Natriuretic Peptides in Clinical Practice

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Abstract

Natriuretic peptides have long been introduced into clinical practice. These biomarkers have certainly been shown to provide useful information in the diagnosis, prognosis and risk stratification in heart failure and also may have a role in the guidance of heart failure therapy. Although, there are some limitations in using of these markers such as lack of specificity, aging, renal dysfunction or obesity, among the huge number of candidates for heart failure biomarkers, only natriuretic peptides are currently widely used in daily clinical practice in heart failure. Recent heart failure guidelines recognize natriuretic peptides as an essential tool in the new diagnostic and therapeutic algorithms. Furthermore, natriuretic peptides are not only used in the diagnosis or prognosis of heart failure, but also these biomarkers are referred to have some potential role in primary prevention, cardio-oncology, advanced heart failure, assessment of response to cardiac resynchronization therapy, pulmonary arterial hypertension, acute coronary syndromes, atrial fibrillation and valvular heart disease. In this article, natriuretic peptides have been reviewed for their updated information and new recommendations in heart failure and also potential role of these biomarkers in the management of various clinical conditions have been addressed in the form of expert opinion based on the available data in the literature. *(Anatol J Cardiol 2019: 21 Suppl 1; 1-40)*

Key words: natriuretic peptides, heart failure

1.0 Introduction – Yüksel Çavuşoğlu

Natriuretic peptides (NP) are commonly used diagnostic biomarkers in heart failure (HF). While the American HF guideline strongly recommends NPs as class I indication with the level of evidence A in the diagnosis of both acute and chronic HF (1), the European HF guideline recommends them as class I indicationwith the level of evidence A for acute HF and as class IIa indication with the level of evidence C for chronic HF (2). Similarly, NPs have been proven to be strong biomarkers for prognosis and risk assessment in HF. The American HF guideline recommends NPs as class I indication with the level of evidence A in the assessment of prognosis of both acute and chronic HF (1). Moreover, the American HF guideline recommends NP monitorization as class IIa indication with the level of evidence B for achieving optimal treatment target in chronic HF (1). However, it

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is very difficult to make a clear recommendation on NP-guided HF therapy in the guidelines since there are both positive and negative results from the clinical trials.

In the last two decades, the use of NPs in daily practice has become gradually widespread and their indications and recommended usage expanded beyond diagnosis, prognosis and risk assessment in HF. Thus, it is striking that the use of NPs stands out in the latest European HF guideline (2). Even though class indication is not specified, some of the new recommendations in the European HF guideline include the measuring NP in patients with a risk factor, symptom, signs or ECG abnormality for HF in the diagnosis algorithm of HF; making NP measurement a mandatory diagnostic criterion in the diagnosis of HF with preserved ejection faction (HFpEF) and HF with mid-range ejection fraction (HFmEF); establishing NP level criteria for initiating sacubitril-valsartan and mineralocorticoid receptor antagonist (MRA); recommending NPs as prognostic indicators in follow-up and monitorization in HF; and highlighting the role of NP in diagnosis and monitorization of cardio-oncologic cases (2). The recommendation of using NPs as class IIa indication with the level of evidence B-R for screening to determine early-stage left ventricular dysfunction in primary prevention to prevent the development of evident clinical HF in the latest updates of the American HF guideline (3) and the recommendation of using NPs for primary prevention without any class indication in the European guideline (2) are other attention-grabbing developments in the HF guidelines.

Increasing evidence suggest the use of NPs not only for diagnosis, prognosis, risk assessment, treatment guidance and primary prevention in HF but also in the evaluation of advanced HF cases with ventricular assist device or who have undergone heart transplantation; determination of response to cardiac resynchronization therapy, and in the assessment of pulmonary arterial hypertension, acute coronary syndromes, atrial fibrillation and valvular diseases. Therefore, their use in the clinical practice as a supplementary method that guides the decision of clinicians is on the agenda although clear guideline recommendations are not available in such cases. This document addresses the potential roles of NPs in the management of various clinical conditions with new recommendations and updated information on NPs in the clinical evaluation and treatment of HF as expert opinion based on the available literature data.

2.0 Natriuretic Peptides in Heart Failure – Hakan Altay

Natriuretic peptides (NPs) are peptide hormones that are a part of endocrine, autocrine and paracrine system which regulate the vessel tonus, cardiac remodeling and intravascular hemostasis by affecting heart, vessels and kidneys. There are three genetically different but structurally associated NPs: atrial natriuretic peptide (ANP), B-type or brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). ANP is the first described NP. It consists of 28 amino-acids and is released from the atria secondary to atrial distension (4). ANP is available in the circulation much more than BNP in healthy individuals. This demonstrates that ANP acts as a 'physiological' hormone of NP system and controls the heart-kidney activity under normal conditions. BNP is mainly created and released by cardiac myocytes associated with cardiac wall stress due to volume overload (4). Myocardial wall stress increasing with volume or pressure overload is the most significant signal that causes the activation of the BNP gene in the cardiomyocytes. Apart from myocardial wall stress, cardiomyocyte damage or hypoxia may also cause the activation of BNP gene. Natriuretic peptide B (NPPB), a precursor molecule, is produced in the cell as a consequence of BNP gene transcription. Later, a pre-propeptide of 134 amino-acids is produced and rapidly cleaved into a signal peptide of 26 amino-acids. This process creates proBNP108, an important intermediate precursor molecule of 108 amino-acids. This intermediate molecule breaks down into various amounts with corin and furin and is cleaved into a biologically inactive molecule, NT-proBNP of 76 amino-acids, and a biologically active molecule, BNP of 32 amino-acids (BNP1-32). After being produced, NT-proBNP, BNP and non-fragmented proBNP108 are released into circulation within minutes so that proBNP108, NT-proBNP, bioactive BNP1-32 and other inactive BNP fragments are present in serum. Conventional tests that are used for measuring BNP or NT-proBNP have cross-reactivity with proBNP108, which shows that the measured NP value is essentially the sum of fragmented and non-fragmented peptides. Unlike ANP, BNP is present in very small amounts in the circulation of healthy individuals and its serum level dramatically increase in heart failure (HF). CNP is a 22 amino-acid peptide and released upon the stimulation of proinflammatory cytokines (interleukin-1 and tumor necrosis factor) and endothelium-dependent agonists (acetylcholine) by vascular endothelium (5). Like BNP, CNP's serum level is low under normal conditions, and its serum level increase in case of pathological conditions (Table 1).

Natriuretic peptides interact with three different NP receptors: NPR-A, NPR-B and NPR-C. While ANP and BNP bind to NPR-A, CNP binds to NPR-B. As a consequence of binding of NPs to NPR-A or NPR-B, membrane-bound guanylate cyclase is activated leading to the stimulation of cyclic guanosine monophosphate (cGMP) and the secondary messenger cascade, which is responsible for most of the physiological effects of NPs. NPR-C is essentially known as a clearance receptor and helps removal of NPs from circulation via binding and internalization of NPs. Another way for clearance of natriuretic peptides from the circulation is through enzymatic breakdown by neprilysin, which is a neutral endopeptidase and is mainly found as membrane-bound in the kidney. Neprilysin is also responsible for the breakdown of vasodilators such as substance P and bradykinin.

Natriuretic peptide system forms the key neurohormonal system together with RAAS and the sympathetic nervous system. Interaction of these three systems plays a significant role

Table 1. Natriuretic Peptides

NP	ANP	BNP	NT-proBNP	CNP
Structure	28-amino-acid peptide	32-amino-acid peptide	76-amino-acid peptide	22-amino-acid peptide
Site of synthesis	Atrium	Ventricle	Ventricle	Vessel endothelium
Signal	Atrial distension	Ventricular wall stress (volume load)	Ventricular wall stress (volume load)	Cytokines (IL-1,TNF), endothelium-dependent agonist (Ach)
Main physiological action	Natriuresis Vasodilation RAAS and SNS suppression Antifibrotic Anti-hypertrophic	Natriuresis Vasodilation RAAS and SNS suppression Antifibrotic	Inactive	Vasodilation? Antifibrotic? Anti-hypertrophic? Anti-inflammatory? Anti-thrombotic?
Receptor	NPR-A	NPR-A	-	NPR-B
Secondary messenger	Guanylate cyclase/cGMP	Guanylate cyclase/cGMP	-	Guanylate cyclase/cGMP
Clearance	NPR-C NEP breakdown	NPR-C NEP breakdown	Passively by skeletal muscle, liver and kidneys	NPR-C NEP breakdown

Ach: acetylcholine; ANP: atrial natriuretic peptide; BNP: Brain natriuretic peptide; CNP: C-type natriuretic peptide; cGMP: cyclic guanylate monophosphate; IL-1: interleukin-1; NEP: neutral endopeptidase; NP: natriuretic peptide; NPR: natriuretic peptide receptor; RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system; TNF: tumor necrosis factor

in the pathophysiology of HF. While biologically active BNP1-32 provides benefits such as natriuresis, diuresis and vasorelaxation by binding to NPR-A receptor, it also antagonizes the harmful effects of RAAS and the sympathetic nervous system. Moreover, it inhibits the development of fibrosis in kidney, heart and the vascular system. NPs play a significant role in the compensation process of HF. However, studies using sensitive mass spectrophotometry have shown that biologically active BNP1-32 level decreases even though the total BNP seems to increase as a consequence of the changes in the anabolism and catabolism process of BNP in HF (6). Again, an increase in myocardial neutral endopeptidase mRNA levels showing accelerated breakdown of NPs in HF supports the fact that HF is somehow characterized by NP deficiency (7). It was demonstrated that increased activity of sympathetic nervous system in HF also decreases ANP release (8).

Among NPs, BNP and NT-proBNP are most frequently used, particularly for diagnostic and prognostic purposes in the clinical practice of HF. Although they are released in a ratio of 1:1, the level of NT-proBNP in circulation is higher than the BNP level. The reason for this is slower clearance of NT-proBNP from the circulation. (The half life of NT-proBNP is 120 minutes and the half life of BNP is 20 minutes). While NT-proBNP is eliminated from the circulation passively by the skeletal muscles, liver and kidneys, BNP is cleared through NPR-C receptors and the neutral endopeptidase system (neprilysin) (9). Elimination of both molecules is equally affected by renal functions and their levels increase in case of renal failure (10). Decreased activity of neprilysin, reduced renal functions and volume overload might be among the causes of increased BNP and NT-proBNP levels in renal failure. Although circulating NP level increases in both HF types, BNP or NT-proBNP levels increase less in HF with preserved ejection fraction (HFpEF) than HF with reduced ejection fraction (HFrEF) (11). Apart from these, right HF (associated with primary cardiac pathology or pulmonary embolism or pulmonary hypertension), valvular heart diseases, acute coronary syndrome, myocarditis and arrhythmias (such as atrial fibrillation) might also cause elevation in BNP or NT-proBNP levels (12-14). In addition to cardiovascular factors that affects NP levels, advanced age and renal dysfunction, might also elevate BNP or NT-proBNP levels without overt HF, obesity, on the contrary, may cause unexpectedly lower levels of these NPs by potentially suppressing formation or secretion even in the presence of HF (15).

Even though information about NPs are obtained mainly from those related to BNP and NT-proBNP, the first described NP is ANP. Recently, the use of ANP as a biomarker in HF has drawn much attention. Although it is found in the circulation of healthy adults, its level further increases in HF. Although formation of BNP is stimulated by myocardial stress, ANP is already produced and stored in the myocardium, particularly in the atrium. The fact that it is analytically unstable and difficult to measure due to a very short half life (2-5 minutes) prevents common use of this peptide. However, the half life of the precursor protein proANP is longer and its measurement in serum is possible. Recently, mid-regional

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MR-proANP assay has been tested in a large prospective study (16). This study reported that MR-proANP could be used for the diagnosis of HF like BNP and NT-proBNP, and moreover this molecule could be more useful in patients with obesity and renal failure in whom the use of BNP and NT-proBNP was less reliable. However, information collected in the subsequent studies showed that factors influencing BNP or NT-proBNP levels (age, renal function, obesity) could also influence the MR-proANP level in the same way (17).

3.0 Natriuretic Peptides in the Diagnosis of Heart Failure and New Diagnostic Algorithms – Tolga Sinan Güvenç

Natriuretic peptides (NPs) are the name given to a group of peptide hormones that are primarily released from cardiac chambers. The structure and effects of natriuretic peptides will not be elaborated on here as they have been previously discussed. However, it is necessary to remember some points about NP physiology in order to better understand the role and diagnostic limitations of NPs. Both hormones increase in heart failure (HF) due to myocardial stretch that occurs as a result of pressure and volume load in the heart (18-20). Therefore, natriuretic peptides do not reflect structural/functional changes but shows increased myocardial wall stretch caused by these changes. NP blood levels can be normal or close to normal when intracardiac pressures are relatively low and the general scheme is dominated by low-flow symptoms. A study that included 558 patients with reduced ejection fraction found a BNP level of <100 pg/ml in 24% of patients (21). Common characteristics of these patients include being relatively young women, presenting with non-ischemic cardiomyopathy and having normal kidney-liver functions (21). In addition, NP levels may vary due to demographic factors such as cardiovascular diseases, renal insufficiency and age and gender, where the primary etiology is not left ventricular cardiomyopathy (22-26). Moreover, as one of the mechanisms of action of recently introduced angiotensin receptor blocker/neprilysin inhibitors is reducing the breakdown of BNP, BNP levels increase in patients who are using these drugs (27). It was suggested that even though it is not expected for NT-proBNP levels to be affected by neprilysin inhibition, increased BNP levels could decrease proBNP and thus NT-proBNP through negative feedback mechanisms, and therefore, NT-proBNP might not be correlated with the severity of HF (28). While using natriuretic peptides for diagnostic purposes, all demographic and clinical factors should be taken into consideration.

As natriuretic peptides reflect myocardial stretch, elevated NP levels are observed both in patients with HFrEF and HF with preserved ejection fraction (HFpEF). However, as myocardial wall stretch is lower in HFpEF, the magnitude of increase in natriuretic peptide levels is also lower as compared to HFrEF (25). As HFpEF and HF with mid-range ejection fraction (HFmEF) are discussed in the other articles featured in this issue, this article mostly covers HFrEF. However, as studies including the general population do not make a distinction between HFrEF and HFpEF, and ejection fraction limit values defined for HFrEF may vary in the methodology of some studies, some topics to be mentioned also cover HFpEF and HFmEF to a degree.

3.1 Natriuretic Peptides in the Diagnosis of Chronic Heart Failure

Recommendations in the international guidelines for NP measurement for the diagnosis of chronic HF, and their place in diagnostic algorithms are provided in Table 2 and Figure 1. As natriuretic peptides are very sensitive to myocardial stretch, their sensitivity in HF diagnosis is quite high; however, their specificity is low as they can be elevated secondary to cardiac or non-cardiac causes. NPs can be low in compensated chronic HF patients or HF patients undergoing optimized treatment (29, 30). Despite such limitations, there are several studies showing that BNP or NT-proBNP measurement increases diagnostic accuracy for HF when combined with past medical history and physical examination findings (31-33). Both the updated 2017 AHA/ACCF/HFSA guideline for heart failure and 2016 ESC guideline for heart failure recommend measuring BNP or NT-proBNP levels in addition to routine clinical assessment for the diagnosis of chronic HF (2, 34). However, the diagnostic algorithm in the ESC guideline recommends NP measurement for chronic HF only in patients who have at least one sign and symptom consistent with HF (2). Additionally, there are clear differences between the guidelines in terms of cut-off values and diagnostic algorithms recommended for the diagnosis of chronic HF (Table 2, Fig. 1). The updated 2017 AHA/ACCF/HFSA guideline avoided specifying a cut-off value for NPs and did not make any distinction between acute and chronic HF (34). On the other hand, the 2016 ESC guideline specified cut-off values for BNP and NT-proBNP as 35 pg/ml and 125 pg/ml, respectively, and stated that negative predictive value was high (0.94-0.98) but positive predictive value was low (0.44-0.57) for these aforementioned cut-off values (2). The ESC guideline does not refer to a single study for these cut-off values but instead cites several observational studies which do not include a prospective, multicenter, determinative study, such as one similar to the Breathing Not Properly (BNP) trial (31, 35-39). In the more recent STOP-HF screening study, BNP cut-off value was accepted as 50 pg/ml for the diagnosis of chronic HF and this study has demonstrated that outcomes could be improved with optimized medical treatment in participants who had a BNP value above this limit (40). Therefore, it should be noted that these cut-off values are not absolute but continuous, and that other parameters should also be taken into consideration in diagnostic decisions.

All relevant international guidelines recommend measurement of NPs in the initial assessment as a part of work up in patients with suspected chronic HF and they emphasize that NPs should precede imaging studies. NP level on the first admission is useful for screening, diagnostic and prognostic purposes (41).

Table 2. Recommendations, levels of evidence and recommendation, and recommended cut-off values in major guidelines for the use of natriuretic peptides for patients who present with symptoms and findings that are compatible with chronic heart failure

Guideline	Recommendation	Level of Evidence/ Recommendation	Recommended Cut-off Value(s)
2017 AHA/ACCF/HFSA HF Update (34)	To diagnose HF or rule it out in patients who present with acute or chronic dyspnea	I/A	No certain cut-off value is specified.
2016 ESC HF Guideline (2)	To exclude HF diagnosis in non-acute conditions	1. For diagnosis– not specified 2. After diagnosis – IIa/C	For Exclusion BNP: 35 pg/ml NT-proBNP: 125 pg/ml
2010 NICE HF Guideline (55)	1. All patients without previous MI and with suspected HF. 2. Patients with normal EF on 2D echocardiography	Not specified	For Exclusion BNP <100 pg/ml NT-proBNP <400 pg/ml High Suspicion/Emergency Assessment BNP >400 pg/ml NT-proBNP >2000 pg/ml
2017 Canadian HF Guideline (57)	In acute or ambulatory patients, particularly if there is suspicion in diagnosis	Strong Recommendation /High-Quality Evidence	For Exclusion BNP: 50 pg/ml NT-proBNP: 125 pg/ml
2010 HFSA HF Guideline (58)	All patients for whom HF diagnosis is considered	Evidence level A	No certain value is specified.

BNP, Type B natriuretic peptide; EF, ejection fraction; HF, heart failure; NT-proBNP, N-terminal pro Type B natriuretic peptide

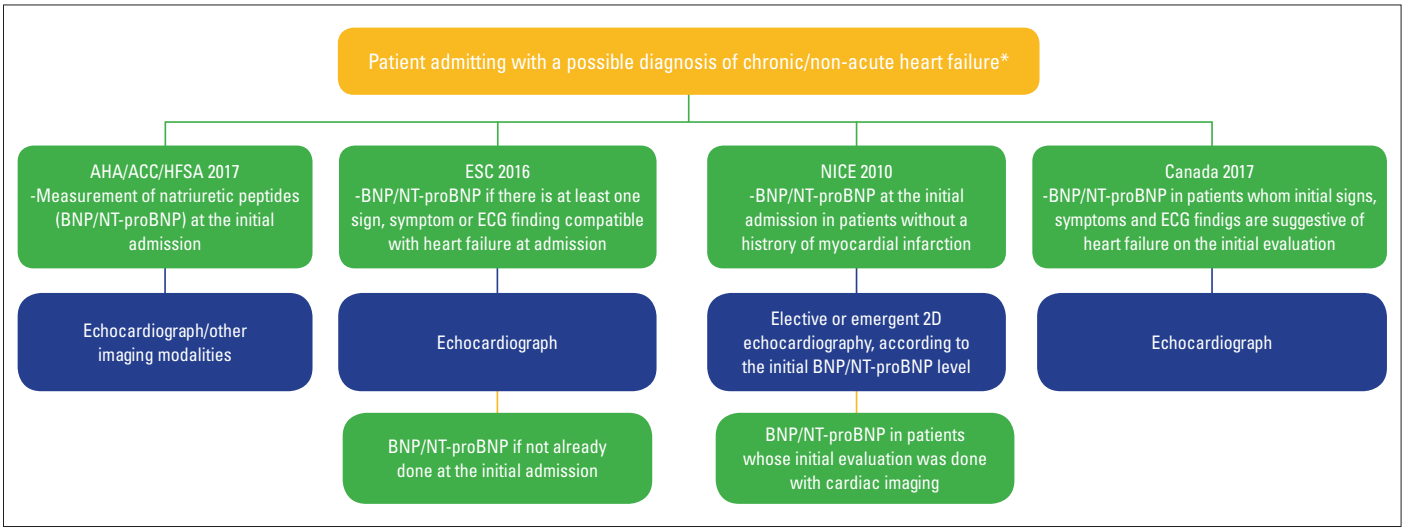

Figure 1. Admission approaches in patients presenting with chronic (non-acute) symptoms, as mentioned in various guidelines. Cut-off values recommended in guidelines to exclude diagnosis or continue with the next line are provided in the text and tables. 2016 ESC and 2017 Canadian guidelines remark that the diagnostic approach can be maintained with echocardiography in case natriuretic peptide measurement cannot be performed (2, 57). The figure was created by compiling data from update of the 2017 AHA/ACCF/HFSA guideline for heart failure (34), 2016 ESC guideline for heart failure (2), 2010 NICE guideline for chronic heart failure (55) and 2017 Canadian guideline for heart failure (57)

*The updated 2017 AHA/ACCF/HFSA guideline for heart failure emphasizes that natriuretic peptides can be used for diagnostic purposes only in those presenting with de novo symptoms among patients with suspected chronic heart failure (34)

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As data from echocardiography and other non-invasive imaging methods are not sufficient for the diagnosis of diastolic heart failure, the 2016 ESC guideline for heart failure emphasized that non-invasive imaging results should be supported with NPs (2). Therefore, NP measurement is significant in terms of supporting the diagnosis and providing prognostic information even in patients whose diagnostic assessment was initially made by an imaging method (42, 43).

3.2 Natriuretic Peptides in the Diagnosis of Acute Heart Failure

The recommendations in the international guidelines and their place in the diagnostic algorithms for NPs in patients with acute dyspnea and suspected HF are presented in Table 2. Contrary to chronic HF, recommendations and specified cut-off values for NPs in acute HF do not demonstrate heterogeneity between the guidelines. The Breathing Not Properly (BNP) trial, which was conducted in 2002, is the first large-scale study that demonstrated diagnostic significance of BNP in patients who presented to emergency services with acute dyspnea (44). Although a similar diagnostic accuracy was demonstrated for several cut-off values in this study, a cut-off value of 100 pg/ml was considered as the optimal value, giving a sensitivity of 90% and specificity of 76% (44). Similar results were also reported for NT-proBNP in patients who presented with acute dyspnea - in the PRIDE study, the negative predictive value of NT-proBNP was reported as 99% for a 300 pg/ml cut-off value (45). As NT-proBNP increases with age, it was recommended that the specific cut-off value for the diagnosis of HF should be determined according to the patient's age. In a retrospective study, the cut-off values for NT-proBNP were found as 450, 900 and 1800, respectively, for those aged <50, 50-75 and >75, with a sensitivity and specificity of 90% and 84% for the diagnosis of acute HF (46). Based on these findings, both American (34, 47) and European (2, 48) guidelines have recommended since the mid-2000s that NPs should be used in the first assessment in patients presenting with acute dyspnea. Although a clear cut-off value was not given in the updated 2017 ACCF/AHA/HFSA guideline for heart failure, the ESC 2016 guideline specifies cut-off values for BNP and NT-proBNP as 100 pg/ml and 300 pg/ml, respectively, for the diagnosis of acute HF (2, 34).

Both international guidelines recommend measuring NP on admission and combine it with other findings. NP measurement is more sensitive than clinical assessment but has a lower specificity (49). However, NPs increase diagnostic accuracy for HF when combined with clinical assessment (49). The IMPROVE-HF trial demonstrated that using NT-proBNP along with clinical assessment was a cost-effective strategy that increased diagnostic accuracy (50). Since measuring baseline NP value allows comparing this value with subsequent measurements and has a predictive value in acute HF, first NP measurement should be done on admission (25, 34, 41).

ANP is secreted secondary to atrial stretch and, similar to BNP, increases in acute HF (51). As blood levels are more stable, mid-regional proANP (MR-proANP) is preferred over ANP as a biomarker. The Biomarkers in Acute Congestive Heart Failure (BACH) trial showed that a cut-off value of 120 pmol/ml and above for MR-proANP had a diagnostic accuracy similar to BNP and a high MR-proANP value supported the diagnosis of HF in cases where BNP was within the diagnostic grey zone (16). The 2016 ESC guideline for heart failure recommended that a MR-proANP value of 120 pmol/ml and below could be used to exclude diagnosis in cases presenting with acute dyspnea (2). On the other hand, the 2017 ACCF/AHA/HFSA update did not make any specific comments on the diagnostic usefulness of MR-proANP and did not provide a diagnostic cut-off value (34).

Unlike the other NPs, C-type natriuretic peptide (CNP) is primarily released from the kidneys and, contrary to what its name suggests, its main effect is tissue repair and vasodilation rather than natriuresis (52). In patients with decompensated heart failure, CNP is rather concentrated in urine and not in serum, thus making it a potential biomarker for the diagnosis and grading of cardiorenal syndromes (52-54). Unlike other NPs, there are no large-scale observational studies on the role of CNP as a biomarker in the diagnosis of acute or chronic HF; considering the current diagnostic performance of other NPs, it is not possible to see such a study in the near future. Major international guidelines do not give specific recommendations for CNP at this time.

3.3 The Role of Natriuretic Peptides in Other Diagnostic Algorithms

Apart from the AHA/ACCF/HFSA and ESC guidelines, some national guidelines with international relevance also supply recommendations for the role of NPs in the diagnosis of acute and non-acute (chronic) HF and provide diagnostic algorithms (Tables 2 and 3, Fig. 1). The 2010 NICE (the National Institute for Health and Care Excellence) guideline for chronic HF recommends BNP or NT-proBNP measurement during the first admission in ambulatory patients with suspected HF but no previous MI, and suggests ruling out HF or referring patients to two-dimensional echocardiography using NP measurement (55). Cut-off values recommended to exclude HF diagnosis are 100 pg/ml and 400 pg/ml for BNP and NT-proBNP, respectively. According to the same guideline, if ejection fraction is normal in two-dimensional echocardiography in patients with possible HF whose NP levels were not measured initially, NP measurement should be considered for the diagnosis of HFpEF (55). The 2014 NICE guideline for acute HF recommends referring patients with possible new-onset HF to two-dimensional echocardiography depending on the results of BNP or NT-proBNP measurement (56). Cut-off values provided in this guideline are the same as those in the ESC guideline (BNP: 100 pg/ml, NT-proBNP: 300 pg/ml). The recently published 2017 Canadian HF guideline recommended different cut-off values for acute and chronic HF with an approach similar to ESC. This guideline recommended

Table 3. Recommendations, levels of evidence and recommendation, and recommended cut-off values in major guidelines for the use of natriuretic peptides for patients who present with acute dyspnea and have suspected heart failure

Guideline	Recommendation	Level of Evidence /Recommendation	Recommended Cut-off Value(s)
2017 AHA/ACCF/HFSA HF Update (34)	To diagnose HF or rule it out in patients who present with acute or chronic dyspnea	I/A	No certain cut-off value is specified.
2016 ESC HF Guideline (2)	To exclude HF diagnosis in patients who present with acute dyspnea	For diagnosis – not specified After diagnosis – IIa/C	To Exclude BNP: 100 pg/ml NT-proBNP: 300 pg/ml MR-proANP: 120 pmol/ml
2014 NICE HF Guideline (56)	All patients who present with acute dyspnea and have suspected HF	Not specified	BNP: 100 ng/L NT-proBNP: 300 ng/L
2017 Canadian HF Guideline (57)	In acute or ambulatory patients, particularly if there is suspicion in diagnosis	Strong Recommendation/ High-Quality Evidence	To Exclude BNP <100 pg/ml NT-proBNP <300 pg/ml High HF Suspicion BNP >400 pg/ml <50 years of age: NT-proBNP >450 pg/ml 50-75 years of age: NT-proBNP >900 pg/ml >75 years of age: NT-proBNP >1800 pg/ml
2010 HFSA HF Guideline (58)	All patients for whom HF diagnosis is considered	Evidence level A	No certain value is specified.

BNP, Type B natriuretic peptide; HF, heart failure; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro Type B natriuretic peptide

NP measurement for HF diagnosis in both acute and non-acute (ambulatory) patients,and emphasized that NP measurements alone was not sufficient for the diagnosis and the primary aim of NPs was ruling out a diagnosis (57). Similar to the ESC diagnosis algorithm, this guideline also recommends NP measurement for chronic HF not in the initial assessment but only in patients who still had suspected HF after the initial assessment (57). The cut-off values recommended for NPs in the 2017 Canadian HF guideline are provided in the tables.

3.4. Conclusion

Measuring NPs during the first assessment for the diagnosis of heart failure is strongly recommended in contemporary international guidelines. However, the same guidelines highlight that NPs have low specificity and diagnosis should be made not only based on NPs but also by taking other parameters into account. All current diagnostic algorithms recommend measuring NPs preferably in the initial clinical assessment in patients who present with either acute dyspnea and chronic symptoms, and this measurement should be used to determine the necessity of non-invasive imaging. However, NPs can be measured after imaging to exclude HFpEF in patients whose NPs were not measured in the initial assessment and found to have a normal ejection fraction on non-invasive imaging. Recommendations for NPs mostly cover BNP and NT-proBNP; however, if it can be measured, MR-proANP can also be used for differential diagnosis of acute dyspnea. There are no sufficient data regarding the use of MR-proANP in chronic HF. This article only mentions the role of NPs in diagnostic algorithms, and the role of NPs in HF screening, and their effect on prognosis and optimization of HF treatment with NP targets will be addressed in other articles.

4.0 Natriuretic Peptides in the Diagnosis of Heart Failure with Preserved and Mid-Range Ejection Fraction – Özlem Yıldırımtürk

Patients with heart failure with preserved ejection fraction and mid-range ejection fraction constitute an ever-increasing medical and epidemiological problem. Like HF patients with reduced EF, similar symptoms and findings are observed in patients

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Table 4. Identification of HF with preserved EF and mid-range EF (2)

Type of HF		HFmEF	HFpEF
	1	Symptom±Findings	Symptom±Findings
	2	Left ventricular EF 40-49%	Left ventricular EF ≥50%
CRITERIA	3	1. Increased natriuretic peptide levels (BNP>35 pg/ml or NT-proBNP>125 pg/ml) 2. Minimum one additional criterion: a. associated structural heart disease (LVH and/or left atrial enlargement) b. diastolic dysfunction	1. Increased natriuretic peptide levels (BNP>35 pg/ml or NT-proBNP>125 pg/ml) 2. Minimum one additional criterion: a. associated structural heart disease (LVH and/or left atrial enlargement) b. diastolic dysfunction

Prepared as amended from ESC guideline for heart failure
Abbreviations: BNP: brain natriuretic peptide; EF: ejection fraction; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFmEF: heart failure with mid-range ejection fraction; LVH: left ventricular hypertrophy

with HFpEF and HFmEF clinically. Previous publications about patients with preserved EF demonstrate that they have better prognosis than those with reduced EF; however, recent studies demonstrate similar mortality rates (59-61). In addition, although survival can be improved in patients with reduced EF through new approaches, such improvement cannot be provided in patients with HF with preserved EF and mid-range HF. In the COACH study, the highest mortality was observed in HFmEF patients after a 18-month follow-up of patients with HF (62). In this respect, diagnosing these patients is even more important.

Studies show that patients with HFpEF and HFmEF are generally female and older and comorbidities such as hypertension and atrial fibrillation are more frequent in these patients while patients with HFrEF more frequently coexist with coronary artery disease (63, 64). Coexisting diseases may show similar symptoms with HF, which may lead to misdiagnosing patients and providing unnecessary treatments to patients without HF. Therefore, it is seen that both the European Society of Cardiology (ESC) and American College of Cardiology HF guidelines included biomarkers in addition to symptoms, findings and preserved EF for diagnosing HF (2, 34).

Data obtained in the last 15 years have demonstrated that an increase in plasma concentrations of both BNP and NT-proBNP are clearly correlated with HF as well as New York Heart Association (NYHA) classification of the patients (65). Many studies put forth the benefit of these biomarkers in diagnosing acute HF. The Breathing Not Properly study, which is the most well-known study, assessed 1600 individuals and revealed that HF diagnosis could be ruled out with 90% sensitivity in patients with BNP plasma levels <100 pg/ml. In this study, negative predictive value was calculated at 96% when cut-off value was 50 pg/ml (44). In another similar multicenter study, this cut-off value for NT-pro BNP was <300 pg/ml (46). According to the results of the majority of the studies, a positive predictive level is very high for HF in cases of plasma BNP concentration >400 pg/ml and NT-pro BNP concentration >2000 pg/ml (66). However, in the recently published ESC HF guideline, that value was determined as >35 pg/ml and >125 pg/ml, respectively, for BNP and NT-pro BNP. According to this guideline, increased NP levels in addition to HF-related symptoms and results as well as HF-related structural functional changes as well as echocardiographically determined preserved EF are necessary for the diagnosis of HFmEF and HFpEF (Table 4) (2).

An increase in plasma BNP levels could suggest diagnosis of HFpEF and HFmEF with similar precision as in HF with reduced EF; however BNP levels are generally lower in patients with HFpEF and HFmEF (38, 67). In the Breathing Not Properly study, when patients diagnosed with HF were evaluated echocardiographically, EF was assessed as >45% in 452 of them and a significant difference was found between BNP levels of these patients and HFrEF patients. However, the trial showed that a clear differentiation cannot be made between HF diagnoses by only assessing BNP levels (68, 69).

Neither the ESC heart failure guideline nor ACC/AHA heart failure guideline made a distinction between HFpEF, HFmEF or HFrEF in terms of the use of biomarkers. It was recommended to use biomarkers in heart failure for prevention, diagnosis and risk stratification, and the determination of prognosis (2, 34) (Table 5).

Table 5. Recommendations of ESC and ACC/AHA guidelines for heart failure regarding the use of biomarkers in patients with heart failure (2, 34)

Acute Heart Failure	Chronic Heart Failure
Diagnosing	Diagnosis, prognosis and determination of the severity of disease
Determination of prognosis	Determination of prognosis after discharge
Determination of prognosis after discharge	Stratification of additional risk

5.0 Conditions Causing Natriuretic Peptide Elevation Other Than Heart Failure – Tamer Sayın

The use of natriuretic peptide levels released in response to overloaded conditions in the diagnostic processes for heart failure (HF) was introduced to clinical diagnostic processes and accepted and started to be commonly used in the 2000s (25, 70). Today, natriuretic peptides (BNP, NT-proBNP) have an important place in diagnosis and prognosis assessment in clinical practice. However, their guidance in HF treatment is still controversial and not yet widely accepted.

In up-to-date guidelines for heart failure, the use of natriuretic peptides is defined as mandatory especially in the diagnosis of heart failure with preserved ejection fraction (HFpEF) and HF with mid-range EF (2). On a chronic basis, values lower than predictive levels of 35 pg/mL for BNP and 125 pg/mL for NT-proBNP strongly rule out diagnosis; however, higher values suggest further examination, asserting the possibility of heart failure diagnosis but do not provide diagnosis alone.

Although BNP and NT-proBNP are very significant diagnostic and prognostic tests in HF, several clinical presentations affect test values (age, gender, renal functions, acute coronary syndromes, left ventricular dysfunction, atrial fibrillation, etc.) (25, 28, 71-73). Therefore, these clinical presentations should be well-known and diagnostic and prognostic processes should be carefully considered in a coherent history including physical examination, echocardiography and other well-known prognostic markers of HF. Cardiac and non-cardiac causes that elevate natriuretic peptide levels are provided in Table 6.

Table 6. Conditions that Elevate Natriuretic Peptide Levels

Cardiac
Heart failure
Myocarditis
Pericarditis / tamponade
Left ventricular dysfunction (systolic / diastolic)
Acute coronary syndrome
Pulmonary embolism
Hypertrophic or restrictive cardiomyopathy
Left ventricular hypertrophy
Valvular heart disease
Congenital heart disease
Cardiac trauma
Atrial/ventricular tachyarrhythmia
Pulmonary hypertension
Cardioversion/ICD shocks
Cardiac surgery
Non-cardiac
Advanced age
Renal dysfunction
Ischemic stroke/subarachnoid hemorrhage
Severe hepatic dysfunction (liver cirrhosis generally presenting with ascites)
Chronic obstructive pulmonary disease
High cardiac rate setting
Anemia
Severe burn setting
Severe infections
Anemia
Severe metabolic and hormonal abnormalities
Paraneoplastic syndrome

5.1 Interpretation of BNP and NT-proBNP Levels and Daily Practice

In the last two decades, natriuretic peptides gained an undeniable place in diagnostic and prognostic processes of HF. However, numerous limitations of this valuable examination are well known by many clinicians and it should be used as a tool that is part of the entire clinical picture. The current European HF guideline highlights the use of natriuretic peptides primarily for excluding diagnosis (2). Three of these presentations that increase natriuretic peptide levels and cause interpretation difficulties during the diagnostic process have been highlighted in this guideline: advanced age, atrial fibrillation and renal dysfunction (2). However, the studies that report predictive value for exclusion in these frequent clinical presentations are limited. As the levels of natriuretic peptide elevate, the possibility of HF diagnosis increases. Some authors defined diagnostic ("rule-in") values on the basis of acute heart failure: 450 pg/mL, 900 pg/mL and 1800 pg/mL for ages below 50, between 50-75 and above 75 years, respectively, for NT-proBNP; and 400 pg/mL without any age criterion for BNP (74).

It is known that natriuretic peptide levels are lower in HFpEF presentations than in HF with reduced ejection fraction (HFrEF). Similarly, it is known in daily practice and literature that natriuretic peptide levels are low in obese individuals with unclear mechanisms. I think that borderline natriuretic peptide levels (especially in the absence of atrial fibrillation and renal dysfunction) are valuable for diagnosis in clinical presentations of elderly, hypertensive, obese women with suspected heart failure (classical HFrEF demography) in my daily practice. Some authors advocate that borderline values might be diagnostic in obese patients for whom echocardiographic imaging windows can be insufficient (75).

A study conducted in patients who underwent angiography demonstrated that borderline NT-proBNP levels could predict stable ischemic heart disease in a group of selected patients without clinical heart failure, with normal left ventricular functions, and without cardiac and non-cardiac conditions which might increase natriuretic peptides (76). It would be appropriate to keep in mind that coronary artery disease could be an explanation for patients who do not correlate with heart failure and have borderline NT-proBNP.

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In a study, chronic severe BNP elevation was reported in eight patients with non-specific symptoms without a clear cause and heart failure was detected in detailed examinations (AxSYM Plus BNP assay, Abbott Diagnostics, IL, USA) (77). In patients whose results were normal based on BNP tests and NT-proBNP values of two different firms, the authors thought that the laboratory technique of microparticle enzyme immunoassay could be responsible and warned about false positivity regarding the method of examination for Abbott AxSYM Plus BNP assay.

In summary, strengths and weaknesses of natriuretic peptide measurements which broke new revolutionary grounds in the diagnosis and prognosis of heart failure in the last two decades should be well-known. Natriuretic peptides should be used as an examination that supplements a thorough history as well as physical examinations, ECG, telecardiography and biochemical analyses. It should be kept in mind that further unnecessary examination can be prevented with also diagnostic algorithms and natriuretic peptide measurements defined in the guidelines.

6.0 Natriuretic Peptides in the Identification of Heart Failure Prognosis and Risks – Mehmet Birhan Yılmaz

Even though it is not frequently used in clinical practice, cardiovascular risk assessment is among the leading topics that are taken into consideration in the modern world. At this point, the role of natriuretic peptides in HF is, in spite of its limitations, at the point of being the HbA1c of diabetes mellitus, or even beyond. In the literature, there are several studies conducted with natriuretic peptides evaluating the prognoses in both HFrEF and HFpEF patients (78, 79). Interestingly, although absolute values are generally lower in HFpEF than HFrEF, prognosis can be poorer in HFpEF at a certain NP value (62). The ACC/AHA/HFSA HF guideline, which was updated in 2017, thoroughly summarizes the body of knowledge on the subject and makes suggestions in this regard (3).

With the exception of advanced HF, natriuretic peptides generally have a good performance of identifying prognosis and risks in chronic HF and acute HF4 (Table 7). It has been demonstrated that even if it is among the diagnostic criteria for advanced stage HF and even if high values indicate adverse prognosis, a random value does not perform well in indicating mechanical support device or transplantation list, etc (80).

The effect of change in natriuretic peptides in follow-ups on the prognosis in chronic HF was also evaluated. It does not seem to have a great effect on optimally treated patients. However, an increase of >30% was associated with a poor prognosis (81). Prognosis assessment could be strengthened by integrating NP change with other biomarkers (82). However, biological variation is one of the significant issues in chronic follow-ups. The place of natriuretic peptides in prognosis assessment for chronic HF is in the range of biological variation (83). Absolute and follow-up levels of NP in an early-stage HF patient might remain within biological variation limits. In such cases, greater changes should be sought out.

Guidelines suggest that admission values of NP are more significant in AHF. On the other hand, there is still no answer to whether absolute value or percentage change is more significant (84). Admission value is significant; however, percentage change is generally more widely accepted in scientific research (84). By also taking natriuretic peptide values on discharge into account and observing the change, it is possible to obtain a significant discharge risk score in prognosis assessment of patients (85). Adding NT-proBNP to other risk markers provides an improvement of 62% in risk assessment of AHF patients; and this fact reveals the effect and strength of NPs in prognosis assessment. Therefore, due to practical reasons, more than one result is needed in prognosis assessment. Moreover, using multiple biomarkers can be significant in assessing prognosis, particularly in AHF patients. However, it should be kept in mind that a biomarker performing well in prognosis assessment might not show the same performance in therapy guidance.

6.1 Natriuretic peptide-guided treatment in acute heart failure

There are several scientific studies in the literature on the use of natriuretic peptides on hospital admission, discharge or between the two for diagnostic or prognostic purposes in patients who are monitored in hospital due to acute heart failure; however, the use of NP guidance in the management of AHF is not a frequently studied topic even though it is encouraged in scientific literature (86). As a general concept, increased, decreased or stable NPs (as absolute or percentage change) are useful and semi-quantitatively reflect ventricular wall stress at that time. As an absolute value, BNP <350 pg/ml or 30% decrease on discharge was found to be correlated with positive prognosis in AHF patients (87-89). It is known that this prognosis improvement is also associated with hemodynamic improvement (89). On the contrary, absolute BNP >700 pg/ml or a lack of decrease was correlated with an adverse prognosis and this can be more signif-

Table 7. Natriuretic peptides in prognosis assessment and therapy guidance in Acute and Chronic Heart Failure

Acute heart failure	On admission	In-hospital change prognosis	On discharge	In-hospital change therapy guidance
	+++	++	++	-?
Chronic heart failure	**At baseline (dry)**	**Change in follow-up, prognosis**		**Change in follow-up, therapy guidance**
	+++	++		+/-

icant in terms of revealing patients at risk12. On the other hand, it is also known that a NT-proBNP level ≤1000 pg/ml in patients with chronic HF is correlated with a positive prognosis (88). The logic behind therapy guidance, which is one step ahead of this concept, is based on the expectation that NPs will decrease and the patient will improve through HF treatment; and this can be partially true in the event that certain conditions are provided. The initiation and/or up-titrating treatment with an ACE inhibitor, MRA, beta-blocker, and CRT treatment reduce NP levels in chronic HF, and it is known that these agents also improve life expectancy. This parallel relationship in chronic HF has been partially confirmed through scientific studies; however, according to a meta-analysis, this relationship is not strong and contains uncertainties (88). In this group of patients, cardiovascular events may decrease and left ventricular reverse remodeling might be performed. However, it is also known that prognosis remains poor if NP levels do not change or increase after the start and/or up-titration of treatment. Therefore, therapy guidance is promising as a concept but suitability of NPs to this concept, especially to AHF, is doubtful.

On the other hand, it is also known that standard AHF treatment, i.e. diuretics and nitrates, alters NP levels although no therapy changing prognosis of AHF has been found yet. Changes in NP levels also have prognostic significance apart from HFpEF (90). The idea of using NP guidance in drug treatment that does not change prognosis (at least not currently known) is not attractive to investigators. Natriuretic peptides may not meet expectations as a biomarker reflecting only a part of the problem, i.e., ventricular wall tension, in a multi-dimensional problem with hemodynamic and systemic effects such as acute HF. For instance, very high NP levels on admission are concerning; however, they have not been found to be associated with congestion in proportion to elevation and do not lead to re-hospitalization due to HF (91). Moreover, it has been demonstrated that a single measurement cannot reflect the degree of congestion and thus, the real course can be established through repeated measurements (92). NP elevation is one of the distorted laboratory tests in AHF and correcting a single figure by ignoring other tests might not provide the expected outcome. The first large study confirming all these questions (PRIMA II) has recently been published. In the aforementioned study, the investigators randomized AHF patients to standard treatment and treatment that targeted NT-proBNP decrease >30% from admission to discharge (93). In conclusion, NP-guided therapy did not decrease mortality or hospitalization rates in AHF patients. However, there is a striking problem at this point. Even though there was a statistical difference, a NT-proBNP decrease of >30% was achieved in 64% of patients in the standard treatment arm and this ratio was 80% in the active treatment arm. In summary, the fact that a standard treatment, whether or not it exactly reflects real life is not known, decreases NT-proBNP with a known effect of improving prognosis demonstrates the success of standard treatment, and although the absolute difference is 16%, the results are not reflected in endpoints as NP guidance does not constitute a sufficiently great difference compared to standard treatment. The available findings might limit the efforts in terms of AHF therapy guidance until a drug that clearly changes prognosis is discovered. On the other hand, the fact that standard treatment is too good to represent real life might be associated with the "contamination" problem in such studies. When a contaminated standard treatment arm is treated better than usual, the difference can minimize the statistical significance of the treatment effect. There is an ongoing study about prognosis assessment after early discharge that takes this aspect into consideration (NCT03412201, STRONG-HF).

7.0 Natriuretic Peptide-Guided Treatment in Chronic Heart Failure – Yüksel Çavuşoğlu

Elevated natriuretic peptide (NP) levels in heart failure (HF) are accepted as an indicator of neurohormonal activation and hemodynamic abnormality. An increase in ventricular filling pressure or ventricular volume triggers NP release (94). There is a close relationship between the severity of the clinical picture and NP levels. As the NYHA class deteriorates, NP levels increase. On the other hand, NP levels decrease with effective treatment. This situation suggests the idea that decreasing NP levels with optimal therapy can positively affect clinical HF as well as prognosis. Therefore, it seems reasonable to increase and optimize treatment intensity according to NP level measurements (under NP guidance) during clinical follow-up.

When NP-guided studies on chronic HF are examined, it is seen that the rates of reaching target dose with maximum dose in ACEI/ARB, beta-blocker, MRA and diuretic treatments are much better in NP-guided treatment arms than symptom-guided treatment arms (95). Some of these studies aimed to lower NT-proBNP value below 1000 pg/mL. However, fast optimization and fast dose up-titration performed to achieve the target during treatment optimization in the groups treated with NP guidance might lead to the occurrence of more adverse outcomes.

According to some of the studies which compared NP-guided treatment approaches and standard treatment approaches in chronic HF so far, the NP-guided treatment approach to improve the prognosis tends to improve prognosis in some cases and has no benefits in others (Table 8).

One of the positive studies, in which the natriuretic peptide-guided treatment approach has been shown to improve prognosis, is the PROTECT study (96). The study included 150 chronic HF cases with NYHA II-IV and <40% EF, monitored them for one year and compared NP-guided treatment and standard treatment approaches. The NP-guided treatment arm aimed to lower NT-proBNP levels below 1000 ng/L. At the end of the study, it was demonstrated that the NP-guided treatment strategy significantly decreased total cardiovascular events (HF worsening, HF hospitalization, ventricular arrhythmia, acute coronary syndrome, stroke, cardiac death) better than standard treatments (p=0.009). Moreover, HF worsening alone (p=0.001) and HF hospitalization (p=0.002) alone significantly decreased with the NP-guided treatment strategy. Additionally, a significant improvement in

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Table 8. Randomized clinical studies investigating the efficacy of natriuretic peptide-guided treatment

	PROTECT	TIME-CHF	BATTLESCARRED	STARBRITE	GUIDE-IT
Number of patients	151	499	364	137	894
Age	63	77	76	61	65
Randomized	Randomized	Randomized	Randomized	Randomized	Randomized
EF	28	30%	37%	20%	24%
NP	NT-proBNP	NT-proBNP	NT-proBNP	BNP	NT-proBNP
Duration of follow-up	10 months	18 months	Minimum 12 months	3 months	15 months
Conclusion of study	CV events (p=0.009) and CV hospitalizations (p=0.002) decreased	Mortality (p=0.02) and CV hospitalizations (p=0.002) decreased in cases aged <75	Mortality (p=0.021) decreased in cases aged <75	No difference in hospitalization and survival. More medical treatments were reached in the NP arm	No difference in CV hospitalization and CV death (p=0.88).

echocardiographic EF (p=0.01) as well as a significant decrease in left ventricular end-systolic (p=0.001) and end-diastolic volume (p=0.008) indices were detected with the NP-guided treatment strategy. The lowest NT-proBNP levels obtained showed a correlation with low clinical event rates.

One of the studies suggesting that natriuretic peptide-guided treatment approach tends to improve prognosis is the TIME-CHF study (95). In the TIME-CHF study, which lasted for 18 months and included 499 chronic HF cases who were hospitalized in the last year, aged > 60 years, had NYHA ≥II, EF <45% and NT-proBNP ≥2 times, showed that there was no difference in terms of mortality despite a significant decrease in HF-related hospitalizations in the NP-guided treatment arm (HR: 0.60 (0.49-0.90), p<0.008). However, when the group of cases aged <75 were taken into consideration, it was reported that both mortality (p=0.02) and HF-related hospitalizations (p=0.002) significantly decreased in the NP-guided treatment arm but no difference was found in terms of both mortality and HF-related hospitalizations in ≥75 age arm. Similarly in the BATTLESCARRED study comparing intensive clinical care and standard clinical care with the guidance of NP in a three-year follow-up, it was observed that mortality rates significantly decreased in the group of cases aged <75 (15.5%, 30.9% and 31.3%, respectively, p=0.021); however, mortality benefit was lost in the ≥75 age group (97). These results indicate that NP-guided treatment can be beneficial for mortality and HF-related hospitalizations especially in cases aged <75. It is thought that, in the ≥75 age group, increased comorbid conditions limit the potential benefits of NP guidance.

Analyses of studies such as STARBRITE (98) and SIGNAL-HF (99) asserting that natriuretic peptide-guided treatment has no benefit indicate that no significant decrease in NP levels was seen in the NP-guided treatment arms compared to the control arm in these studies.

One of the latest studies that tested natriuretic-peptide guided treatment is the GUIDE-IT study (100). The study included high-risk systolic HF cases with an EF <40% and a history of previous HF hospitalization. The NP-guided treatment arm aimed to lower NT-proBNP levels below 1000 pg/ml. In the control group, treatment was optimized according to standard follow-up. It was planned to include 1050 cases in the study, but 894 cases were enrolled. The results of the study, which was terminated prematurely, demonstrated that there was no difference between the groups in terms of primary endpoints of the first HF hospitalization or cardiovascular death (37% and 37%, respectively, p=0.88). There was no difference in terms of cardiovascular deaths alone and the first hospitalization alone, either. It is noteworthy that the rate of patients with NT-proBNP <1000 pg/ml drops is similar in both groups, suggesting that this may have affected the results.

In a meta-analysis of studies on clinical benefits of natriuretic peptide-guided treatment, it was seen that NP-guided treatment provided a significant mortality advantage in chronic HF compared to a standard treatment strategy (HR: 0.69, 95% CI 0.55-0.86) (101). Other studies showing that NP-guided treatment provides significant improvement in the quality of life, significant decrease in the severity of mitral regurgitation and significant decrease in hospital costs support an NP-guided HF treatment strategy. However, different results from the studies prevent making a clear recommendation regarding an NP-guided treatment strategy. Therefore, NP-guided treatment optimization is recommended with class IIa indication and the strategy of decreasing mortality and hospitalizations through serial NP measurements is recommended with class IIb indication in chronic HF (1).

7.1 Natriuretic peptide criteria required for initiating medication in new treatment algorithms

Heart failure guidelines take inclusion criteria used in clinical studies with the relevant drugs into account while determining drug indications that they recommend for HF treatment. Thus, it is thought that clinical benefit will occur in the patient group with the criteria for evidence of efficacy of the drug. For that reason, HF

Table 9. The NP criteria in the ESC 2016 HF guideline for starting MRA and sacubitril/valsartan

	BNP criterion	NT-proBNP criterion
MRA	≥250 pg/mL	≥500 pg/mL in men, ≥750 pg/mL in women
Sacubitril/valsartan	≥150 pg/mL ≥100 pg/mL in case of hospitalization in the last 1 year	≥600 pg/mL ≥400 pg/mL in case of hospitalization in the last 1 year

guidelines, particularly the European HF guideline, recommend that if NP criteria have been used in the studies, this should be taken into account as a criterion of the indication for starting the drug.

By taking the criteria of the PARADIGM HF study into account, the 2016 European HF guideline (2) requires BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL to start sacubitril/valsartan, or BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL if the patient was hospitalized in the last year (Table 9). 2016 ACC/AHA HF guideline (102) does not stipulate NP criteria for initiating sacubitril/valsartan. By taking the NP criteria in the MRA-related studies into account, the 2016 European HF guideline requires BNP ≥250 pg/mL, or NT-proBNP ≥500 pg/mL in men and NT-proBNP ≥750 pg/mL in women to start MRA. On the other hand, the ACC/AHA guideline does not stipulate NP to start MRA. As the studies on ACEI/ARB, beta-blocker, digoxin and ivabradine do not have NP criteria, HF guidelines do not require a NP criterion to start these drugs.

7.2 Natriuretic peptides in the follow-up of patients who are taking sacubitril/valsartan

Neprilysin is an enzyme that breaks down NPs. When this enzyme is blocked, NPs (ANP, CNP, BNP) cannot be broken down and blood levels increase (103, 104). NPs demonstrate their beneficial effects on HF by primarily causing vasodilation and diuresis/natriuresis. Neprilysin is not responsible for the breakdown of only NPs. It also plays a role in the breakdown of vasoactive peptides such as angiotensin (AT) II, bradykinin, substance-p and adrenomedullin. Therefore, AT II levels also increase with the inhibition of neprilysin (103).

Sacubitril causes an increase in NP levels by inhibiting neprilysin (104). This is a desirable effect. However, increased AT II levels resulting from the inhibition of neprilysin is an unfavorable result. Therefore, ARB should accompany sacubitril to block the effects of AT II. The sacubitril / valsartan compound promotes a useful mechanism by causing neprilysin inhibition to increase NP levels, while it inhibits the effects of an abuse mechanism by blocking the effects of increased AT II with valsartan (103, 104).

Natriuretic peptides are peptides that are released as a result of an increase in myocardial wall stress (94). Ventricular filling pressure or volume increase triggers NP release. Pro-brain natriuretic peptide, a prohormone, is divided into BNP and NT-proBNP. BNP is its active form and NT-proBNP is its inactive form. Inhibition of neprilysin by sacubitril decreases BNP breakdown and increases its levels (103, 104). However, as the elimination of NT-proBNP is not mediated by neprilysin, it is not affected by the inhibition of neprilysin. Therefore, it is strongly recommended to use NT-proBNP while evaluating NP levels in patients who take sacubitril/valsartan (103, 104).

8.0 Natriuretic Peptides in the Management of Chemotherapy and Radiotherapy Patients – Cafer Zorkun

Even though classifications and definitions used in the preparation of cardio-oncology guidelines or clinical studies might differ, all articles reported a decrease in LVEF value and a mild distortion in LV functions following the completion of anti-cancer therapy (105-109). Studies evaluating LV functions with biomarkers and echocardiographic parameters focused on patients who did not previously receive cardiotoxic treatment, required very high doses of tyrosine kinase inhibitor, HER2 (Human Epidermal growth factor Receptor 2) and anthracycline (>450 mg/m^2 of cumulative dose) in treatment, and had more than two cardiovascular risk factors (110).

Considering the fact that heart failure associated with chemotherapy and radiotherapy (with a significantly extended life span) might develop 28-30 years after the administration, it is easily understood that patient admission criteria do not accord with real life and the research diverged from the patient population which should be really examined. Guidelines and recommendations published so far have been prepared without taking these limitations into account, and fall behind in classifying and assessing a significant portion of patients with cancer and heart disease. Whereas, cardiovascular diseases which are not detected or diagnosed late in cancer patients play a more important role in mortality than the cancer. Therefore, there is a need for safe and easy biomarkers which can predict mortality and morbidity. Natriuretic peptides are tests that can satisfy this need and be studied in almost every laboratory meeting the standards. In order to gain a place in daily practice, these tests should be used in different patient groups, with other diagnostic methods in various treatment periods (clinical, imaging, other biomarkers such as cTnI, hsTnT, etc.), and be standardized and assessed on a patient-basis (Table 10) (110, 111).

As potential markers of cardiotoxicity, BNP and NT-proBNP are mentioned in the Common Terminology Criteria for Adverse Events (CTCAE) that is used in AHA/ACC and ESC guidelines as well as oncology studies. However, natriuretic peptides might increase in cancer patients without evidence of a cardiac disease

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Table 10. Cardiovascular hormones at various stages of tumor (112)

Biomarker	Stage 1 (96 Pts)	Stage 2 (50 Pts)	Stage 3 (108 Pts)	Stage 4 (183 Pts)	*P*
hsTnT (ng/ml)	0.005 (0.003-0.009)	0.004 (0.003-0.007)	0.006 (0.003-0.011)	0.007 (0.004-0.012)	<0.001
NT-proBNP (pg/ml)	103 (48-190)	105 (58-191)	118 (73-257)	168 (74-377)	0.002
MR-proANP (pmol/l)	56.2 (45.3-83.8)	61.1 (51.4-71.2)	59.4 (41.6-99.9)	67.7 (47.4-113.5)	0.016

which can be explained through available examinations and test methods. There are both; studies which assess this increase as false positive and publications which state that malign cells can secrete atrial natriuretic peptide (ANP) and Type B natriuretic peptide (BNP) in a manner by which the mechanism cannot be entirely explained (113-116).

Another study in patients who received anthracyclines reported that an elevation in BNP values was associated with E/A increase, which could indicate diastolic dysfunction (117, 118). The same study concluded that signs of heart failure occurred in the presence of permanently elevated BNP values during the use of anthracycline (119). Additionally, there are other studies reporting that there is no correlation between echocardiographic LV parameters and BNP levels unless a cumulative doxorubicin dose of >500mg/m^2 is reached (120), that BNP levels increase as LVEF decreases in patients on chemotherapy (121), and that baseline BNP values and BNP levels that increased during the study are not associated with LVEF (122).

It is not possible to evaluate patients who receive anti-cancer therapy in all aspects with today's heart failure classifications (such as HFpEF, HFmrEF and HFrEF). There is no possibility to evaluate myocardium which might be damaged during or after each CT, IT or RT session and can partially lose its function, based on this classification. Although several studies assert that gradually elevated BNP values in patients receiving anthracycline treatment are associated with decreased LVEF values, there are also some studies which stated no significant correlation between these two parameters. Such studies tried to explain elevated BNP and NT-proBNP developing without clinical signs of heart failure with the presence of anemia and circulating cancer cells. These studies could not measure baseline (before treatment) NT-proBNP and perform echocardiography, and the presence of patient comorbidities could not be addressed in a sufficient manner (122).

LV functions can be rapidly disrupted depending on the anti-cancer therapy applied. Coronary artery spasm, alterations of coronary blood flow, permanent myocardial damage due to myocardial infarction or myocarditis, and transient LV dysfunction might occur starting form the first dose of medication (122). Recent studies have defined chronic heart disease as inter-correlated damage (myocardial infarction, cardiotoxic drugs), fatigue (advanced age, diabetes, chronic kidney diseases, microvascular dysfunction, myocardial fibrosis, arterial hypertension) and injury (generally transient clinical pictures such as Takotsubo or viral myocarditis), i.e. "damage, fatigue and injury concept". However, natriuretic peptide values fitting these clinical pictures have not been defined (123).

When physiopathology of heart failure is considered, ischemia has a significant place in the etiology of heart failure characterized by reduced LVEF (HFrEF), while fibrosis due to pro-inflammation, increased LV filling pressure, affected coronary vascular endothelium and decreased nitric oxide bioavailability are significant in the etiology of heart failure characterized by preserved LVEF (HFpEF) (Fig. 2).

According to the results of a prospective study with a follow-up period of 16-31 months (mean 25 months) involving 555 patients who did not receive previous cardiotoxic treatment (34% mortality throughout the study), NT-proBNP (N-Terminal pro–B-type Natriuretic Peptide) and MR-proANP (Mid-Regional pro-atrial Natriuretic Peptide) are significant markers of mortality. Additionally, as seen in the results of BIOSTAT-CHF (BIOlogy Study to TAilored Treatment in Chronic Heart Failure) study, elevation of NT-proBNP was associated with the patient's LVEF level (Table 11). It was not

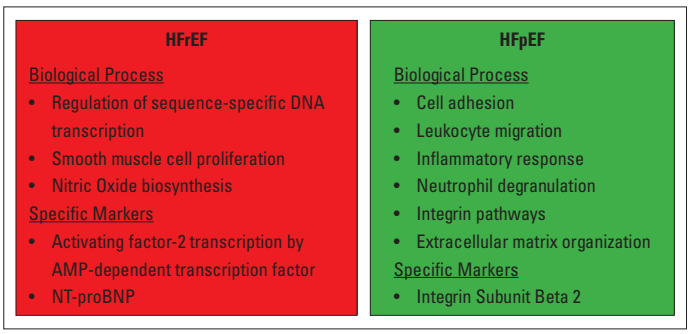

Figure 2. Biomarkers in the physiopathology of heart failure (HFrEF vs. HFpEF). Modified from Tromp J et al. J Am Col Cardiol 2018;72,(10):1081-90

Table 11. Scottish cohort of BIOSTAT-CHF study. Correlation between NT-proBNP level, LVEF values and HF classification is significant (cited from Tromp J et al. J Am Col Cardiol 2018;72,(10):1081-90 as modified)

	HFrEF (718 Pts)	HFmrEF (395 Pts)	HFpEF (431 Pts)	*P*
LVEF%	30.1±7.1	43.7±2.8	57.3±6.0	<0.0001
NT-proBNP (ng/l)	1672 (667-4615)	1209.5 (428-2942)	1062 (392-2820)	<0.0001

noted whether patients who were diagnosed with malignancy were enrolled in this study or not. Study group characteristics and comorbidities were not different from any oncology cohort.

Our routine practice at Cardio-Oncology Clinic of Trakya University School of Medicine is investigating anemia and thyroid functions before CT, IT and RT as well as baseline NT-proBNP and cTnI in addition to echocardiographic assessment in patients with cancer.

At most (depends on patient referral from oncologists), we measure NT-proBNP and obtain ECG prior every CT, IT and RT sessions. In the presence of increased NT-proBNP (in patients without a significant decrease in LVEF value), anti-cancer therapy continues without interruption, more intensified diuretic treatment is applied in patients and they are recommended to restrict the use of salt.

Treatment and follow-up of all patients continue in the light of ECG, cTnI and NT-proBNP values that are checked before each session (depending on classification and guideline recommendations by also taking LVEF levels into account). Clinical findings obtained in the follow-up period that has been ongoing for more than two years in a very homogenous patient group demonstrate by 2D strain echo assessment that NT-proBNP levels are correlated and closely related.

Consequently, NT-proBNP and MR-proANP can be used as predictors of early cardiotoxicity diagnosis and mortality through myocardial strain imaging in patients to undergo CT, IT and RT or any combination of them for cancer therapy. Furthermore, despite publications asserting the contrary, natriuretic peptides have a guiding role in the treatment of heart failure (124, 125). It should be kept in mind that treatment should be customized in patient with cancer and heart disease who have many coexisting variables.

8.1 Points to Keep in Mind:

1. We will see patients with cancer and heart disease much more frequently than reported, with very different clinical vignettes. Medications that are used in such patients do not vary provided that attention is paid to the drugs which may interact with cancer therapy (e.g. statins and oral anti-coagulants), and they offer a classical heart failure treatment as mentioned in the published guidelines. As each application of CT/IT and RT might lead to a rapid decompensation, controls and measurements should be performed at frequent intervals.
2. NT-proBNP should definitely be measured before anti-cancer therapy (at baseline).
3. Before the treatment, pathologies such as anemia and thyroid dysfunction should be investigated and treated as required.
4. Echocardiographic examination should be performed at the time of NT-proBNP measurement. Although superiority of echocardiographic GLS (Global Longitudinal Strain) imaging is advocated, measurement and registration of LVEF should be done meticulously.
5. It should be taken into consideration that NT-proBNP might not always correlate with HFrEF, HFmrEF and HFpEF, that cardiac signs might be absent when it is elevated. Therefore, it cannot be used alone in determining such patients.

9.0 Natriuretic Peptides in Advanced Heart Failure: – Sanem Nalbantgil

The role of natriuretic peptides has been proven in determining the prognosis in the diagnosis of chronic heart failure, and it has been included in the guidelines with Class I recommendation (2, 25). Natriuretic peptides are guiding in determining prognosis in patients with advanced stage heart failure. A study by Logeart et al. demonstrated that discharge values were more determinant than in-hospital natriuretic peptide changes in terms of mortality and rehospitalization in patients who were hospitalized due to congestive heart failure (87). A BNP value >700 ng/L in the follow-up of approximately 100 patients was associated with a risk increase of 31% and 93% for mortality and rehospitalization, respectively, at month 1 and 6. Risk started to increase at values of BNP above 350 ng/L. In another study with approximately 700 patients who had advanced heart failure and were hospitalized for decompensation, ADHF/NT-proBNP risk score assessment including NT-proBNP was closely associated with short-term prognosis (126). In this study, 90-day mortality exceeded 15% and heart transplantation or ventricular assist devices were used in 5% of the patients. Other prognostic indicators of this study were age, chronic obstructive pulmonary disease, systolic blood pressure, eGFR, serum sodium, Hb, left ventricular ejection fraction and tricuspid regurgitation, and two of the most powerful variables were repeated hospitalization and NT-proBNP values. Another study conducted by the same investigators examined kidney functions and NT-proBNP values in a similar patient group and found that a NT-proBNP value > 5180ng/dL was correlated with poor prognosis regardless of kidney function (127). In a study conducted in Germany, the most powerful parameters for mortality were found as INTERMACS class, vasoactive drug use and high natriuretic peptide values in the follow-up of patients who were in a heart transplantation program (128). A similar study by Jasseron et al. in France revealed that high natriuretic peptide values were among the indicators of one-year mortality during a waiting period in more than 2000 patients who were listed for heart transplantation (129).

A position paper on advanced heart failure published this year by ESC-HFA, stated that NT-proBNP ≥1000 µg/mL was a factor for referring patients with heart failure to centers which were more experienced in heart failure, so that advanced treatment options could be evaluated for those patients (80).

The strongest data about the use of natriuretic peptides in planning treatment for advanced heart failure patients is from the GUIDE-IT study (100). This study included around 450 high-risk patients and a group was treated according to NT-proBNP values. The primary endpoints of the study were hospitalization and cardiovascular mortality, and study results could not demonstrate the superiority of treatment which was planned according to natriuretic peptide values.

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9.1 Natriuretic peptides in patients with mechanical support devices:

Ventricular assist devices help unloading by mechanically supporting the left ventricle in advanced heart failure, and reduce mechanical stress on the heart. Studies showed that these devices could restore myocardial function and morphology in a small group of patients. Reduced stress would also decrease neurohumoral activation which plays a significant role in hemodynamic restoration and pathophysiology of heart failure. A limited number of studies showed that biomarkers of heart failure in patients in whom left ventricular assist devices were used did not reach normal values despite a significant decrease after implantation (130). It is emphasized that these biomarkers can be beneficial in the follow-up of recovery after an assist device. However, available data are insufficient (131).

A study by Ahmad et al. demonstrated that pre-implantation natriuretic peptide values correlated with the severity of the disease and these values decreased after implantation, but were still higher than in those with chronic heart failure (132). It was determined that NT-proBNP values were more distinctive in the Caucasian race with normal body mass index, and post-implantation ACEI/ARB and beta-blocker treatment did not affect the values.

A study by Bruggink et al. involving a limited number of patients detected that BNP mRNA and protein expression decreased in the samples from myocardium. The study also demonstrated that stretch in cardiomyocytes and myocyte 'cross-sectional' areas decreased, which resulted in a significant decrease in BNP production. The same study determined that BNP was released not only by myocytes but also heart-infiltrating T cells and macrophages as well as endothelial cells (133).

NT-proBNP values were also used in treatment planning after LVAD implantation. In one study therapy with inotropic drugs, diuretics and device's RPM settings was adjusted with frequent control of natriuretic peptides. Similar treatment was applied in the other group without checking natriuretic peptide levels. It was demonstrated that NT-proBNP-guided treatment significantly reduced the duration of hospitalization. However, more comprehensive studies are needed for a definite conclusion (134).

Right heart failure is a common complication that occurs after device treatment. It was demonstrated that natriuretic peptide values measured before implantation could be predictive for postoperative right heart failure (135). Another complication is postoperative ventricular arrhythmia. High BNP values were found to be the most significant markers that reveal the development of this complication (136).

In summary, it can be said that natriuretic peptide values decrease after the application of a cardiac assist device but do not completely return to normal, and high values can be associated with complications. Complications should be kept in mind especially in the case of elevated values in the patient's follow-up. There is a need for studies to support this limited data.

9.2 Natriuretic peptides after heart transplantation:

Natriuretic peptides are expected to return to normal levels when hemodynamic values return to normal after heart transplantation. However, a study revealed that this biomarker value was still high in stable transplant patients (137). It was reported that post-transplantation natriuretic peptide levels decreased over the months after reaching peak level in the first couple of months but did not return to normal values (138, 139). It was found that high natriuretic peptide levels in transplant patients were not only affected by intracardiac pressure alterations but correlated with BNP gene expression and release throughout the ongoing inflammatory process of cytokines such as IL-1β, TNFα (140).

Acute rejection is an important cause of post-transplantation mortality and morbidity. The relationship between natriuretic peptides and acute rejection has been evaluated in some studies. The results of the studies are controversial. A study by Hervas et al. found a correlation between BNP values and Grade 2 and above acute rejection in the biopsies performed within the first three months (141). Another similar study highlighted that BNP values were only significant in predicting severe rejection such as Grade 3 rejection (142). A study by O'Neill et al. could not find any correlation between post-transplantation early-stage acute rejection and BNP values (143). Another study did not detect any correlation between acute rejection and natriuretic peptide levels; however, described a weak correlation between cardiac allograft functions and elevating values after the first six months (144). It is not possible to establish a 'cut-off' value for the diagnosis of rejection with natriuretic peptide based on the data from studies. It is recommended to consider acute rejection in elevated values as repeated natriuretic value for each patient is more prognostic (145). The specificity of the NT-proBNP value doubling for acute rejection 2R and above was 91%, and the specificity of a ten-fold increase was 99.5% (146). A recently completed study of more than 4000 biopsies from 205 patients reported that the specificity of >100 pg/ml increase in the BNP value (Δ BNP) for 3A and above rejection (severe rejection) was 93.3% and negative predictive value was 97.3% (147).

One of the important points that correlated with high natriuretic peptide values in these patients was right ventricular systolic and diastolic function. A study by Almenar et al. found that BNP values correlated with mean pulmonary artery pressure, right ventricular end-diastolic and systolic pressures as well as right ventricular size (148). In another study, they revealed that patients with higher BNP values (considered as ≥150 pg/mL in this study) had more clinical complaints such as fatigue and weakness, high right atrial/systolic pulmonary artery pressure/capillary wedge pressure, low cardiac index, and high left ventricular dysfunction and tricuspid regurgitation (149).

A study investigating post-transplantation survival with natriuretic peptides found that NT-proBNP value ≤800 pg/ml was predictive of survival (95% confidence interval 92-100) (150). However, it should be kept in mind that the number of patients in this study was low and the observation period was short.

In summary, it has been demonstrated that natriuretic peptide values do not return to normal after heart transplantation. High values were associated with allograft dysfunction as well as ongoing inflammation. Rather than a single value, values elevating in serial measurements in a patient suggest complication and particularly acute rejection in the early period.

10.0 Natriuretic Peptides in Predicting Response to Cardiac Resynchronization Therapy and Evaluating its Efficacy – Bülent Özin

Systolic heart failure (HF) is a severe clinical issue manifesting with high mortality rates despite all treatments. Brain natriuretic peptide (BNP) is an indicator of volume, pressure load and stress in heart failure and plays an important role in diagnosis and prognosis determination. In recent years, cardiac resynchronization therapy (CRT) has emerged as a treatment method that provides significant improvements in mortality and morbidity in patients with systolic heart failure and asynchrony. By using this method, systolic functions can be restored by ensuring synchronous contraction of the left and right ventricles via the atria. In the guidelines of the European Society of Cardiology, published in 2013, CRT indication is accepted as a Class I indication, with evidence level A in patients with ejection fraction at or below 35% in sinus rhythm, QRS duration above 150 ms and left bundle branch block despite adequate medical therapy (151). In spite of very favorable outcomes in many patients, around 35-45% of patients do not respond to CRT (151). Therefore, many studies tried to predetermine the patients who would respond to CRT, through various methods. Although many promising studies were conducted to determine response to CRT primarily through echocardiography, it was understood in the PROSPECT study that this method was ineffective in determining the response (152). Some other studies examined the role of BNP levels in determining CRT response.

10.1 Efficacy of natriuretic peptide levels in predicting response to CRT

Delgado et al. assessed 70 patients who underwent CRT (153). They measured the BNP of all patients at the baseline and saw that the BNP values were not significantly different between the patients who responded and the patients who did not respond to CRT. However, another study evaluating 50 successive patients who underwent CRT showed that elevated BNP values both at the baseline and one month after CRT application could determine heart failure progression in both single- and multivariate analyses (154). Contrary to this study's results, another study evaluating a total of 164 patients detected that pre-implantation values of BNP were clearly higher in patients who responded to CRT than those who did not respond (800±823 vs. 335±348 pg/ml $p<0.0002$) (155). In the multivariate analysis, BNP level was the only factor that could predict CRT response. It was found that a BNP level of 447 pg/ml or above could determine CRT response with 62% sensitivity and 79% specificity (155). In another multicenter study, Shalaby et al. evaluated the effect of baseline BNP and troponin values on prognosis after CRT. The patients were evaluated in three groups depending on the presence of risk factors such as high troponin (at detectable level) and high BNP (>440 pg/ml) (156). At the end of a one-year follow-up, the rate of mortality or heart failure-related hospitalization was clearly higher in the group with high troponin or high BNP values compared to the group without any risk factors. It was also found that the highest mortality was seen in the group with both risk factors. Another study enrolling some of the patients who were examined in this study found that high baseline BNP values were the only parameter that predicted both mortality and heart failure-related hospitalizations in a multivariate analysis (157).

After these studies with a relatively low number of patients, the results of the CARE-HF study, which examined the factors determining CRT response, were published (158). 813 patients were monitored for 29.4 months in this study. The outcome of a multivariate analysis by the Cox proportional hazard model, found that factors such as ischemic heart failure, severe mitral regurgitation and elevated N-terminal pro BNP (NT-proBNP) value were independent factors in determining heart failure-related hospitalization and mortality. Again in another analysis of the CARE-HF study, Cleland et al. investigated predictive factors in response to CRT (159). This study found that, among all other parameters investigated, high NT-proBNP levels, as measured three months after implantation, were the most significant criterion in identifying endpoints such as mortality and heart failure-related hospitalizations. Another study evaluating the same data with different methods found that baseline NT-proBNP values were the most significant parameter in determining sudden death and death due to heart failure. At the end of the study, mortality rate was found to be 12% and 35% in patients with low and high NT-proBNP values, respectively (160).

All studies that have been summarized herein show that BNP plays an important role in terms of predicting CRT response. However, it is not possible to predict the use of this measurement alone based on this data when selecting patients for CRT. The complicated pathophysiology of heart failure and asynchrony, and the complicated treatment mechanisms of CRT already show us that it is not possible to predict response to this treatment based on a single parameter. Therefore, even though BNP values play a significant role in determining prognosis, it is still not deemed possible to use these values clinically in predicting CRT response.

10.2 Efficacy of natriuretic peptide levels in assessing response to CRT

Natriuretic peptides play a pre-eminent role in assessing the efficacy of treatment as well as diagnosing and identifying heart failure. Because of this property, they are commonly used in evaluating CRT treatment and identifying the response. However, there is not a method that definitely makes a distinction between the patients who respond and do not respond to CRT. The patients are generally assessed according to their clinical or echocardiographic characteristics but clinical response and echocardiographic response do not usually show parallelism. Therefore, it is thought that natriuretic peptides yield more ob-

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jective results in assessing response to CRT as they provide a quantitative outcome regarding the condition of the patient.

In the first study using natriuretic peptides in this regard, Braun et al. examined 124 patients with heart failure (161). 65 of these patients underwent CRT and 59 of them formed the control group. At one- and 12-month follow-ups plasma norepinephrine and BNP values showed a statistically significant decrease in CRT patients while these values remained unchanged in the control group. A sub-group analysis of the PATH-CHF study evaluated functional capacity, neurohumoral activation and cytokines in CRT patients (162). This study, evaluating a total of 22 patients, found that functional capacity and ejection fraction increased, while BNP and norepinephrine values as well as cytokine levels decreased with CRT. In another study, it was observed that heart failure progressed clinically in 13 of 43 patients who underwent CRT (163). It was found that baseline BNP values clearly decreased in responders; however, no change occurred in non-responders (BNP values at month 12: 227.1±308.8, 361.5±328.3, $p<0.05$). The largest data in this area also comes from the CARE-HF study (164). This analysis assessed pre-implantation, 3 month and 18 month NT-proBNP values of 813 patients. While baseline median NT-proBNP values were similar in CRT and medical therapy groups (1920 pg/mL vs. 1809 pg/mL p=AD), values in the CRT group decreased gradually throughout the study. While the median NT-proBNP difference between the treatment group and the control group was 537 pg/mL ($P<0.0001$) at month 3, the difference was found to be 567 pg/mL ($P<0.0001$) at month 18. The study by Delgado et al. also observed that BNP values significantly decreased in the follow-up in patients responding to CRT (from 758±611 pg/mL to 479±451 pg/mL, P=.044), while it significantly increased in patients who did not respond (from 1191±466 pg/mL to 1611±1583 pg/mL, P=.046) (153).

The relationship between natriuretic peptide levels and clinical and echocardiographic improvement in CRT patients was examined in a series of studies involving 170 patients (165). It was found that 71% of patients who responded to echocardiography also had neurohumoral responses (NT-proBNP decrease >15%); however, this rate was only 58% in patients who showed clinical improvement. The investigators thought that natriuretic peptide levels may be more closely associated with echocardiographic responses rather than clinical responses.

Natriuretic peptides are closely associated with diastolic functions in patients with heart failure. A study conducted in Turkey to evaluate 54 patients who underwent CRT found that improved diastolic function was closely correlated with the decrease in BNP levels (from 270.5 pg/mL to 47.2 pg/mL, $p<0.05$) and BNP levels remained unchanged in patients without any improvement (from 646 pg/mL to 387.7 pg/mL, p=NS) (166). The study also showed that NT-proBNP levels were correlated with the improvement in mitral regurgitation (167); pro-atrial natriuretic peptides could also determine prognosis (168); natriuretic peptides gave information about prognosis in patients with mild heart failure (169); and natriuretic peptide levels were also associated with the improvement in right ventricular functions (170).

It is understood by these studies, all of which yielded parallel results, that natriuretic peptides can definitely demonstrate response to CRT. Moreover, the fact that many studies found a close correlation between the degree of treatment response and decrease in natriuretic peptide levels further increases the significance of this biomarker. Although not applied clinically in a routine manner, natriuretic peptides appear to be at least as significant as clinical and echocardiographic parameters in assessing CRT response.

Consequently, natriuretic peptides are examinations which provide highly clinical contribution in both predicting response to CRT and in the assessment of this response. By using these examinations in the routine follow-up of patients, response to CRT can also be monitored continuously and early intervention can be applied to patients in case natriuretic peptides elevate during clinical course.

11.0 Natriuretic Peptides in Primary Prevention – Ahmet Çelik

It has been showed through a plethora of data that natriuretic peptides are effective in the identification of cardiovascular (CV) disease risks, and it is indisputable that, when used alongside classical risk factors, they further contribute to such factors. In preclinical CV damages, NPs elevate early as an endogenic response and save time for treatment management. BNP and NT-proBNP have significant diagnostic and prognostic values in selected populations such as those with heart failure (HF), early-stage and asymptomatic CV diseases (171-173). In 2016, a large meta-analysis including 95,617 patients without a history of CV disease (coronary heart disease, stroke, transient ischemic attack, peripheral vascular disease, pulmonary heart disease, atrial fibrillation and HF) in 40 prospective studies showed that NT-proBNP was a predictor of HF, coronary heart disease and stroke which could develop in the future (174). Today, BNP and/or NT-proBNP measurements are used more commonly and they can already be accessed at many centers in our country. The fact that the use of these markers is affordable, CV diseases are the most common causes of death in the world and place a great burden on the country's economy, and that it is possible to prevent HF before it develops makes the use of NPs even more attractive for primary prevention, particularly in individuals who are at risk.

Two randomized studies examined the role of NP in identifying high-risk patients for CV prevention. One of these studies, St. Vincent's Screening to Prevent Heart Failure Study (STOP-HF) study, randomized 1374 asymptomatic patients who had at least one risk factor for CV disease and were over 40 years of age, to BNP-guided therapy (biomarker arm) and usual standard care (control arm) arms (175). CV risk factors accepted for the study are summarized in Table 12.

The BNP of the patients in the biomarker arm was measured every year, and cardiology consultation was requested for those

Table 12. Conditions that are beneficial in natriuretic peptide-guided clinical follow-up in primary protection as shown in STOP-HF and PONTIAC studies

STOP-HF Study (Conditions that are considered as CV risk factors in individuals aged >40 years)	PONTIAC Study (Conditions that are considered as cardiac diseases in patients with type 2 DM)
➢ Hypertension	➢ Cardiac disease history
➢ Hypercholesterolemia	➢ Sign of cardiac disease in electrocardiography
➢ Diabetes mellitus	• Atrial fibrillation
➢ Vascular disease	• Bundle branch block
• Coronary	• ST-T variations
• Cerebrovascular	➢ Abnormal echocardiographic results
• Peripheral	• Low ejection fraction
➢ Arrhythmias requiring treatment	• Wall motion disorder
➢ Moderate-to-severe valvular disease	• Severe valvular disease
➢ Obesity (body mass index >30kg/m^2)	• Other severe changes

CV: cardiovascular, DM: diabetes mellitus

with a BNP value above >50 pg/mL in addition to echocardiography and cardiac assessments. The primary endpoint was left ventricular dysfunction regardless of the presence or absence of HF. The secondary endpoints were urgent hospitalization due to arrhythmia, transient ischemic attack, stroke, myocardial infarction and peripheral or pulmonary embolism. The patients were followed up for 4.2 years on average, and the mean age was 64.8±10.2. In the follow-ups, the BNP level was detected above 50 pg/mL at least once in 41% of patients in the biomarker group (263 patients), and further CV investigations and examinations were performed in this group of patients (Advanced CV assessment was performed in 850 and 496 patients for each 1000 patient years, respectively, in the biomarker group and the control group. Incidence rate: 1.71; 95% CI, 1.61-1.83; p<0.001). Additionally, patients in the biomarker group received more RAAS-based (renin-angiotensin-aldosterone system) therapies (56.5% and 49.6%, respectively, in the biomarker group and the control group, p=0.01). At the end of a mean follow-up of 4.2 years, left ventricular dysfunction (regardless of HF), which was the primary endpoint, developed in 5.3% (37/697) of the patients in the biomarker arm and in 8.7% (59/677) of the patients in the control arm (OR 0.55; 95% CI:0.37-0.82, p=0.003). Asymptomatic left ventricular dysfunction alone was detected in 4.3% (30/697) and 6.6% (45/677) of patients in the biomarker group and the control group, respectively (OR 0.57; 95% CI:0.37-0.88; P=0.01). While heart failure developed in 1.0% of patients in the biomarker group (seven patients), this rate was 2.1% in the control group (14 patients) (OR 0.48, 95% CI:0.20-1.20; P=0.12). The rate of hospitalization due to major CV events was higher in the control group (22.3 for each 1000 patient years in the biomarker group, and 40.4 for each 1000 patient years in the control group) (OR 0.60; 95% CI:0.45-0.81; P=0.02).

Another randomized controlled study was a study which looked at NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of diabetic patients without A history of Cardiac disease (PONTIAC). They evaluated 300 patients with type 2 diabetes mellitus (DM) but without a known CV disease (176). The conditions that are considered as cardiac diseases in patients with type 2 DM in the PONTIAC study are summarized in Table 12. DM patients without a previously known cardiac disease but with NT-proBNP >125 pg/mL were divided in two groups as the intensive follow-up group and the control group, and all patients were monitored and treated in diabetes care units based on the recommendation of guidelines. Additionally, patients in the intensive follow-up group were also monitored at cardiology clinics, and RAAS antagonists and beta-blockers were up-titrated. At the end of 12 months, the utilization rate of RAAS antagonists and beta-blockers as well as reached doses were significantly higher in the patients in the intensive follow-up group (p<0.0001). When the rates of target doses that reached 100% for RAAS antagonists were examined, 79% were found in the intensive follow-up group compared to 42% in the control group (p<0.0001). For beta-blockers, 51% of patients in the intensive follow-up group were up-titrated to 100% of the target dose while only 10% of patients in the control group could reach 100% of the target dose (p<0.0001). When the rates of reaching 100% of the target dose was examined for both RAAS antagonists and beta-blockers, it was seen that 46% of patients in the intensive follow-up group reached the target dose while 5% of patients in the control group could reach 100% of target doses (p<0.0001). The rate of death or hospitalization due to cardiac disease, which was the primary endpoint at the end of two years, was 65% lower in the intensive follow-up group than the control group (HR 0.35; 95% CI [0.13–0.98]; p=0.044).

Besides these two randomized controlled studies, there is the "Personalised Prospective Comparison of ARni With ArB in Patients With Natriuretic Peptide eLEvation" (PARABLE) study,

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Table 13. Recommendations of the Canadian HF guideline and ACC/AHA HF guidelines for the use of NPs in primary protection

Recommendations of the 2014 Canadian HF Guideline	Recommendations of the 2017 ACC/AHA HF Guideline
NPs can be used as a strategy for preventing HF in individuals with risk factors that have an effect on the development of HF. It is recommended to perform more frequent monitoring and intensify the current therapy in individuals with BNP >100 pg/mL and NT-proBNP >300 pg/mL.	NP-guided screening that includes guideline-driven medical therapy optimized by a cardiovascular disease specialist in patients who are at risk of developing HF can be used to prevent left ventricular systolic or diastolic dysfunction or new-onset HF. Class IIa, Evidence Level B-R

HF: heart failure

the results of which are expected to be obtained in the future. PARABLE is an ongoing study designed to investigate the effect of sacubitril/valsartan on the change of left atrial volume index with cardiac MR (primary endpoint) at the end of 18 months in 250 patients who have hypertension and/or diabetes mellitus and high natriuretic peptide level (BNP>50 pg/mL, NT-proBNP> 150 pg/mL) and are over 40 years of age (177).

Recommendations of international guidelines regarding NPs in primary prevention are summarized in Table 13. Based on the STOP-HF and PONTIAC studies, 2014 the Canadian HF Guidelines recommended the use of NPs for preventing HF in individuals with risk factors playing a role in HF development (178). The Canadian guidelines recommended the use of BNP level of >100 pg/mL and NT-proBNP level of >300 pg/mL to prevent unnecessary screenings. Referring to the same studies, the 2017 American Guideline for the Management of Heart Failure recommended NP-based screening in patients with HF risk factors as the optimization of guideline-directed medical therapy by a cardiovascular disease specialist could prevent the development of left ventricular systolic or diastolic dysfunction or new-onset HF in individuals with risk factors for HF development (34).

There is a need for conducting studies to determine optimal levels in risk classification of natriuretic peptides and their concurrent use with other cardiac biomarkers such as troponin, ST-2, galectin-3, etc. It is clear that additional evidence is also necessary to determine the optimal medical treatment recommended for preventing the development of, particularly, HF and other CV diseases in patients with elevated NP and without a history of CV disease.

Consequently, it is very important to prevent HF and CV diseases before they develop when both mortality rates and the excessive burden on the country's economy are taken into consideration. It is inevitable to obtain satisfactory results in order to prevent the development of CV diseases as a result of good definition of the individuals at risk in primary prevention, measurement of NP in these individuals, and evidence of optimal follow-up and treatment in high-risk individuals.

12.0 Natriuretic Peptides in the Pulmonary Arterial Hypertension – Mehmet Serdar Küçükoğlu

Although many biomarkers related to pulmonary arterial hypertension (PAH) and pulmonary vascular remodelling were investigated, only BNP and NT-proBNP were found to be associated with myocardial dysfunction and prognosis in the follow-up. Therefore, PH centers generally use these two biomarkers in routine practice and clinical studies. These two biomarkers are not specific to PH and their levels might increase in many structural and functional heart diseases. As they are released secondary to pulmonary vascular disease induced afterload increase on the right ventricle, they are indirect indicators of vasculopathy. Both of them are released in response to overstretch of cardiomyocytes and are strongly correlated with right ventricular dysfunction which is the cause of death in PAH patients. The use of these two biomarkers are recommended by the up-to-date international guidelines for risk and prognosis assessment of PAH patients at the time of diagnosis and in follow-up (22, 179).

There is no evidence showing the superiority of BNP use to the use of NT-proBNP. While BNP is less affected by kidney functions and more correlated with pulmonary hemodynamic parameters, NT-proBNP is a more potent indicator of prognosis (180).

BNP levels increase with many diseases that cause PH. These diseases primarily include idiopathic PAH (IPAH), PAH associated with connective tissue disorders, PAH associated with congenital heart disease, PH associated with interstitial lung disease and chronic obstructive lung disease, and chronic thromboembolic PH (CTEPH). BNP levels are correlated with hemodynamic indicators, functional capacity and exercise capacity. BNP also has a prognostic significance in patients with IPAH, chronic lung disease and pulmonary embolism (181). Recently, the NT-proBNP molecule, which is an alternative to BNP and provides the same information but has a more stable structure, has become more popular. There are many studies that investigate the role of NT-proBNP in PAH patients. In these studies, NT-proBNP levels were found to be higher in PAH patients than in the con-

trol group and correlated with hemodynamic parameters and peak oxygen consumption. Again, many studies showed that high NT-proBNP levels correlated with high mortality and a decrease in NT-proBNP levels through treatment increased survival (182).

BNP and NT-proBNP are important biomarkers in detecting right ventricular dysfunction in PAH patients. A study comparing patients with right ventricular pressure (CTEPH) and/or volume (atrial septal defect-ASD) overload with the control group found plasma BNP levels to be significantly higher in the patients with pressure overload than in the other two groups (183). BNP levels were also found to be significantly higher in patients with volume loading than the control group. In this patient group, plasma BNP levels negatively correlated with RVEF and positively correlated with right ventricular end-diastolic volume index (RVEDVI).

Apart from right ventricular function, various studies showed BNP and NT-proBNP's correlation with functional capacity, exercise performance (six-minute walking distance, peak oxygen consumption), echocardiographic and hemodynamic indicators which had previously found to be associated to survival in PAH patients. In a study which investigated prognostic significance of plasma natriuretic peptides in PAH patients and demonstrated that baseline plasma BNP levels were an independent indicator of mortality, it was seen that baseline plasma BNP levels increased as the functional capacity of patients deteriorated. Another study showed that baseline BNP values were negatively correlated with exercise performance indicators (6MW distance and peak VO^2), and based on hemodynamic indicators, BNP had a positive correlation with pulmonary vascular resistance (PVR), pulmonary artery pressure (PAP) and right atrial pressure (RAP) and a negative correlation with cardiac index (CI) in PAH patients (184).

The relationship of NT-proBNP with echocardiographic right ventricular function indicators, baseline functional status and long-term survival was also investigated in PAH patients. Accordingly, NT-proBNP was found to have a positive correlation with echocardiographic RV/LV diastolic area ratio, right ventricular diameter, Tei index, diameter and respiratory collapsibility of inferior vena cava (IVC) and presence of pericardial effusion, and a negative correlation with RV acceleration time. No correlation was found between tricuspid regurgitation peak velocity and NT-proBNP.

Many studies used BNP and NT-proBNP to determine clinical severity of the disease in PAH patients. These two natriuretic peptides are attention-grabbing as simple, non-invasive and observer-independent parameters particularly in identifying PAH patients who develop right heart failure. They are correlated with parameters that show the severity of the disease like functional class, 6MW distance, peak VO^2 and hemodynamic variables (RAP, PVR, CI). Many studies conducted in recent years showed that NT-proBNP also, correlated with many parameters (CI, RAP, PVR and mixed venous O_2 saturation) showing the severity of PAH, and used as prognostic indicators. Investigating the relationship between high baseline NT-proBNP levels and prognosis in PAH patients, Mauritz et al. (185) found that serial NT-proBNP measurements in 198 PAH patients predicted survival better than a single baseline NT-proBNP measurement. According to the results of this study, ≥1256 pg/ml serum NT-proBNP level at the time of diagnosis correlated with poor prognosis in PAH patients. Additionally, a decrease of >15%/year NT-proBNP was associated with increased survival. Nickel et al. showed in their study that changes in NT-proBNP lev-el closely correlated with hemodynamic changes in terms of prognosis. Prognosis of patients whose baseline NT-proBNP level was >1800 pg/ml and decreased with treatment was similar to those with baseline NT-proBNP <1800 pg/ml (186).

In a study by Fijalkowska et al. (187), baseline NT-proBNP level >1400 pg/ml was associated with long-term poor prognosis both in all PH patients and in the IPAH group. This study also showed that survival was better in patients whose NT-proBNP levels reduced below this value through treatment. In a study by Nagaya et al. (181), patients with a baseline plasma BNP level ≥150 pg/ml had more mortalities in the long-term follow-up. Patients whose BNP levels during PAH-specific treatment could be maintained below 180 pg/ml had better survival outcomes. Consequently, this study highlighted that baseline BNP levels were the only non-invasive marker that could be associated with mortality in a multivariate analysis, and follow-up BNP levels were significant in terms of prognosis and should be monitored regularly to predict the endpoint. It is also mentioned that mortality can be lower in patients whose BNP levels can be maintained within the targeted interval through treatment. A study monitoring patients who developed scleroderma-associated PAH concluded that increased NT-proBNP levels were directly associated with the severity of PAH, NT-proBNP >395 pg/ml levels meant high potential of PH development in programs which screened scleroderma patients in terms of PH development, and baseline and serial NT-proBNP measurements directly correlated with survival. Accordingly, it was emphasized that a ten-fold increase in follow-up NT-proBNP levels was associated with three times more mortality and demonstrated treatment failure (188, 189).

BNP and NT-proBNP are also used to monitor response to treatment in PAH patients. A study monitoring PAH patients compared baseline and follow-up BNP levels of patients who survived and died under prostanoid therapy. The comparison revealed that while BNP levels tended to decrease in follow-ups in patients who survived the prostanoid therapy, they tended to increase in the patients who died despite therapy (190, 191). Another study showed that NT-proBNP levels decreased in a 12-month follow-up under IV epo-prostenol therapy in PAH patients, and this decrease correlated with a decrease in PVR (192, 193). Hemodynamic improvement with postoperative IV epoprostenol therapy in CTEPH patients who have undergone endarterectomy can be monitored with BNP levels. Persistently elevated BNP in the postoperative period shows the presence of residual PH (194, 195).

The fact that natriuretic peptides are closely associated with the severity of the disease, the degree of right ventricular

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dysfunction and prognosis in PAH, has led to these biomarkers being included in the guidelines. BNP or NT-proBNP levels measured at the time of diagnosis of a PAH patient can identify one-year mortality risk of the disease when accompanied with other prognostic parameters (functional capacity, clinical right heart failure and its symptoms, six-minute walking distance, cardiopulmonary exercise test and hemodynamic parameters) (22). The Pulmonary Arterial Hypertension guideline published in 2015 determined low-risk (annually <5% mortality risk) values for BNP and NT-ProBNP as <50 ng/dl and <300 ng/dl (Table 14). BNP >300 ng/dl and NT-proBNP >1400 ng/dl indicate that annual mortality risk is >10%. Monitoring BNP/NT-proBNP levels with treatment in the follow-up and reducing these values to a low-risk level stand out among the most important findings in terms of prognosis. Therefore, measuring BNP/NT-proBNP regularly during the follow-up period is recommended with some other tests (Table 15) (22).

Some studies also questioned whether BNP and NT-proBNP could be used as a screening biomarker in the early diagnosis of disease in PAH patients. Although the use of natriuretic peptides in the diagnosis of right heart disease lacks specificity compared to their use in the diagnosis of left heart disease, they still have a potential for use for this purpose (196). However, both peptides should be examined in large studies to be used as diagnosis markers in diagnosing PAH and ruling out the disease. Their efficacy and safety in diagnosing and ruling out in patient groups which constitute PAH risk should be examined. Moreover, using them with other biomarkers in current diagnosis algorithms will

Table 14. Risk Assessment in PAH (22)

Determinants of prognosis[a] (estimated l-year mortality)	Low risk <5%	Intermediate risk 5-10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165-440 m	<165 m
Cardiopulmonary exercise testing	Peak VO^2 >15 ml/min/kg (>65% pred.)	Peak VO^2 11-15 ml/min/kg (35-65% pred.)	Peak VO^2 <11 ml/min/kg (<35% pred.)
	VE/VCO_2 slope <36	VE/VCO_2 slope 36-44.9	VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l	BNP 50-300 ng/l	BNP >300 ng/l
	NT-proBNP <300 ng/l	NT-proBNP1400 ng/l	NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2	RA area 18-26 cm^2	RA area >26 cm^2
	No pericardial effusion	No or minimal, pericardial effusion	Pericardial effusion
Haemodynamics	RAP <8 mm Hg	RAP 8-14 mm Hg	RAP >14 mm Hg
	CI ≥2.5 l/min/m^2	CI 2.0-2.4 l/min/m^2	CI <2.0 l/min/m^2
	SvO_2 >65%	SvO_2 60-65%	SvO_2 <60%

Table 15. PAH follow-up recommendations (22)

	At baseline	Every 3-6 months	Every 6-12 months	3-6 months after changes in therapy	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+
Echo	+		+	+	+
Basic lab	+	+	+	+	+
Extended lab	+		+		+
Blood gas analysis	+		+	+	+
Right heart catheterization	+		+	+	+

Basic Laboratory: Blood count, serum creatinine, sodium, potassium, AST, ALT, Bilirubins, BNP/NT-proBNP
Advanced Laboratory: TSH, Troponin, uric acid, blood iron levels and other necessary tests

increase their screening sensitivity. A study including 49 scleroderma patients (23 with PAH and 26 without PAH) detected NT-proBNP levels to be higher in scleroderma patients with PAH than those without PAH (3365 pg/ml vs. 347 pg/ml). The study found a positive correlation between NT-proBNP and PVR, mean PAB and right ventricular end-diastolic pressure (RVEDP). The area under curve (ROC) analysis showed that the upper normal limit of 395.34 pg/ml for NT-proBNP had 69% sensitivity and 100% specificity in diagnosing PAH in this patient group. Consequently, it was highlighted that NT-proBNP was a potentially beneficial biomarker with its high specificity and negative predictive value in diagnosing scleroderma-associated PAH and could play a significant role in risk assessment and treatment follow-up algorithms in the future (194). Another study investigating the role of NT-proBNP in scleroderma-associated PAH found NT-proBNP elevation directly correlated with the severity of PAH and emphasized the safety of NT-proBNP in screening this patient group. DETECT (DETECTion of PAH in SSc) is a prospective study that questions the development of PAH in patients with scleroderma and includes 500 patients. Electrocardiography (ECG), echocardiography (echo) and NT-proBNP were used in the screening. The values of these parameters in diagnosis and differential diagnosis were compared to right heart catheterization (RHC), a gold standard in diagnosis. Scleroderma patients with and without PAH were identified and all three variables were examined in these patient groups. Consequently, it was emphasized that ECG, echo and natriuretic peptides as well as clinical assessment and physical examination were beneficial in terms of early detection of PAH development in the first assessment and follow-up of PAH patients (197).

In conclusion, natriuretic peptides are beneficial in the diagnosis, risk stratification, follow-up and prognostic assessment of PAH patients. NT-proBNP stands out more as a more stable biomarker. Both natriuretic peptides can show early RV dysfunction and haemodynamic deterioration. Their use in prognostic assessment and treatment follow-up is beneficial. The increase in BNP levels in treated patients indicates worsening of PAH and inadequate target-oriented therapy. Our potential treatment targets are <50 ng/ml for BNP and <300 ng/ml for NT-proBNP. The use of natriuretic peptides for screening in the early diagnosis of disease should be examined in larger studies in terms of validity.

13.0 Natriuretic Peptides in the Assessment of Risk and Prognosis in Acute Coronary Syndromes – Murat Özdemir

Prognostic assessment by biomarkers in acute coronary syndromes (ACS) traditionally utilizes cardiac troponins as the biomarker. An increase of troponin in the presence of ischemia severe enough to cause myocardial damage is an absolute component in the contemporary definition of "myocardial infarction", and it is known that prognosis is impaired as troponin levels increase. However, troponins are associated with only one (myocardial ischemia) of many pathobiological processes that occur in the course of ACS and do not quite reflect other potential events (such as hemodynamic stress, left ventricular dysfunction and strain). In recent years, various biomarkers were investigated in ACS cases for both short-term (in-hospital) and long-term prognosis. Natriuretic peptides (NPs) have a significant place among these biomarkers.

This review will try to summarize the current status of NPs in risk and prognosis assessment in ACS.

13.1 Natriuretic peptides (NPs):

There are different types of NPs (A, B and C). As Type B natriuretic peptide (BNP) is the one whose prognostic significance has been investigated the most in ACSs, this article will focus on BNP's prognostic significance in ACS.

Type B NP (BNP) and its precursor N-terminal proBNP (NT-proBNP) are released from atrial and ventricular myocytes as a result of myocardial stretch (due to pressure or volume load). Myocardial ischemia that occurs in ACS may create both diastolic and systolic left ventricular dysfunction and therefore myocardial stretch and may lead to an increase in BNP levels. Thus, it should be expected that the greater the extent of ischemia is, the greater the myocardial stretch and elevation in BNP levels will be. Based on this logic, BNP is rationally expected to be a prognostic indicator (both short- and long-term) in ACS.

13.2 BNP in the assessment of risk and prognosis in ST-segment elevation (STE) ACS:

In cases of ST-segment elevation myocardial infarction (STEMI) treated with thrombolytics, it was reported that BNP above 80 pg/mL on admission was associated with inadequate reperfusion and a 7.2 fold increase in 30-day mortality (198).

ASSENT-2 and ASSENT-PLUS sub-studies reported that NT-proBNP on admission was an independent determinant of one-year mortality in STEMI cases treated with thrombolytics (199).

In 142 STEMI cases treated with primary PCI, it was reported that left ventricular systolic function deteriorated more at follow-up in those with higher NT-proBNP at 72-96 hours of admission (200).

In an analysis of 589 STEMI cases treated with primary PCI, NT-proBNP >2300 pg/mL was found to predict in-hospital mortality (201).

In another analysis of 145 ACS cases (80 % with STEMI) complicated with cardiogenic shock, NT-proBNP>4500 ng/L at the 12th hour of admission was reported to contribute to the prediction of 30-day mortality (202).

In acute MI cases treated with PCI, BNP was shown to predict one-year major adverse cardiac events (203).

In summary, it is possible to say that high NP levels at admission or in-hospital denote poor short- and long-term prognosis in STE ACS cases treated with either thrombolytics or PCI.

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13.3 BNP in the assessment of risk and prognosis in non-ST elevation (NSTE) ACS:

The TACTICS-TIMI 18 study reported that BNP levels on admission determined six-month mortality independent of Troponin I and heart failure in 1676 NSTE ACS cases (204). Therefore, it should be considered that BNP provides an additional contribution to troponin in terms of risk identification in NSTE ACS cases.

In NSTE ACS cases monitored in the GUSTO-IV trial, it was shown that NT-proBNP, sampled at a median of 9.5 hours from the onset of symptoms, was strongly correlated with one-year mortality (205). The analysis of diabetic patients in this same study reported that NT-proBNP was an independent determinant of one-year mortality (206).

In ACS cases with normal Troponin T value on admission, six-month mortality was found to be five to ten times higher (different ratios in two different cohorts) when NT-proBNP on admission was above 474 pg/mL (207). This interesting finding is significant as it draws attention to the role of NT-proBNP in medium-term prognosis assessment of cases who are considered to have unstable angina pectoris (ACS+normal troponin).

A study examining a total of 390 ACS cases (a mixed group of unstable angina, STEMI and NSTEMI) found that proBNP performed better than Troponin T in predicting major adverse cardiac events both in-hospital and at six-month follow-up (208).

A follow-up of 132 ACS cases showed that heart failure and duration of hospitalization was longer, and in-hospital mortality and cardiogenic shock development trended to increase among those with NT-proBNP>474 pg/mL at hospitalization (209).

An analysis of 5174 NSTE ACS cases who were all revascularized in the PLATO study reported that NT-proBNP at randomization played a role in predicting the occurrence of one-year death/spontaneous MI (210).

A single center registry analysis of 1324 NSTE ACS cases reported that NT-proBNP on admission played a role in predicting 30-day mortality (211).

A study on cardiovascular safety of an antidiabetic drug in 7226 cases with ACS and Type 2 Diabetes Mellitus (DM) found that NT-proBNP was among the independent total mortality determinants at a median two-year follow-up (212).

Another study on cardiovascular safety of an antidiabetic drug in 5225 Type 2 DM cases with recent ACS reported that, in a mean follow-up of 26 months, BNP and NT-proBNP were the most powerful predictors of all cardiovascular endpoints (death, cardiovascular death, heart failure, MI and stroke) independent of heart failure or any cardiovascular disease history (213).

In a report which investigated the "very long-term" prognostic value of NT-proBNP in 224 NSTE ACS cases, NT-proBNP on admission was an independent determinant of total mortality at a median follow-up of 9.34 years;a level > 100 pg/mL was associated with a 6.24 fold increased risk (214).

In summary, on the basis of data from many studies, it is possible to say that NP measurement plays a role in both short- and long-term prognosis assessment in NSTE ACS.

13.4 When to collect samples, and can temporal changes in NP levels be clinically significant?

The time of drawing a serum sample for NP levels during the course of ACS is a point that should be discussed. As seen above, most of the studies in this regard used the levels of samples taken on hospital admission. An analysis of NSTE ACS cases in the FRISC-II trial concluded that "NT-proBNP predicts two-year mortality regardless of the time of sampling (on admission, day 2, week 6, months 3 and 6)". However, NT-proBNP sampled in the "acute phase" and NT-proBNP sampled in a "chronic and relatively stable period" can be a better indicator of "myocardial damage" and "mortality", respectively (215).

The importance of NP level changes over time (temporal changes) after ACS has not been adequately evaluated. A study investigating this issue reported that in 276 cases admitted to the emergency service with chest pain, five successive measurements of NT-proBNP in the first 24 hours did not contribute to its 90-day prognostic value (216).

On the other hand, a large observational study including 4497 ACS (STEMI and NSTEMI) cases demonstrated that serial measurements of NT-proBNP in one year could provide valuable information. In fact, although BNP values above 80 pg/mL on admission, at month 4 and month 12 could predict two-year mortality or development of heart failure with different hazard ratios (hazard ratios=2.5, 3.9, 4.7, respectively), what is more impressive is that BNP values which were normal at baseline and increased at month 4 indicated a 4.7 fold increased risk and, on the contrary, BNP values which were high at baseline and returned to normal at month 4 indicated only a 1.7 fold increased risk (217). Consequently, one might say that BNP levels which tend to rise at follow-up indicate a poor prognosis, and which tend to decrease indicate a good prognosis in cases with ACS. A similar finding was observed in a sub-study of the OPTIMAAL trial. In this analysis, while baseline NP levels did not have any prognostic significance in cases with acute MI complicated with clinical or radiographic heart failure, NT-proBNP which remained high (non-decreasing pattern) on day 30 pointed to a poor prognosis (218).

An analysis on NSTEMI cases monitored in the TRILOGY ACS study reported that each 40% increase in NT-proBNP level at the 6th month as compared to baseline was associated with a 14% increase in both cardiovascular and total mortality (219). Another study reported that, in 5450 Type 2 DM cases with recent ACS, a 3-4 times increase in NP levels measured at follow-up compared to baseline could point out to the emergence of a need for hospitalization related to heart failure (220).

In summary, it seems reasonable that sampling for NP in the course of ACS be done at admission. There is evidence showing the potential benefits of measuring NP levels in a serial manner at follow-up; however, it is not possible to make a conclusive comment in this regard at the moment.

13.5 Conditions that might affect the prognostic value of NT-proBNP in ACS:

An analysis investigating whether the prognostic value of NT-proBNP in ACS was affected by age or not reported that dif-

ferent NT-proBNP cut-off values were observed in different age groups for the prediction of total mortality and this cut-off value increased with age; however, NT-proBNP was an independent predictor of total mortality in all age groups (221).

Other factors potentially affecting the prognostic value of NT-proBNP in ACS might be body weight and composition. A study reported that NT-proBNP lost its prognostic significance in predicting total and CV mortality in ACS in cases with high body mass index, lean mass index and percent body fat (222).

13.6 Can natriuretic peptides contribute to other risk stratification methods (scoring systems)?

NT-proBNP is one of the biomarkers used in the BETTER risk scoring system which was established for one-year prognosis assessment in unstable angina pectoris and reported to perform well in this regard (223).

In STEMI cases treated with primary PCI, NT-proBNP was reported to provide additional contribution to predict in-hospital mortality using the Canada Acute Coronary Syndrome Risk Score, which is another risk prediction score for ACS (201).

An analysis evaluating many biomarkers in NSTE ACS demonstrated that, when NT-proBNP was added to the GRACE risk score which is a risk scoring system frequently used in acute coronary syndromes, the predictive strength of the score increased for six-month death/MI (224). On the other hand, a registration report of 1324 cases showed that NT-proBNP measured on admission for NSTE ACS was similar to the GRACE score and superior to the TIMI risk score in terms of predicting 30-day mortality; it did not contribute to the GRACE score (211). An analysis conducted in 1892 cases to investigate the contribution of various biomarkers (high-sensitivity troponin T, NT-proBNP and high-sensitivity CRP) to the GRACE score reported that NT-proBNP (at a threshold of 174 ng/L) could contribute to the GRACE score in predicting 30-day and one-year mortality and non-fatal MI recurrence (225).

The seven-component OASIS risk score that was created by using five classical risk markers (age, gender, history of MI or stroke, ST-segment deviation and Troponin T) and two additional biomarkers (NT-proBNP and HbA1C) was found to be superior to the TIMI and GRACE risk scores in predicting the one-year rate of the composite endpoint of CV death/MI/stroke in NSTE ACS cases. The NT-proBNP values used in this scoring system was evaluated in four quartiles and the scoring system looks quite complex and unpractical (226).

13.7 Can natriuretic peptides guide the treatment approach in ACS?

Myocardial function after ACS is one of the most significant factors that determine prognosis. Myocardial dysfunction observed in the early period of an event might be misguiding, and it is important to predict the possibility of improvement at follow-up. A study reported that, when NT-proBNP measured on day 3 of infarction in STEMI cases treated with primary PCI was above 1115 pg/mL, no improvement occurred in global and regional myocardial function at follow-up (227).

A meta-analysis of five studies investigating the role of BNP/NT-proBNP in the guidance for early invasive treatment strategies in acute coronary syndromes showed that such strategies could play a role, but its contribution to the existing approaches was controversial (228).

An analysis reported that NT-proBNP played a role in the identification of ACS cases that would benefit from ACE-i treatment in prognostic sense (death/MI/hospitalization for HF), and ACE-i treatment showed prognostic benefit only in cases with NT-proBNP levels in the highest quartile (229).

13.8 Is there a cut-off value that can be helpful in clinical use?

It is seen that different cut-off values have been used for BNP or NT-proBNP in studies conducted over time.

The TACTICS-TIMI 18 study showed that if BNP on hospitalization was >80 pg/mL, seven-day and six-month mortality rates were higher (204).

The ENTIRE-TIMI 23 sub-study showed that reperfusion was insufficient and seven-day mortality was higher in STEMI cases treated with thrombolytics and had a BNP > 80 pg/mL (198).

A sub-group analysis of diabetic cases in GUSTO-IV trial recorded that NT-proBNP above 669 ng/mL in samples taken at a median 9.5 hours of NSTE ACS increased one-year mortality by 2.0 times (95% CI: 1.1-3.6) (206).

NT-proBNP above 474 pg/mL indicated a five to ten fold increase in six-month total mortality in ACS cases with normal Troponin T levels (207). When the same cut-off value was used by another group, NT-proBNP above 474 pg/mL indicated a poor in-hospital prognosis in ACS (209).

In acute MI cases treated with PCI, it was reported that a BNP value above 285.73 pg/mL predicted one-year major adverse cardiac events with 96% sensitivity and 77% specificity (203). Another study reported that the best threshold NT-proBNP value for predicting in-hospital mortality in STEMI cases treated with primary PCI was 2300 pg/mL (201).

In ACS complicated with cardiogenic shock, the best threshold NT-proBNP value for predicting 30-day mortality was 4500 ng/L in samples taken at the 12th hour (202).

It was reported that NT-proBNP of 100 pg/mL or above on admission for NSTE ACS was associated with 6.24 times increased total mortality at an approximately ten-years long follow-up (214).

Another very recently published study reported that a 174 ng/L cut-off value of NT-proBNP contributed to the GRACE score in predicting the 30-day and 1-year mortality and non-fatal MI recurrence rates (225).

As is seen, various NPs were measured in various patient populations in different studies, and most of them reported different NP cut-off values for prognosis assessment.

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13.9 What do the guidelines recommend?

When the current North American and European guidelines are examined, it is seen that STE ACS guidelines do not refer to natriuretic peptides in either risk stratification or prognosis assessment.

Among the guidelines for NSTE ACS, the ACC/AHA guideline published in 2014 (230) recommends BNP or NT-proBNPmeasurement at a Class IIb (Evidence level=B) indication for assessing risk in cases with suspected ACS. Similarly, NP measurement is recommended as a Class IIB (Evidence level=B) indication in terms of providing prognostic data in addition to troponin, and the biomarker that is recommended for prognostic assessment in NSTE ACS as a Class I (Evidence level=B) indication is troponin (230).

The ESC NSTE ACS guideline published in 2015 (231) accepts that natriuretic peptides have been intensively evaluated and confirmed to provide prognostic data in addition to troponin. However, as such assessment does not have any demonstrated benefit in disease management yet, the benefit of these biomarkers in addition to GRACE 2.0 risk calculation is considered marginal and NP measurement for prognostic purposes is not recommended.

13.10 Conclusion and summary:

The role of natriuretic peptide levels in both in-hospital and mid-to-long term prognosis assessment in acute coronary syndromes has been investigated comprehensively in registry studies and post hoc analyses of prospective trials. There is a large body of evidence showing that high NP levels indicate high in-hospital risk and poor mid-to-long term prognosis. However, it is not quite clear how this information can contribute to disease management and whether or not there is a contribution of measuring NP levels in addition to troponins and/or the established risk scoring systems. There are still some questions that remain answered, such as on which phase/day of acute coronary syndrome should sampling be performed and what, if any, the ideal cut-off value that will indicate the relevant risk is.

14.0 Natriuretic Peptides in the Management of Mitral and Aortic Valve Diseases – Burcu Demirkan

The timing of surgical interventions for valvular disease is generally determined based on the development of symptoms, left ventricular (LV) diameter and systolic function changes or elevation in systolic pulmonary artery pressure (232). However, advanced age or comorbidities might lead to incorrect evaluation of patients in terms of symptoms. Echocardiography is an examination mainly used in the assessment and follow-up of valvular diseases and it is a method which is dependent upon image quality and requires experienced operators. Therefore, the use of biomarkers can play a supplementary role in the management of valvular diseases, allow for easy and serial monitorization, reflect the severity of the disease, increase in parallel with the progression of the disease and help distinguish the patients who will become symptomatic in the near future. Natriuretic peptides are well-known examples to these biomarkers.

Natriuretic peptides (NPs) are endogenous cardiac hormones which have prognostic value in diagnosing heart failure and guiding the treatment. They are released as a result of myocyte stretch from the atrial and ventricular myocardium. The pressure load on aortic stenosis, mitral regurgitation and the volume load in aortic insufficiency lead to the increase of natriuretic peptides (233, 234).

14.1 Aortic Stenosis

As society gets older, the prevalence of aortic stenosis (AS) increases (232). In particular, elderly patients might describe atypical symptoms, or existing symptoms can be attributed to other concomitant diseases. Therefore, it might not always be possible to clearly evaluate when AS becomes symptomatic. The optimal treatment method in symptomatic patients is aortic valve replacement; however, the timing of interventions should be discussed for asymptomatic patients (235). Even though a follow-up option is an optimal and safe approach for asymptomatic patients, the risk of sudden death cannot be eliminated completely (236). In addition to other non-invasive methods, NP can be added as a supplementary method.

Natriuretic peptides increase in relation to the severity of AS (237, 238). This correlation exists with both the transvalvular gradient and aortic valve area (239, 240). NPs were found to be higher in symptomatic AS patients than asymptomatic ones. A study revealed that >66 pg/ml serum BNP levels could determine symptomatic patients (241). Another study shows that the development of symptoms and the occurrence of the need for surgical intervention in the subsequent six to nine months is less in patients with BNP <130 pg/ml and NT-proBNP <592 pg/ml (239). Both NT-proBNP and BNP levels increase with the severity of aortic stenosis, onset of symptoms and development of LV dysfunction. While BNP is very helpful, particularly in diagnosing patients in the New York Heart Association (NYHA) functional class III-IV, its benefits in distinguishing asymptomatic patients from mildly symptomatic patients are much less (242). However, it was observed that symptoms develop earlier in the follow-up in asymptomatic patients with high NP levels compared to those with low NP levels (243). Abnormal blood pressure response to exercise is higher in patients who are asymptomatic but have high BNP levels (244). On the contrary, as opposed to dyspnea, the presence of angina or syncope as a symptom does not appear to correlate with NP levels (243).

Increased NP levels is a significant marker of mortality in both symptomatic and asymptomatic AS (241). In a prospective study by Katz et al. that included patients who were diagnosed with severe AS and had normal LV systolic function, it was observed that patients with BNP >135 pg/ml and NT-proBNP >1150 pg/ml had a higher mortality risk in the long term (245). In another study assessing patients with normal left ventricular ejection fraction and AVA <1.2 cm^2, the mortality rate was

around 60% in patients with BNP > 819 pg/ml among patients who were monitored without surgical intervention during a one-year follow-up while no mortality occurred in those with BNP <100 pg/ml during the same period (246). In another study using the BNP ratio calculated with the adjusted BNP value according to age and gender, survival rates were around 44%, 25% and only around 15% in patients with a BNP ratio of 1-2, a BNP ratio of 2-3, and ³a BNP ratio of 3, respectively (247). Although BNP levels are not helpful in distinguishing true AS patients from pseudo-AS patients in low-flow, low-gradient AS, one-year survival rate is again quite low in patients with ³550 pg/ml BNP levels in a similar way (248). In this study, furthermore, high BNP levels predicted poor outcome independently of contractile reserve, defined by increase in stroke volume greater than 20% on dobutamine stress echocardiography (248). This evidence shows that NPs have prognostic value independent of symptoms and LV functions.

It was found that BNP levels showed postoperative all-cause mortalities in a more accurate manner compared to the logistic EuroSCORE risk classification, which is frequently used to identify operational risk in patients who will undergo aortic valve replacement surgery (249). On the other hand, AVR has benefits in terms of mortality in patients with high BNP similar to those with low BNP (247). It was found that BNP levels decreased in patients following aortic valve replacement surgery (250). If BNP elevation continues in the postoperative period, this can be an indicator of patient-valve mismatch or permanent ventricular dysfunction (251). BNP levels can help distinguish risky patients in the postoperative period and offer guidance with respect to patients who need follow-ups with closer and more intense treatment.

Among the patients who underwent transcatheter aortic valve implantation (TAVI), an alternative treatment approach for patients with severely symptomatic AS and high surgical risk, those with a baseline BNP > 428 pg/ml were found to have less than a 30-day survival rate (252). In another study monitoring longer-term results, BNP > 202 pg/ml on discharge after a TAVI procedure was found to be correlated with two-year all-cause mortalities and a repeated need of hospitalization (253). There is evidence again in the group of patients who underwent TAVI that NP levels can be helpful in both identifying operational risks and distinguishing patients who could be associated with adverse outcomes after the procedure.

In summary, NPs;

- Reflect the severity of the disease in patients with aortic stenosis
- Provide guidance for safe follow-ups without intervention in asymptomatic AS patients, and play a determinative role in the development of symptoms
- Help identify risks in terms of mortality
- In patients who underwent intervention, evaluate the success of the procedure can and differentiate patients who may experience negative outcomes after the procedure.

14.2 Aortic Regurgitation

In patients with severe aortic regurgitation (AR), the indication for surgery is mainly the presence of symptoms and a 50% LV ejection fraction (232). However, there is no intervention suggestion for the group of patients who have asymptomatic but hemodynamically severe AR and preserved LV systolic function. Although there is echocardiographic data suggesting a correlation between poor outcome and effective regurgitant orifice area, there is a need for a parameter that can determine the risky ones in this group of asymptomatic patients (254).

NT-proBNP is correlated with the degree of AR and functional capacity (255).

In a study by Pizzaro et al. involving 294 patients with asymptomatically severe AR and preserved LV systolic function, BNP >130 pg/ml was found to be correlated with the development of congestive HF, LV dysfunction and adverse events including death (256). This study found that echocardiographic LV end-systolic diameter, regurgitant orifice area and BNP levels were independent indicators of adverse outcomes and the prognostic value of BNP was higher than other parameters. The risk of adverse events is also increased in patients who show increased BNP elevations within one year in serial measurements (256).

Detection of AR after the TAVI procedure is a frequent complication that determines mortality. In a study by Kaneko et al. which included 856 patients who underwent the TAVI procedure and development of more than mild AR was considered to be significant at the end of the procedure, and it was found that not every patient who developed significant AR was at the same risk and some baseline characteristics could influence the risk status. This study also revealed that the factors that identified patients with higher risk were baseline LVEF and NT-proBNP levels. In patients with ³40% baseline LVEF and £5000 pg/ml NT-proBNP, it was found that the presence of significant AR did not increase one-year mortality at the end of the procedure. However, on the contrary, the presence of significant AR after the procedure in patients with LVEF <40% and NT-proBNP >5000 pg/ml, increases mortality in the patients (257).

In summary, NPs;

- Reflect the severity and functional capacity of the disease in aortic regurgitation.
- Are prognostic markers that can predict the development of adverse events in the follow-up.
- Might play a potential role in determining patients with high risk of poor outcome in case of AR developing after a TAVI procedure.

14.3 Mitral Regurgitation

Degenerative mitral regurgitation (MR) is a common valvular disease that is treated surgically. Surgical intervention indications are determined depending upon the presence of symptoms and/or LV ejection fraction <60%, widened LV end-systolic diameter and the development of pulmonary hypertension and/or atrial fibrillation. Criteria that define surgical indications are factors that also define the development of postoperative mor-

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tality and heart failure (232). Mitral regurgitation is a commonly well-tolerated disease and patients with MR can live without symptoms for years. Preload and afterload, contractility and LV ejection fraction are normal in this period, and total stroke volume increases depending on the increased end-diastolic volume. However, this adaptation will eventually deteriorate and the patient will go towards a process that leads to irreversible myocardial damage (258). If patients are not given surgical intervention within the appropriate time, HF, pulmonary hypertension and right HF development may potentially occur (258). While the success of procedures has been increasing over the years thanks to developments in the methods of mitral valve repair, a tendency has occurred towards applying early surgical intervention in patients in the asymptomatic period based on the evidence of decreased risk and better results of early surgery (259). On the contrary, there is data suggesting that early surgical intervention does not reduce all-cause mortalities compared to patients who are monitored without intervention and can even be associated with more fatal strokes and AF developments (259). It is not possible even at the most experienced centers to eliminate the risks of surgical interventions and eliminate the need of mitral valve replacement completely in the case of a failed repair. Therefore, there have been some studies suggesting that NP levels might be helpful in determining the time of surgical intervention more correctly in MR.

BNP increases depending on the severity and symptoms of MR (260). However, it is not possible to assess the degree of MR by taking only BNP values into account (261).

There is evidence of the prognostic value of BNP in asymptomatic MR patients. In a study evaluating patients with normal LV ejection fraction, asymptomatically severe organic MR and exercise capacity of 7 METs or above documented through exercise tests, it was seen that patients with a baseline BNP value >105 pg/ml reached the composite endpoint comprising congestive HF symptoms, LV dysfunction or death at the one-year follow-up significantly more than those with a BNP value <105 pg/ml (262).

A study by Magne et al. found in the follow-up that BNP levels increasing with exercise in asymptomatic patients with MR was an indicator of adverse cardiac events (263).

Another multicenter study that included 1331 patients with degenerative mild to moderate MR and normal LV ejection fraction revealed that BNP activation was an indicator of survival and that mortality reached 60% in eight years in patients in the medical follow-up group with a BNP ratio > 4. On the other hand, BNP activation was not an independent indicator of survival in the group who had surgery. Another significant finding from this study was that patients with non-elevated BNP activation (BNP £1) had better prognosis (264). If the patients with asymptomatic severe MR do not have the criteria for surgical intervention and the BNP ratio is low, conservative follow-up of these patients is a very safe approach. Moreover, if surgical intervention indication occurs in a patient and BNP activation also increases in patients, it is still possible to obtain better long-term results with surgical intervention in such patients (264).

In summary, NPs;

- Reflect the severity and symptom status of MR
- Help determine the patients for whom conservative follow-ups are safe among those with asymptomatically severe MR
- Determine pre- and post-surgery prognosis in patients who had surgery.

14.4 Mitral Stenosis

Mitral stenosis (MS) is a valvular disease that frequently develops due to rheumatic fever, that carries the risk of pulmonary hypertension and AF development, and that develops slowly with symptoms occurring in adulthood. The indications for intervention are presence of mitral valve area (MVA) £1.5 cm^2 and symptom development (232). However, the development of symptoms might not be noticed in the early stage if the patient changes their life style during the long-term asymptomatic course of the disease. A parameter which is easily accessible, repeatable and comparable in the follow-up of mitral stenosis might provide additional contribution to echocardiographic data.

Sharma et al. revealed that both ANP and BNP levels increased in parallel to the severity of disease, ANP and BNP levels correlated with one another, but for reduced exercise capacity, BNP was a more powerful indicator than ANP in MS patients. An interesting finding from this study is that when MS patients with NP levels within the normal range were compared to the control group, it was found that the left atrial area was wider, resting and exercise pulmonary artery pressures were higher and exercise capacity was reduced in patients with MS (265). Accordingly, cardiac remodeling and early dysfunction might develop in MS patients without BNP increase as well. However, increased BNP levels (> 82 pg/ml) was found to be correlated with wider left atrial area index, higher pulmonary artery pressure and poorer exercise capacity (265). Another study investigated NT-proBNP levels in patients with MS and found that NT-proBNP levels were higher in patients with MS than the control group. NT-proBNP levels were found to be higher in patients with atrial fibrillation than those in sinus rhythm. Also, it was seen in patients who were assessed through exercise tests that these levels correlated with left atrial diameter after resting and exercise, right ventricular end-diastolic diameter, exercise duration, heart rate and pulmonary artery pressure. Again in this study, NT-proBNP level >251 pg/ml was an indicator of pulmonary artery pressure increasement with exercise above 60 mmHg (266).

Percutaneous mitral balloon valvuloplasty is the method of choice for intervention for eligible patients in the treatment of severe symptomatic MS. It was demonstrated that BNP and NT-proBNP levels decreased after a successful procedure in patients who underwent percutaneous mitral balloon valvuloplasty (267). In another study, again assessing the relationship between NPs and procedure success, NP levels decreased after the procedure in patients only in sinus rhythm while no effect was observed on NP levels in patients with AF. According to the in-

terpretation of the investigators, procedures performed without development of AF might be more beneficial for patients (268).

In summary, NPs;

- Reflect the severity of MS, cardiac remodeling and increased pulmonary artery pressure.
- Can reveal the relationship between the existing symptoms and MS.
- Can provide information about the success and outcomes of the procedure.

Consequently, NPs elevate depending on myocardial stretch that develops as a result of increased pressure and volume load in valvular diseases. There is evidence showing that NPs can be useful in follow-ups with asymptomatic patients with severe valvular disease, confirming that the existing symptoms are associated with valvular disease in symptomatic patients, monitoring the progression of the disease, determining the prognosis and determining patients who need close follow-up. From this perspective, they might provide information in addition to echocardiographic findings. However, there are some limitations that should be taken into consideration while using NPs in valvular diseases. First of all, unlike HF, defined diagnostic predictive values are not available. In addition, conditions such as age, gender, obesity and renal function have an effect on NP levels. Some studies preferred to use BNP ratio so that age and gender factors did not affect the assessment adversely. Cardiac conditions such as coronary artery disease, pulmonary embolism and AF which affect NP levels can also coexist. On the other hand, the presence of multiple valvular diseases is not rare and it may not be possible to understand the extent to which the pathology of which valve was altered based on NP levels. It might be helpful for the clinicians to evaluate the changes in NP levels with sequential measurements after baseline value, instead of making an assessment with only one NP value in the follow-up of patients with valvular diseases. There is not sufficient evidence for the necessity of performing an intervention in case of elevated NP levels in patients with severe valvular disease without intervention indications defined in the guidelines, and comprehensive studies are needed to shed light on this issue.

15.0 Natriuretic Peptides in the Identification of Atrial Fibrillation Risks – Ahmet Taha Alper

15.1 Introduction

Atrial fibrillation (AF) is the most common continuous arrhythmia with a prevalence of 2%, and it is diagnosed in one-third of hospitalizations due to cardiac arrhythmia1. Incidence of AF, which is seen in 5% of the population above the age of 65 and around 8-10% above the age of 80, increases with age. Beyond adversely affecting the quality of life, AF is associated with increased total mortality, cardiovascular mortality and cardiovascular morbidity including heart failure, stroke and systemic embolism (269-271). As these risk factors emerging with atrial fibrillation do not occur equally in all patient groups, treatment strategies are determined through clinical risk scoring systems such as CHADS2 or CHA2DS2VASc scores for risk assessments for stroke. These risk scoring systems exclude some biochemical parameters which are seen to be associated with stroke, and do not provide clear information about risk assessments in other morbidities caused by AF. In our compilation, we tried to summarize the role of natriuretic peptides (NP) in risk identification in the case of different AF-related clinical conditions.

15.2 Identifying the occurrence, duration and progression of AF

In their study, Mandalenakis et al. enrolled 528 men and assessed the occurrence of AF with the baseline ANP levels at the end of 16 years. This study demonstrated that ANP levels (a range of 192-253 pg/ml, HR: 3.14 95% CI: 1.59-6.20 p: 0.001 and above 254 pg/ml, HR: 3.36 95% CI: 1.72-6.54, p<0.001) independently predicted the occurrence of AF (272). Additionally, ANP facilitates the occurrence of AF by shortening atrial transmission time and the effective refractory period even in completely healthy atriums (273). Mutations occurring in atrial natriuretic peptide encoding gene (NPPA) cause the synthesis of mutant ANP (mANP) which has five or ten times higher plasma concentration. In the studies, a correlation between mANP and familial AF development was seen (274).

Today, AF classification is mainly based on the duration of AF and this classification is the main determinant in treatment strategies. Mid-regional pro-ANP (MR-proANP) is a stable fragment of ANP prohormone and, according to studies; it appears to be useful in determining the duration of AF. Median MR-proANP concentration was found to be 147.7 [95.3–197.4] pmol/L and 220.4 [154.0 –303.1] pmol/L in subjects with atrial fibrillation duration below 48 hours and above 48 hours, respectively (P<0.001) (275). This result suggests that NPs might be useful in estimating onset time and determining treatment strategies accordingly in patients without documented AF. In another study investigating progression from paroxysmal AF to persistent AF, predictive ability of NT-proBNP was not observed while NT-proANP levels could predict progression (276). In order to enable NP-guided treatment, extensive studies are necessary to compare different treatment methods in the context of NP levels in patients who are expected to maintain sinus rhythm and have a high likelihood of progression.

15.3 Identification of AF in patients with cryptogenic stroke

Compared to other types of stroke, cardioembolic strokes are repetitive and have poorer prognosis (277). Patients who have stroke and were not diagnosed with AF are considered to have had a cryptogenic stroke and treated with antiplatelets instead of oral anticoagulants. Long-term monitoring of cryptogenic patients showed that approximately 30% of patients had AF (278). In Find-AF study that included patients with acute cerebral ischemia, BNP, NT-proBNP and NT-proANP were compared in terms of identifying AF, and BNP levels were established as an

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independent AF predictor in this patient group. In this study, the cut-off value with the highest precision and specificity of BNP was 118 pg/ml (279). A meta-analysis evaluated ten prospective studies testing BNP and six prospective studies testing NT-proBNP. BNP and NT-proBNP were found to have equal diagnostic value in the identification of cardioembolic stroke. However, BNP was more precise (0.65 95% CI: 0.63-0.68) and NT-ProBNP was more specific (0.93, 95% CI: 0.91–0.94) in the diagnosis (280). In light of this information, long-term monitoring might be recommended for excluding AF in the presence of elevated NP in patients who have had a cryptogenic stroke.

15.4 Biomarker-based scoring in the identification of stroke risk in patients with AF

Up-to-date guidelines recommend the CHA2DS2VASc score for assessing stroke risk in patients with AF. This is a clinical scoring system and does not include biochemical markers. Recent studies have shown that many biomarkers which can show renal and cardiac functions and reflect inflammation and oxidative stress can be used in determining the risk of stroke (281). In light of this, the ABC score have been derived from the ARISTOTLE (282) study (Table 16). Later, validity of this score was confirmed by using data from the STABILITY (283) study (284). In the ABC score, each risk factor (within intervals) is scored from one to ten to calculate the risk of stroke. In this way, it is possible to calculate the risk of stroke by using the total score (Fig. 3). Clinical risk factors that are used in CHA2DS2VASc scores such as hypertension, diabetes mellitus, heart failure, cardiovascular diseases and gender do not provide additional prognostic benefit for the biomarkers that are used in the ABC score. Therefore, these risk factors are excluded from scoring. Compared to the CHA2DS2VASc score, the ABC score predicts stroke better (c-indices are 0.68 vs. 0.62, P<0.001, respectively) and significant sub-groups have a similar superiority. In addition, particularly in patients who have not previously had a stroke or without a TIA history, superiority of the ABC score to the CHA2DS2VASc score (c-indices are 0.68 vs. 0.59 P<0.001, respectively) was more clearly observed (284). Risk factors that are used in the CHA2DS2VASc score are non-modifiable risk factors. As an increase or decrease in stroke risk can be determined by biomarkers, the ABC score is presented as a more dynamic scoring system. In parallel to this, treatment strategies that are used in prevention of stroke can vary.

Table 16. ABC score criteria

Scoring Criteria		Interval
Age (years) (age-A)		44-90
Biomarkers	Troponin I Hs (ng/l)	1-180
(Biomarkers-B)	NT-proBNP(ng/l)	25-5900
Clinical history	Stroke or TIA	Yes-No
(clinical history-C)		

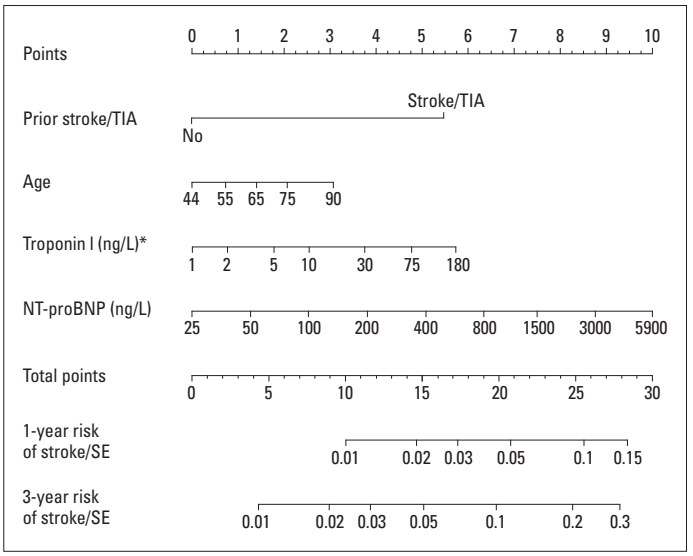

Figure 3. Nomogram to calculate ABC score. The score is determined on the scale for each predictor and the total score is obtained. One-year or three-year risk of stroke is calculated according to the total score. Except for nomogram, it is also possible to make practical calculations with web-based applications
*Troponin T high-sensitivity (ng/L) also could be use

15.5 Identification of recurrence risk in patients who underwent cardioversion and AF ablation

Natriuretic peptide levels are associated with enlarged left atrium volume (285), heart failure and related intracellular calcium increase (286). Also, it is known that NPs increase vagal activity via the cGMP signaling pathway (287, 288). Based on these pathophysiological relationships, their activities were examined to predict AF recurrence after cardioversion and ablation.

A meta-analysis by Xiangdong et al. included 19 studies evaluating recurrence after cardioversion, and it was seen that baseline BNP/NT-proBNP levels were significantly higher in patients with recurrence than patients who maintained sinus rhythm (SMD -0.70, CI [-0.82, -0.58]). Although meta-analysis results present the prognostic value of NPs, today it is not possible to determine the cardioversion based on biomarker level. Also, a clear cut-off value that can reflect the maintenance of sinus rhythm is needed.

Although radiofrequency catheter ablation treatment is one of the main treatment modalities in preventing AF attacks, recurrence after ablation is a significant problem (289). A meta-analysis including 23 studies measuring ANP, BNP and NT-proBNP levels to assess ablation recurrence, all mentioned NPs were shown to predict recurrence after ablation (95% CI:0.12–0.60, P=0.004; 95% CI:0.35–1.11, P=0.0002; 95% CI:0.64–1.87, P=0.0001, respectively) (290). The main ablation strategy in paroxysmal AF is pulmonary vein isolation. However, there is not any consensus on what kind of a strategy can be followed in addition to pulmonary vein isolation in persistent AFs. Studies comparing ablation strategies on the basis of preoperative NP level in patients with AF may allow NP-guided treatment planning in the future.

15.6 Identifying the risk of AF development in postoperative period

It is estimated that more than 5 million thoracic surgeries are performed annually in the world. Atrial fibrillation is a significant complication that develops in patients during the postoperative period, and is associated with long-term mortality (291, 292). A meta-analysis of five studies evaluated NPs for the risk of postoperative AF development. The meta-analysis demonstrated that NP levels could predict the development of AF (OR: 3.13 (95% CI 1.38-7.12; I2=87%) (293). An optimal threshold for NT-proBNP and BNP was calculated in only two of the studies that were included in the meta-analysis. Optimal values were 160 ng/L and 30 ng/L for NT-proBNP and BNP, respectively (293). This information suggests that early diagnosis and treatment of AF can be ensured through more intense monitoring of at risk patient groups during the postoperative period based on NP levels.

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ABBREVIATIONS

ABC score	Age, biomarkers, clinical history
ACE	Angiotensin-converting enzyme
ACEI/ARB	Angiotensin converting enzyme inhibitor/angiotensin receptor blocker
Ach	Acetylcholine
ACS	Acute coronary syndromes
ADHF	Acute decompesated heart failure
AF	Atrial fibrillation
AHA/ACCF/HFSA	American Heart Association/ American College of Cardiology/ Heart Failure Society of America
AHF	Acute heart failure
ANP	Atrial natriuretic peptide
AR	Aortic regurgitation
AS	Aortic stenosis
ASD	Atrial septal defect
AVA	Aortic valve area
BNP	B-type or brain natriuretic peptide
cGMP	Cyclic guanylate monophosphate
CI	Cardiac index
CNP	C-type natriuretic peptide
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CTEPH	Chronic thromboembolic pulmonary hypertension
cTnI	Cardiac troponin I
CV	Cardiovascular
DM	Diabetes mellitus
ECG	Electrocardiography
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
GLS	Global longitudinal strain
HbA1c	Hemaglobin A1c
HER2	Human epidermal growth factor receptor 2
HF	Heart failure
HFmEF	HF with mid-range ejection fraction
HFpEF	HF with preserved ejection faction
HFrEF	HF with reduced ejection fraction
hsTnT	High sensitive troponin T
IL-1	Interleukin-1
LV	Left ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
METs	Metabolic equivalents of task
MR-proANP	Mid-regional pro-atrial natriuretic peptide
MRA	Mineralocorticoid receptor antagonist
MRA	Mineralocorticoid receptor antagonist
MS	Mitral stenosis
MVA	Mitral valve area
NEP	Neutral endopeptidase
NICE	The National Institute for Health and Care Excellence
NP	Natriuretic peptides
NPR	Natriuretic peptide receptor
NPR-A	Natriuretic peptide receptor A
NPR-B	Natriuretic peptide receptor B
NPR-C	Natriuretic peptide receptor C
NSTE ACS	Acute coronary syndromes without ST-segment elevation
NSTEMI	Non-ST segment elevation myocardial infarction
NT-proBNP	N-terminal pro type B natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PCI	Percutaneous coronary intervention
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RAAS	Renin-angiotensin-aldosterone system
RAP	Right atrial pressure
RVEDP	Right ventricular end-diastolic pressure
RVEDVI	Right ventricular end-diastolic volume index
RVEF	Right ventricular ejection fraction
SNS	Sympathetic nervous system
STE ACS	ST elevation acute coronary syndromes
STEMI	ST-segment elevation myocardial infarction
TAVI	Transcatheter aortic valve implantation
TIA	Transient ischemic attack
TNF	Tumor necrosis factor
TNFa	Tumor necrosis factor-alpha

ACRONYMS of CLINICAL STUDIES

BACH	The Biomarkers in Acute Congestive Heart Failure
BATTLESCARRED	NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death study

BIOSTAT-CHF	BIOlogy Study to TAilored Treatment in Chronic Heart Failure
CARE-HF	Cardiac Resynchronization in Heart Failure Study
COACH:	Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure
CTCAE	Common Terminology Criteria for Adverse Events
ESC-HFA	European Society of Cardiology-Heart Failure Association
GRACE	The Global Registry of Acute Coronary Events
GUIDE-IT	The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure
GUSTO-IV	Global Utilization of Strategies To open Occluded arteries)-IV
HER2	Human Epidermal growth factor Receptor 2
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
OPTIMAAL trial	Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan
PARABLE	Personalised Prospective Comparison of ARni With ArB in Patients With Natriuretic Peptide eLEvation
PARADIGM HF	Prospective Comparison of ARNi With ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure
PATH-CHF	The Pacing Therapies for Congestive Heart Failure
PONTIAC	Selected PreventiOn of cardiac eveNts in a populaTion of diabetic patients without A history of Cardiac disease
PROSPECT	The Predictors of Response to CRT study
PROTECT	Pro-B Type Natriuretic Peptide Outpatient Tailored Chronic Heart Failure Therapy
STARBRITE	Outpatient Setting: Brain Natriuretic Peptide Versus the Clinical Congestion Score
STRONG-HF	Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP and GDF-15, of Heart Failure Therapies
TIME-CHF	Trial of Intensified (BNP-guided) versus standard (symptom-guided) Medical therapy in Elderly patients with Congestive Heart Failure
TIMI	Thrombolysis In Myocardial Infarction
TRILOGY ACS	The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes
OASIS	Outcome Assessment Information Set
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial