NP-guided therapy can improve outcomes. These few studies do demonstrate some benefit in aiming to achieve a low BNP or NT-proBNP at discharge, but also partially temper the enthusiasm for using NPs to guide therapy in AHF because of the negative study results. Larger randomized studies focusing exclusively on high-risk patient populations are needed to determine if NPs can guide therapy in AHF. However, before these large studies can be appropriately performed, further research is needed to best define a high-risk patient population to study and determine what the optimal target endpoint is for NP-guide therapy: a percent change in NP levels or an absolute NP value at discharge.

A summary of how the diverse uses of NPs in AHF can be assimilated into a management pathway is displayed in **Figure 1**. NPs can significantly assist in confirming or excluding a diagnosis of AHF in a patient presenting with symptoms or signs suggestive of AHF but still an equivocal diagnosis after considering history and exam. Additionally, the degree of



**Figure 1.** Pathway for using BNP and NT-proBNP in diagnosis, prognosis and management of acute heart failure. In patients with suspected acute heart failure, check a BNP or NT-proBNP and the value can help determine if acute heart failure is unlikely, likely or in the ‘gray zone.’ If a diagnosis of acute heart failure is certain based on history and exam findings, assessment of BNP or NT-proBNP can still be helpful for prognosis as the degree of BNP or NT-proBNP elevation is prognostic for in-hospital outcomes. After a patient has reached clinical stability and is felt ready for discharge, recheck a BNP or NT-proBNP to see if there has been >30% decline from admission. If this has not been achieved, prognosis is guarded, and further interventions should be attempted to see if BNP/NT-proBNP can be further lowered. If the value still cannot be lowered despite further interventions, this identifies a high-risk patient population for higher mortality and heart failure readmission. These patients should be more closely monitored. Boxes are colored to reflect severity of illness at each step with green reflective of a good outcome, yellow is cautionary status and red is area of significant concern for poor outcomes. BNP = B-type natriuretic peptide; NT-proBNP = N-terminal fragment of pro-B-type natriuretic peptide.



NP elevation can assist with prognosis. Recognizing that patients with higher levels of NPs are at an increased risk for in-hospital mortality might lead to triaging these patients to a higher level of care, such as the intensive care unit, consideration of invasive hemodynamic monitoring, and potentially more aggressive cardiac support such as mechanical circulatory support. During hospitalization, intermittent assessment of NPs might assist with determining whether an AHF patient's clinical status is improving or not. For example, when serum creatinine increases during an AHF hospitalization, the change in BNP from admission can assist in determining the prognostic importance of this creatinine change.<sup>36)37)</sup> With resolution of symptomatic AHF and as patients approach discharge, reassessment of NPs can assist with prognostication and guiding therapy. An inability to achieve a  $\geq 30\%$  reduction in NPs or an absolute BNP  $< 250\text{--}350$  pg/mL or NT-proBNP  $< 1,000$  pg/mL identifies a higher-risk patient cohort who might need to remain hospitalized for further optimization and have early follow-up after discharge for close monitoring. If these NP goals cannot be achieved despite further intensification of diuretic therapy, adjustment of neurohormonal therapy, and optimization of co-morbidities, then clinicians might need to consider advanced therapies or even possibly a goals of care discussion. It is from this foundation of NP use in AHF that the other biomarkers will be discussed for their benefits to further improve diagnosis, prognostication and management.

## DIAGNOSIS OF ACUTE HEART FAILURE: THE 'GRAY ZONE'

While NPs are powerful adjunctive tools for assisting with a diagnosis of AHF, there are still approximately 20% of patients that fall into the 'gray zone' where the diagnosis of AHF may remain uncertain. This is an area where additional biomarkers to assist with diagnosing or excluding AHF are needed. An incorrect diagnosis of AHF could lead to an adverse outcome, such as giving diuretics to a patient with an acute pulmonary embolism who is dependent on a higher right ventricular preload. Additionally, this is a zone that patients with HFpEF often fall into since they traditionally have lower levels of NPs from reduced wall stress and comorbidities, such as obesity. Only a few biomarkers though have been shown to assist with improving diagnosis of AHF in this gray zone with recent studies identifying a promising candidate.

### Mid-regional pro-atrial natriuretic peptides

Similar to the ventricles releasing BNP and NT-proBNP during periods of increased intra-ventricular pressure, ANP is released when intra-atrial pressure is increased.<sup>5)</sup> ANP itself is labile and difficult to measure, but the N-terminal fragment of proANP is more stable and an assay has been developed to the mid-region of this fragment (MR-proANP).<sup>5)</sup> As a stand-alone biomarker, MR-proANP has been shown to perform similar to BNP and NT-proBNP for assisting with the diagnosis of AHF with a cut-off  $< 120$  pmol/L making AHF unlikely.<sup>38)39)</sup> When added to BNP or NT-proBNP, MR-proANP does improve diagnostic certainty for AHF with an improved area under the receiver operating curve (AUC) and net reclassification index (NRI), which is a statistical method that evaluates a biomarker's ability to appropriately classify a patient's risk.<sup>38)39)</sup> However, the performance of MR-proANP is still reduced in patients with BNP and NT-proBNP values within the 'gray-zone,' and the MR-proANP assay suffers from many of the same interferences as the assays for BNP and NT-proBNP. Since these early studies of MR-proANP though, there has been limited new data on MR-proANP's diagnostic potential, and MR-proANP is still largely relegated to use in research.

### Insulin-like growth factor-binding protein 7

Since MR-proANP largely reflects similar pathophysiologic processes as BNP and NT-proBNP, it is not surprising that MR-proANP is unable to substantially improve diagnosis of AHF. An ideal biomarker to supplement the NPs would reflect different pathophysiologic processes occurring in AHF. Recently, insulin-like growth factor-binding protein 7 (IGFBP7) has emerged as one such supplemental biomarker. The biological roles of IGFBP7 are still being understood, but studies have shown it plays a role in cardiac hypertrophy, fibrosis, cellular senescence, insulin resistance, endothelial dysfunction and inflammation.<sup>40,41</sup> Many of these pathophysiologic processes play a significant role in the development and progression of HF, specifically diastolic dysfunction. Indeed, IGFBP7 levels have been shown to strongly correlate with echocardiographic parameters of diastolic dysfunction in HF.<sup>42-44</sup> Recently, the diagnostic utility of IGFBP7 was evaluated in the International Collaborative of NT-proBNP-Re-evaluation of Acute Diagnostic Cut-Offs in the Emergency Department (ICON-RELOADED) study, which was originally designed and reaffirmed the diagnostic utility of NT-proBNP for AHF in a more contemporary cohort of patients presenting with acute shortness of breath.<sup>11,19</sup> IGFBP7 alone had a high diagnostic accuracy for AHF with an AUC of 0.87, but this was lower than NT-proBNP which had an AUC of 0.91.<sup>19</sup> However, the addition of IGFBP7 to NT-proBNP further improved the diagnostic accuracy with an AUC of 0.94.<sup>19</sup> Furthermore, IGFBP7 improved the NRI and model calibration and successfully reclassified many patients in the 'gray zone' for NT-proBNP.<sup>19</sup> Thus, IGFBP7 appears to be a new promising biomarker to use in conjunction with NPs to further improve the diagnosis of AHF in patients with diagnostic uncertainty and may further reduce diagnostic uncertainty for patients in the 'gray zone.' Further studies are needed though to fully understand the clinical utility of IGFBP7.

### Procalcitonin

As important as biomarkers are for specifically helping diagnose AHF, biomarkers can also assist with identifying other conditions that can present with HF like symptoms or in conjunction with AHF, such as bacterial pneumonia. Procalcitonin is a 116-amino acid precursor of the hormone calcitonin and is normally produced by the C cells of the thyroid during periods of homeostasis at levels that are barely detectable.<sup>16,45</sup> However, during episodes of inflammation such as in the presence of endotoxin or inflammatory cytokines, procalcitonin can be produced systemically in multiple tissues with levels increasing 100 to 1,000-fold higher than normal conditions.<sup>45</sup> Furthermore, procalcitonin has been shown to specifically increase with bacterial infections and not viral.<sup>46,47</sup> Thus, procalcitonin can assist with diagnosing a bacterial infection and potentially tailoring antibiotic therapy.

One of the earliest studies to evaluate procalcitonin in AHF was from the Biomarkers in Acute Heart Failure (BACH) study.<sup>48</sup> The BACH study recruited 1,641 patients presenting to the emergency department with a complaint of shortness of breath. When procalcitonin was examined in this cohort, Maisel et al. found that AHF patients with a procalcitonin <0.05 ng/mL did not have a bacterial pneumonia and if they were treated with antibiotics, they had a higher mortality.<sup>48</sup> Conversely, AHF patients with a procalcitonin >0.21 ng/mL had a concurrent bacterial pneumonia and if they were not treated with antibiotics, they had a higher mortality.<sup>48</sup> Similarly, the ProHOSP study was a multicenter randomized trial of 1,359 patients presenting with dyspnea and randomized to a procalcitonin guided therapy or usual care. An analysis of the 233 patients with a history of HF found those patients with a procalcitonin <0.25 ng/mL and randomized to a procalcitonin guided approach were less likely to die or be admitted to the ICU within 90-days.<sup>49</sup> These studies among others have



provided the evidence to suggest a randomized trial of procalcitonin guided therapy for antibiotic use in AHF is needed.

The Improve Management of Heart Failure With Procalcitonin (IMPACT EU) study did just this by performing a multicenter randomized trial of procalcitonin guided therapy in 762 AHF patients though it was actually stopped before reaching the original goal of 792 AHF patients because of futility.<sup>50)</sup> In this trial, patients with AHF, based on clinical presentation and elevated NP levels, were randomized to usual care or a procalcitonin guided use of antibiotics where antibiotics were only administered if procalcitonin was >0.20 ng/mL on initial assessment or repeat assessment at 12 hours after admission.<sup>50)</sup> Overall, 90-day mortality was low at 8.2% and only 7.5% of all AHF patients had a concurrent pneumonia. In the intention to treat analysis, there was no difference in mortality between the two arms at 30- or 90-days.<sup>50)</sup> There was actually a higher readmission rate at 30-days in the procalcitonin arm but this was no longer significantly different at 90-days.<sup>50)</sup> Two per-protocol analyses were also performed as nearly 17% of patients in the procalcitonin deviated from the protocol; however, results of these analyses were similar to the intention treat analysis.<sup>50)</sup> There are multiple possible reasons for these negative findings including a lack of power as the actual mortality was much lower than the expected rate of 18%, the large percentage of protocol deviations, a need for serial procalcitonin testing to identify late pneumonia and potentially from not enrolling a high enough risk population.<sup>50)</sup> Regardless of these possible points, evidence does not currently support the use of procalcitonin guided antibiotic therapy in AHF; however, there is clearly a need for more randomized trials. Still, procalcitonin assists in determining the presence of a bacterial infection, such as pneumonia, in patients presenting with AHF or dyspnea.

## PROGNOSIS IN ACUTE HEART FAILURE: IMPROVING RECOGNITION OF HIGH-RISK HEART FAILURE

Research in HF, whether it is novel biomarkers, medications, devices, or treatment pathways, often focuses on improving the outcomes of mortality and HF readmission. While it is important to reduce mortality and readmission whenever possible, it is equally important to identify those subjects that may have progressed in their disease course and have no further options to modify their disease process—that is, the end-stage HF or Stage D HF patient as defined by the ACC/AHA Heart Failure Guidelines.<sup>51)</sup> An AHF hospitalization may be the sentinel event that identifies these patients and their disease trajectory might actually be changed through either evaluation and treatment with advanced therapies, such as heart transplant or left ventricular assist devices, or end-of-life discussions and initiation of hospice. Identifying high-risk AHF patients or Stage D HF patients while also predicting risk of death have classically been difficult. Biomarkers can provide a valuable tool for helping further risk stratify patients and identify those at the highest risk for future adverse outcomes.

### Cardiac troponin: conventional and high-sensitivity assays

Because an ACS event can provoke AHF, cardiac troponins (cTn) are frequently measured in patients presenting with AHF to exclude ACS. However, more often patients with AHF do not have a Type 1 myocardial infarction but rather cTn is elevated from either a type 2 myocardial infarction, acute myocardial injury, or chronic myocardial injury.<sup>52)</sup> Potential pathophysiologic processes causing cardiomyocyte death or injury and leading to cTn release include subendocardial ischemia, increased wall stress, elevated intracardiac

filling pressures, neurohormonal activation, and endothelial dysfunction.<sup>53)</sup> While a type 1 myocardial infarction might be excluded in an AHF patient, an elevated cTn should not be dismissed. Multiple studies have shown an elevated cTn is highly prognostic for an increased risk of mortality and HF readmission.

The prognostic significance of cTn was recognized with a landmark analysis of the ADHERE registry in 2008.<sup>54)</sup> In this analysis of 67,924 AHF patients, cTn was measured with conventional cTn assays at each study site—including local cardiac troponin T (cTnT) and cardiac troponin I (cTnI)—and a positive value was defined as either an admission cTnT >0.1 ug/L or cTnI >1 ug/L.<sup>54)</sup> A total of 4,240 patients, or just over 6% of patients, met these criteria and had a substantially increased risk of death during hospitalization with an odds ratio (OR) of 2.55.<sup>54)</sup> Other studies using conventional cTn assays have confirmed an increased risk for in hospital death with an elevated cTn, and also found an increased risk for death post discharge from an AHF hospitalization.<sup>55-57)</sup> Beyond admission cTn levels, serial assessment of cTn during AHF hospitalization can further risk stratify for death or HF readmission. A study from Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) examined if serial measurement of cTn during hospitalization for AHF is prognostic for different outcomes.<sup>58)</sup> The authors found that patients who had a positive cTnT at admission (defined as >0.03 ng/mL) or that subsequently became positive during hospitalization had a higher mortality and greater readmissions for cardiovascular or renal related conditions than patients whose cTn remained negative throughout hospitalization.<sup>58)</sup> A positive admission cTnT alone was prognostic of 60-day mortality or cardiovascular/renal readmission with an OR of 1.8.<sup>58)</sup> These studies clearly demonstrate the prognostic significance of an elevated cTn in AHF when measured with a conventional assay. However, these findings with conventional cTn assays need to be reassessed with the current era of high-sensitivity cardiac troponin (hs-cTn) assays. With the ability to detect cTn in healthy adults, does an elevated hs-cTn value, even if below a conventional cTn assay's limit of detection, have any prognostic implications in AHF?

Multiple studies with hs-cTn assays have reaffirmed that any elevation in hs-cTn is associated with a worse prognosis but also very low levels portend a good prognosis. An early version of a hs-cTnI assay was evaluated in 808 AHF patients enrolled in the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial.<sup>59)</sup> An elevated admission hs-cTnI was associated with death and worsening HF during hospitalization but not long-term outcomes.<sup>59)</sup> Findings were similar when this study was repeated with a more contemporary hs-cTn assay in the same population.<sup>60)</sup> Other studies though have found an elevated admission hs-cTn value, specifically at levels below those detectable with conventional assays, is associated with an increased risk of death or HF readmission.<sup>61)62)</sup> When serial measurements of hs-cTnT were assessed in 1,074 patients in the RELAXin in Acute Heart Failure (RELAX-AHF) study, both higher baseline and peak hs-cTnT values were associated with an increased risk of cardiovascular death and HF hospitalization at 180-days.<sup>63)</sup> For each doubling of admission hs-cTnT value, the risk of cardiovascular death at 180 days increased by 36%.<sup>63)</sup> While this analysis from RELAX-AHF demonstrates the increased risk associated with elevated hs-cTn values, another analysis from RELAX-AHF examined outcomes in patients who had a hs-cTnT  $\leq$ 14 ng/L.<sup>64)</sup> Remarkably, the investigators found that no AHF patients with a hs-cTnT  $\leq$ 14 ng/ml suffered a cardiovascular death at 180 days. Thus, despite the equivocal findings in ASCEND-HF, multiple studies have affirmed that admission

values of hs-cTn are associated with mortality and HF hospitalization. Additionally, there is a suggestion that serial monitoring of hs-cTn during AHF hospitalization may further improve risk assessment, and AHF patients with very low levels of hs-cTn (below the limits of assay detection) are at a very low risk for cardiovascular death in the short-term.

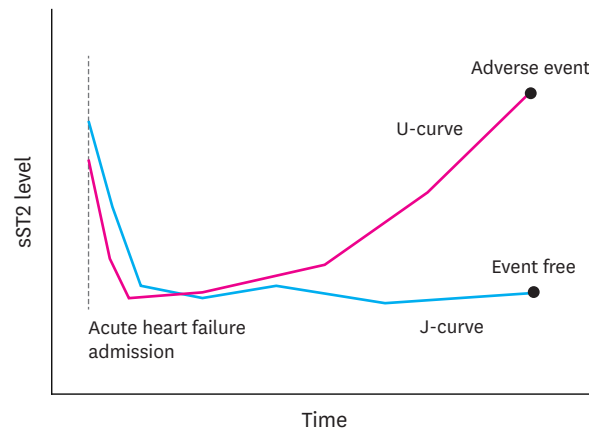
While cTn's utility is predominately in risk assessment, there may be some use in guiding therapy as well. There have not been any cTn guided medical therapy trials in HF like those performed with NP's; however, trials have shown associations with the use of angiotensin converting enzyme-inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) and undetectable levels of cTn.<sup>65)66)</sup> Conversely, a lack of beta-blocker use is associated with higher levels of cTn.<sup>65)67)68)</sup> Furthermore, an analysis from Prospective Comparison of Angiotensin Receptor-Nepriylsin Inhibitor (ARNI) with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial showed that treatment with an ARNI led to a significant and sustained reduction in hs-cTn compared to treatment with ACE-I alone.<sup>69)</sup> These studies do not inform us on whether cTn can be used to decide or direct medical management, but they demonstrate that cTn levels certainly change with appropriately applied medical therapy and thus might 'guide' a clinician to more aggressively apply medical therapy to patients with an elevated cTn in AHF.

### **Soluble suppressor of tumorigenicity-2**

Soluble suppressor of tumorigenicity-2 (sST2) is a biomarker that reflects myocardial fibrosis.<sup>16)</sup> Normally, interleukin 33 (IL-33) binds the ligand form of ST2 on cardiomyocytes resulting in reduced fibrosis and cardiomyocyte hypertrophy.<sup>16)</sup> However, the soluble form (sST2) can bind IL-33 blocking its interaction with the ligand form, thus preventing the normally beneficial antifibrotic effects and effectively promoting fibrosis.<sup>16)</sup> With NPs reflecting myocardial wall stress and cTn reflecting myocardial cell death, sST2 reflects another important pathophysiologic process in AHF—myocardial fibrosis.

Numerous studies have now shown that elevated levels of sST2 on admission are associated with an increased risk of both short-term and long-term mortality.<sup>70)72)</sup> An exact cut-off where risk increases has not been defined, but an analysis from the PRIDE study found risk began to increase when sST2 was  $\geq 20$  ng/mL.<sup>70)</sup> A meta-analysis of 10 studies including 4,835 AHF patients confirmed that increasing levels of admission sST2 are associated with an increased risk of all-cause and cardiovascular death.<sup>73)</sup> For each doubling of admission sST2, the risk of death more than doubled.<sup>73)</sup> Additionally, the meta-analysis found that discharge sST2 is associated with all-cause mortality and cardiovascular death again with a doubling of sST2 associated with more than double the risk of death.<sup>73)</sup> Discharge sST2 values were also associated with HF readmission, but not admission sST2 values.<sup>73)</sup> Thus, both admission and discharge sST2 values can further risk stratify AHF patients especially for the risk of death.

Two studies have shown improved risk assessment with serial sampling of sST2 in AHF patients. In the first study of 150 AHF patients, those patients who experienced a  $<15.5\%$  decrease in sST2 from admission to discharge had a more than four times increased risk of dying.<sup>74)</sup> Many patients who died actually had a rise in sST2 during the hospitalization. The other study followed 496 AHF patients from hospital admission to one year after study enrollment with serial sST2 sampling in the hospital and during outpatient follow up.<sup>75)</sup> Baseline sST2 levels were associated with mortality and HF readmission as other studies have shown.<sup>75)</sup> A unique finding was that serial samples of sST2 in patients with events (death or HF readmission) had a U-shaped trajectory while sST2 levels in patients without events had a



**Figure 2.** The J or U shape of sST2. Serially checking sST2 with admission to the hospital, at discharge and post-discharge can give a trajectory of sST2. This trajectory may appear U-shaped, which is associated with an increased risk of subsequent death or heart failure readmission, or J-shaped, which is associated with a low risk for these outcomes. sST2 = soluble suppressor of tumorigenicity-2.

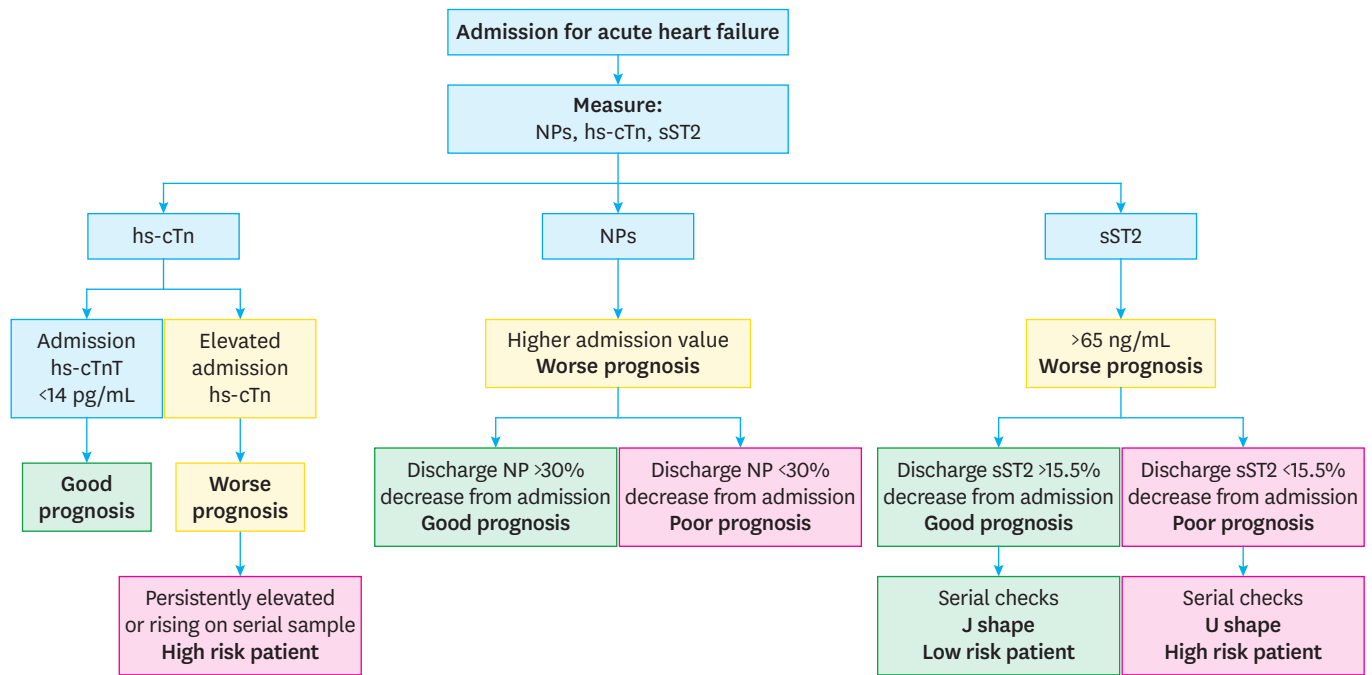
J-shaped trajectory (**Figure 2**).<sup>75)</sup> These studies suggest serial monitoring of sST2 can provide important prognostic insights in AHF patients and may allow clinicians to identify and intervene on AHF patients at an increased risk of death.

### Galectin-3

Galectin-3 (Gal-3) is produced by macrophages and is involved in cardiac fibrosis formation; thus Gal-3 is believed to be a biomarker of fibrosis like sST2.<sup>76/77)</sup> Gal-3 has been primarily examined in one study of AHF patients. In the PRIDE study, Gal-3 was found to be the strongest predictor for mortality at 60-days, even stronger than NT-proBNP.<sup>76)</sup> A few studies have examined Gal-3 in conjunction with other biomarkers in AHF. One study found discharge Gal-3 in conjunction with discharge BNP improved prediction of readmission at 60-days.<sup>78)</sup> However, in a study that evaluated multiple different biomarkers, Gal-3 was not found to be prognostic of mortality compared to the other biomarkers.<sup>79)</sup> Thus, the role of Gal-3 in AHF has yet been determined and further studies are warranted given its initial promising results in the PRIDE study.

### Prognosis with natriuretic peptides, troponin, and soluble suppressor of tumorigenicity-2

As discussed, NPs, cTn and sST2 have each individually been shown to be prognostic for mortality and HF rehospitalization in AHF patients. By reflecting different pathophysiologic processes, their combination may further improve risk prediction. Only one study has evaluated all three biomarkers in AHF.<sup>80)</sup> Admission values of sST2, hs-cTnT and NT-proBNP were measured in 107 patients with AHF who were then followed up for a median of 2 years.<sup>80)</sup> Each biomarker was prognostic for mortality in univariate and multivariate analysis.<sup>80)</sup> Patients with all biomarkers below the optimal cut-off (NT-proBNP  $\leq 2,906$  pg/mL, hs-cTnT  $\leq 23$  pg/mL, sST2  $\leq 65$  ng/mL) experienced no deaths while those with all three biomarkers elevated had a mortality of 53%.<sup>80)</sup> For each biomarker that was elevated at admission above its respective cut-off, the risk for mortality almost tripled.<sup>80)</sup> While this study focused on these three biomarkers together, other studies have examined combinations of two of the three biomarkers or all three in conjunction with other biomarkers, and repeatedly these biomarkers emerge as prognostic for mortality and HF readmission.<sup>79)81-84)</sup> One of these



**Figure 3.** Integration of NPs, hs-cTn, and sST2 into acute heart failure management. Values for these biomarkers should be checked on admission with each individual biomarker associated with worse outcomes when values are elevated. Serial measures of hs-cTn may identify high risk individuals, while serially sampling NPs and sST2 can substantially improve risk stratification. sST2 should be monitored after discharge as well for determining a J or U shape as in **Figure 2**. Boxes are colored to reflect severity of illness at each step with green reflective of a good outcome, yellow is cautionary status and red is area of significant concern for poor outcomes. hs-cTn = high-sensitivity cardiac troponin; NP = natriuretic peptide; sST2 = soluble suppressor of tumorigenicity-2

studies examined seven different biomarkers at various time points and after repeated multivariate analyses, sST2, hs-cTnT and NT-proBNP were found to be the most prognostic for mortality.<sup>79)</sup> The evidence for the use of multi-marker panels is building, and this has been recognized by ACC/AHA Heart Failure Guidelines.<sup>12)</sup> A pathway for incorporating these biomarkers into an AHF admission is presented in **Figure 3**.

## BIOMARKERS FOR MANAGING ACUTE HEART FAILURE: IDENTIFYING CONGESTION

The majority of patients presenting with AHF present with symptoms and signs of volume overload or congestion leading to more than 90% of patients receiving diuretic therapy.<sup>85)</sup> Multiple studies have demonstrated the importance of achieving adequate decongestion, as residual congestion is associated with increased morbidity and mortality.<sup>36)86-89)</sup> When congestion is evaluated though, it should be evaluated in two different compartments: intravascular and within tissues.<sup>90)91)</sup> High NP levels are associated with high intravascular pressures, and NP levels decrease in conjunction with reductions in intravascular congestion. Thus they serve as a useful surrogate to detect congestion in the intravascular compartment.<sup>92-95)</sup> As noted, at least a 30% reduction in NP levels from the admission value is recommended to reduce morbidity and mortality and this should be viewed as a biomarker goal for monitoring intravascular congestion.<sup>22)25)28)89)90)</sup> To evaluate tissue congestion though, two other biomarkers are showing substantial promise as surrogates for tissue congestion and might be used in conjunction with NPs to monitor response to therapy in AHF in the future.

### Bio-adrenomedullin

Adrenomedullin (ADM) is a hormone that induces vasodilation but also plays an important role in maintaining normal endothelial barrier function.<sup>96)</sup> It is secreted by endothelial and vascular smooth muscle during periods of volume overload in an effort to stabilize the endothelium.<sup>96)</sup> By these mechanisms, elevations in ADM theoretically reflect tissue congestion and with a half-life of only 22 minutes, levels can dynamically change to reflect changes in tissue congestion on a day-to-day basis. Recently, an assay has been developed that can measure the biologically active form (bio-ADM) allowing this hypothesis to be tested.

When bio-ADM was measured in 1,562 AHF patients from the PROTECT study, higher levels of bio-ADM were found to correlate with more severe signs and symptoms of congestion on admission.<sup>97)</sup> Additionally, bio-ADM levels changed with the patient's congestion status when it was assessed on hospital day 7.<sup>97)</sup> Notably, BNP levels decreased in most patients regardless of congestion status on day 7.<sup>97)</sup> This observation fits with the hypothetical scenario that an AHF patient is improving from intravascular congestion as assessed by BNP or jugular venous distension on physical exam, while still having residual tissue congestion that may not be appreciated. This study provided the initial evidence that bio-ADM levels correlate with tissue congestion, but it did not explore hard outcomes such as HF readmission, which may correlate with the degree of residual congestion.

Subsequently, the investigators did just this and explored the prognostic ability of discharge bio-ADM as a reflection of residual congestion and risk for HF readmission in 1,236 AHF patients from the PROTECT study.<sup>98)</sup> Discharge bio-ADM levels strongly correlated with a clinical congestion score, with higher bio-ADM levels associated with more severe residual congestion and strongly associated with edema at discharge.<sup>98)</sup> Higher bio-ADM levels were also associated with an increased risk of HF readmission at 60-days.<sup>98)</sup> Further supporting bio-ADM's association with clinical congestion, it was measured in a cohort of 3,882 HF patients that consisted of both acute and chronic HF patients.<sup>99)</sup> Among 20 different biomarkers, bio-ADM had the strongest association with a clinical congestion score and physical exam findings of congestion.<sup>99)</sup> Additionally, higher bio-ADM levels were associated with an increased risk of all-cause mortality and HF hospitalization.<sup>99)</sup> These studies provide strong evidence that bio-ADM can serve as a biomarker of tissue congestion; however, further studies are needed in multiple AHF populations to see if bio-ADM can help guide therapy or improve outcomes by monitoring bio-ADM levels.

### Cancer antigen 125

Cancer antigen 125 or carbohydrate antigen 125 (CA-125) is best known as a biomarker for ovarian cancer monitoring; however, substantial evidence is mounting for CA-125 as a biomarker of tissue congestion useful in both acute and chronic HF. CA-125 is produced by serous epithelial cells and levels are thought to increase in HF from an interplay of inflammation and tissue congestion.<sup>100)</sup> While bio-ADM has a very short half-life, CA-125 has a half-life of more than seven days.<sup>100)</sup> Thus, CA-125 may not reflect the dynamic changes in tissue congestion that bio-ADM does but can provide a broader evaluation of tissue congestion status. This is analogous to the difference between glycemic control measured in the short-term with serum glucose and long-term with hemoglobin A1c in diabetic patients—where bio-ADM may reflect the short-term dynamic changes in tissue congestion and CA-125 can measure the long-term status of tissue congestion. Numerous studies have now strongly associated CA-125 levels with prognosis in AHF and more recent studies have improved our understanding of CA-125 as a marker of congestion.

Given the clinical significance of congestion, early studies explored the prognostic ability of CA-125 in AHF. A study of 529 AHF patients showed higher levels of CA-125 were associated



with increased mortality at 6-months after discharge.<sup>101</sup> Subsequently, a study of 1,111 AHF showed elevated CA-125 levels (>60 U/mL) were associated with higher mortality at 6-months and CA-125 retained prognostic utility when combined with BNP.<sup>102</sup> Other studies in AHF evaluated patient outcomes with diuretic therapy based on CA-125 levels as a surrogate for congestion status. These showed that CA-125 levels could discriminate risk for mortality based on initial BUN levels and loop diuretic dose and predict the different trajectories of kidney function with diuretic therapy.<sup>103)104</sup> More recently, CA-125 was evaluated in almost 4,000 AHF patients, both inpatient and outpatient, in the BIOlogy Study to Tailored Treatment in Chronic Heart Failure (BIOSAT-CHF) registry.<sup>105</sup> CA-125 levels were strongly associated with markers of congestion and higher levels were associated with an increased risk of death and HF readmission at 1 year.<sup>105</sup> These studies have solidified that CA-125 levels are prognostic for multiple different outcomes in acute and chronic HF, but whether CA-125 can actually be used to guide management of congestion in AHF remained unanswered.

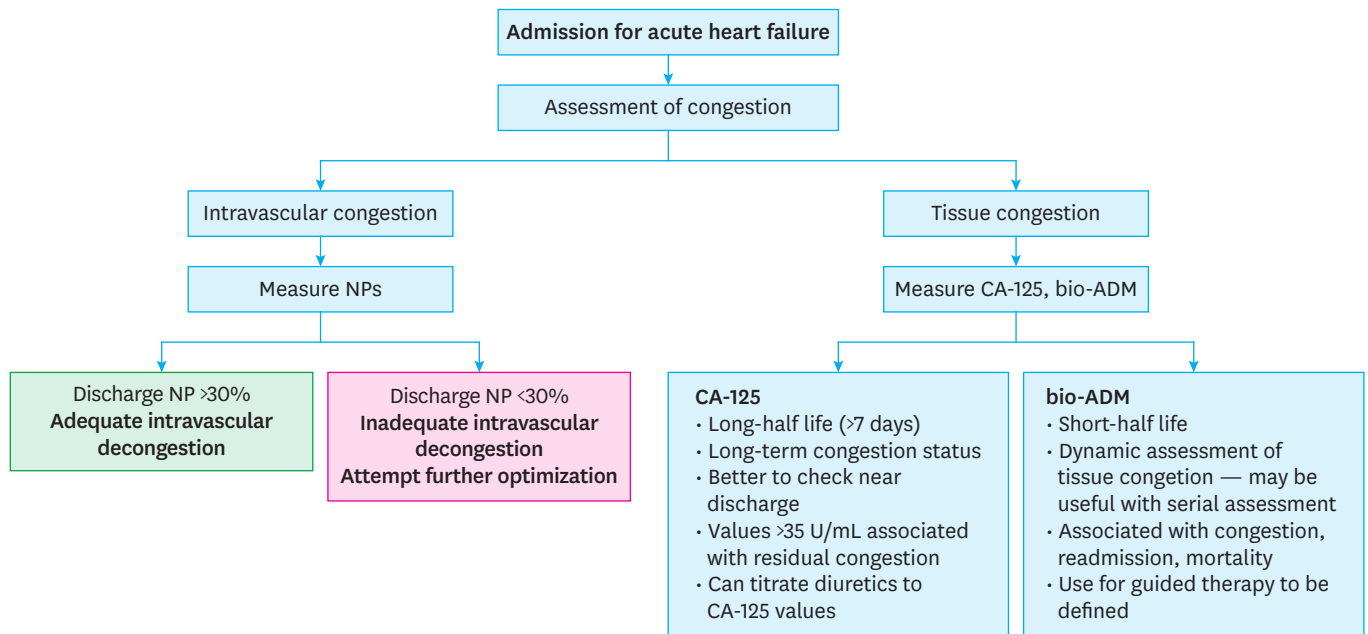
The Carbohydrate Antigen-125-guided Therapy in Heart Failure (CHANCE-HF) began exploring CA-125 guided management.<sup>106</sup> This was a prospective randomized trial of 380 patients recently discharged from an AHF hospitalization and had a CA-125 >35 U/mL.<sup>106</sup> Patients were randomized to usual care or CA-125 guided care with patients in the CA-125 guided arm following a treatment algorithm in an attempt to reduce CA-125 levels.<sup>106</sup> After 1 year, those in the CA-125 guided arm experienced fewer deaths or readmissions for AHF than those in the usual care arm.<sup>106</sup> In a follow-up randomized trial, 160 AHF patients with concomitant renal dysfunction were randomized to usual care or diuretic therapy guided by CA-125.<sup>107</sup> Patients in the CA-125 guided arm (with levels >35 U/mL) were significantly more likely to have improvements in renal function at 72 hours and 30 days and there was a trend towards a reduced risk of death or HF hospitalization.<sup>107</sup> These two randomized trials are some of the first studies to demonstrate potential benefits from a biomarker guided treatment strategy in AHF and strongly suggest that CA-125 may have a role in improving the management of AHF patients.

Further studies are clearly needed to define the role of CA-125 in AHF management. Additionally, there are important caveats for CA-125 to consider before widely adopting. First, the majority of studies with CA-125 are from a single research group. Though many trials of CA-125 have used large multicenter databases or been conducted at multiple sites, reproduction of these findings from different research groups would greatly improve the evidence for the usefulness of CA-125. Additionally, CA-125 is not specific to congestion but can also reflect inflammation in AHF. Indeed, the CHANCE-HF trial treatment algorithm included more than just diuretics to improve CA-125 but also statins, neurohormonal therapy and intravenous iron.<sup>108</sup> Thus, CA-125 is not solely reflective of congestion making its interpretation a bit more difficult; however, most biomarkers are not specific to a single process such as NPs.

A potential pathway to integrate CA-125 and bio-ADM with NPs in AHF patients is presented in **Figure 4**.

## **NEW FRONTIERS IN CARDIOGENIC SHOCK: DIPEPTIDYL PEPTIDASE 3**

The most severe presentation of AHF is in the form of cardiogenic shock, a state associated with a high mortality that has been difficult to manage despite developments in mechanical



**Figure 4.** A potential pathway for using NPs, CA-125, and bio-ADM in acute heart failure for management.

NPs correlate with intravascular congestion and studies have shown improved outcomes when the discharge value is  $\geq 30\%$  lower than the admission value; however, these studies did not specify this reduction was only from decongesting the intravascular compartment. NPs also reflect neurohormonal activation so other biomarkers may be beneficial for monitoring this compartment. bio-ADM shows promise as a biomarker of tissue congestion and levels are prognostic for heart failure outcomes; however, its use is still being defined. Given its short half-life though, serial monitoring might be beneficial during acute heart failure. CA-125 correlates with tissue congestion and prognosis. It has a longer half-life so assessment at admission and near discharge are more useful to assess for residual congestion. Studies support titrating therapy based on CA-125 levels with levels  $>35$  U/mL associated with residual congestion. bio-ADM = bio-adrenomedullin; CA-125 = cancer antigen 125; NP = natriuretic peptide.

circulatory support and other therapies.<sup>109</sup> There are multiple reasons for a failure to improve outcomes in patients with cardiogenic shock, but one potential reason is an inability to distinguish the severity and trajectory of shock. Dipeptidyl peptidase 3 (DPP3) is an intracellular protease that has been shown to have myocardial depressant properties when found in circulation (cDPP3).<sup>110,111</sup> Two studies have recently explored its prognostic utility in cardiogenic shock and notably may have identified it also as a target for pharmacotherapy.

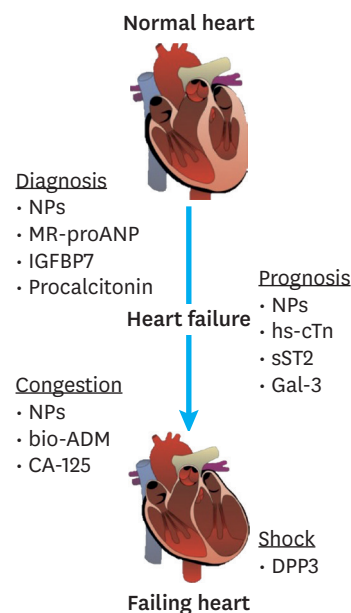
In the Study Comparing the Efficacy and Tolerability of Epinephrine and Norepinephrine in Cardiogenic Shock (OptimaCC), cDPP3 was serially measured in 57 patients with cardiogenic shock after an acute myocardial infarction.<sup>110</sup> cDPP3 levels were found to be significantly higher at admission, 24 and 48 hours in patients with refractory cardiogenic shock (defined as major organ dysfunction and sustained hypotension despite treatment with high dose inotropes or intra-aortic balloon pump support) compared to those in non-refractory cardiogenic shock.<sup>110</sup> Additionally, higher admission cDPP3 levels ( $\geq 59.1$  ng/mL) were associated with an increased risk of death at 90-days.<sup>110</sup> In another study, cDPP3 levels were evaluated in 174 cardiogenic shock patients in the CardShock Study.<sup>111</sup> Similar to findings in OptimaCC, higher levels of cDPP3 on admission were associated with increased mortality at 90-days.<sup>111</sup> When cDPP3 levels were serially assessed, patients with higher mortality had higher cDPP3 levels on the serial assessments.<sup>111</sup> Notably, those patients with high cDPP3 on admission but with a subsequent reduction in cDPP3 levels at 24 hours had a lower mortality than patients whose cDPP3 levels remained elevated.<sup>111</sup> Those with low cDPP3 levels at admission that increased at 24 hours had an increased mortality compared to those patients where cDPP3 levels remained low.<sup>111</sup>

The investigators further examined the physiologic effects of DPP3 by injecting DPP3 and administering procizumab, an antibody that binds and blocks physiologic effects of cDPP3, in a mouse model.<sup>111)</sup> Injection of DPP3 resulted in a decline in left ventricular function and an increased renal resistive index.<sup>111)</sup> In an AHF mouse model induced by isoproterenol infusion, cDPP3 levels increased with the development of AHF and injection of procizumab resulted an improvement in left ventricular systolic function and cardiac output.<sup>111)</sup> Thus, cDPP3 is not just a biomarker for severity in cardiogenic shock, but an actual mediator of shock that may be a target for therapy.

While the sample sizes are small, these two studies provide compelling evidence that cDPP3 might be a very useful biomarker in AHF and cardiogenic shock. Admission levels in severe AHF or cardiogenic shock might help guide therapeutic interventions in the future with higher levels prompting initiation of more aggressive hemodynamic support. Serial assessment might be used to again determine when hemodynamic support should be initiated or escalated and improve risk assessment for risk of death. Furthermore, measuring cDPP3 might lead to a therapeutic intervention by administering a cDPP3 neutralizing antibody such as procizumab. Future studies are certainly needed to confirm these findings and potentially identify a biomarker that is both prognostic and directly actionable upon.

## CONCLUSIONS

Biomarkers have become invaluable adjunctive tests for the diagnosis, prognosis, and management of AHF. NPs alone have substantially improved the evaluation and management of AHF patients; however, given the complex pathophysiology of AHF, no one biomarker can adequately address diagnosis, prognosis, and management. Thus, the use of multiple biomarkers can improve each of these dimensions by applying a multifaceted pathophysiologic approach (**Figure 5**). Both well-established and novel biomarkers are finding increasing utility



**Figure 5.** The different biomarkers through the spectrum of heart failure from diagnosis, prognosis, and management to cardiogenic shock.

bio-ADM = bio-adrenomedullin; CA-125 = cancer antigen 125; DPP3 = dipeptidyl peptidase 3; Gal-3 = galectin-3; hs-cTn = high-sensitivity cardiac troponin; IGFBP7 = Insulin-like growth factor-binding protein 7; MR-proANP = mid-regional pro-atrial natriuretic peptide; NP = natriuretic peptide; sST2 = soluble suppressor of tumorigenicity-2.

**Table 4.** Biomarkers for different aspects of acute heart failure care

Diagnosis	Comments
NPs	<ul style="list-style-type: none"> <li>• Key biomarker for assisting in diagnosis</li> <li>• Correlates with wall stress</li> <li>• Highly sensitive for excluding an AHF diagnosis, less specific</li> <li>• Has a 'gray zone' where diagnosis is less clear</li> </ul>
MR-proANP	<ul style="list-style-type: none"> <li>• Similar performance as BNP and NT-proBNP</li> <li>• Does not substantially improve diagnosis in gray zone</li> </ul>
IGFBP7	<ul style="list-style-type: none"> <li>• Correlates with diastolic function</li> <li>• Useful for diagnosis AHF alone</li> <li>• Additive to natriuretic peptides for diagnosing AHF</li> </ul>
Procalcitonin	<ul style="list-style-type: none"> <li>• Specific for bacterial infection</li> <li>• Can assist with diagnosing a concomitant bacterial infection</li> <li>• Has not yet been shown to improve outcomes in AHF</li> </ul>
Prognosis	
NPs	<ul style="list-style-type: none"> <li>• Admission value prognostic for in-hospital mortality</li> <li>• Discharge value prognostic for mortality and HF readmission</li> <li>• Absolute value at discharge prognostic</li> <li>• A <math>\geq 30\%</math> decline in the value from admission to discharge is associated with improved outcomes</li> </ul>
cTn	<ul style="list-style-type: none"> <li>• Admission value prognostic for mortality</li> <li>• Serial changes during hospitalization can further inform on prognosis</li> <li>• Undetectable levels at admission are associated with good prognosis</li> </ul>
sST2	<ul style="list-style-type: none"> <li>• Admission values prognostic for mortality</li> <li>• Discharge values prognostic for mortality and HF readmission</li> <li>• Change from admission to discharge may identify high risk patients</li> <li>• Serial measurements may identify 'J' versus 'U' trend in sST2</li> </ul>
Gal-3	<ul style="list-style-type: none"> <li>• May be prognostic for mortality, but data limited</li> </ul>
Management	
NPs	<ul style="list-style-type: none"> <li>• Correlates with intravascular congestion</li> <li>• Decline of <math>\geq 30\%</math> from admission to discharge associated with improved outcomes</li> <li>• Randomized trials have not shown benefit of biomarker guided strategy, but studies are underpowered and patients who achieve targeted reduction in natriuretic peptides have improved outcomes</li> </ul>
bio-ADM	<ul style="list-style-type: none"> <li>• Correlates with tissue congestion</li> <li>• Short half-life allows dynamic assessment of congestion</li> <li>• Associated with risk of mortality and HF readmission</li> <li>• Unknown if bio-ADM can be used to guide medical therapy</li> </ul>
CA-125	<ul style="list-style-type: none"> <li>• Correlates with tissue congestion</li> <li>• Half-life over a week allows long-term evaluation of congestion</li> <li>• Associated with mortality and HF readmission</li> <li>• Randomized trials show improved outcomes using CA-125 to guide diuretic therapy</li> </ul>
Cardiogenic Shock	
DPP3	<ul style="list-style-type: none"> <li>• Admission levels associated with risk of mortality</li> <li>• Change in values associate with risk of mortality</li> <li>• Delivery of an antibody blocking DPP3 may help reverse shock</li> <li>• Unknown if DPP3 can be used to direct management</li> </ul>

AHF = acute heart failure; bio-ADM = bio-adrenomedullin; BNP = B type natriuretic peptide; CA-125 = cancer antigen 125; cTn = cardiac troponin; DPP3 = dipeptidyl peptidase 3; Gal-3 = galectin-3; HF = heart failure; IGFBP7 = insulin-like growth factor binding protein 7; MR-proANP = mid-regional pro-atrial natriuretic peptide; NP = natriuretic peptide; NT-proBNP = N-terminal pro-B type natriuretic peptide; sST2 = soluble suppressor of tumorigenicity-2.

in these dimensions in AHF. This review has covered some of established and more promising biomarkers in AHF (**Table 4**); however, each year novel biomarkers continue to emerge. Improving clinicians' understanding of the abilities and uses of these different biomarkers will improve outcomes in AHF in the future.

## ACKNOWLEDGEMENTS

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