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BNP/NTPROBNP: BEYOND HEART FAILURE

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BNP/NTproBNP: Beyond Heart Failure

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Abstract

Brain Natriuretic Peptide is an amino acid polipeptide produced by cardiac myocytes, whose synthesis results mainly from hemodynamic changes that lead to atrial or ventricular volume expansion. The peptide is released primarily by the ventricular myocardium and its fragmentation and cleavage lead to the formation of NTproBNP.

Several studies have been discovering different applications of these biomarkers, with special focus on diagnosis, prognosis and monitoring of therapy of congestive heart failure. However, in the past few years several other disease states have been associated with changes on the systemic levels of these proteins.

Therefore, we aimed to review the possible applications of NTproBNP and BNP beyond Congestive Heart Failure, with specific emphasis in the following diseases: Ischemic Stroke, Atrial Fibrillation, Carotid Artery Stenosis, Aortic Valve Stenosis, Coronary Heart Disease, Hypertrophic Cardiomyopathy, Tachycardia-mediated Cardiomyopathy, Takotsubo Cardiomyopathy, Heart Surgery, Kawasaki Disease, Central Sleep Apnea, Sepsis, Chronic Kidney Disease and Pleural Effusions.

Keywords: BNP; NTproBNP; Clinical applications; Stroke; Cardiomyopathy; Kawasaki disease; Sepsis; Coronary artery disease; Aortic valve stenosis.

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Introduction

The use of biomarkers as a noninvasive tool, has become common in several areas of medicine, due to its usefulness in the diagnosis and prognosis of countless diseases [1].

Brain natriuretic peptide (BNP) and amino terminal pro-brain natriuretic peptide (NTproBNP) are neurohormones secreted by cardiomyocites in response to volume expansion and increased pressure [2]. Therefore, they have a high potential for application in several fields of medicine.

They are used primarily in emergency situations, namely in the differential diagnosis of dyspnea, which may in some circumstances be difficult only by clinical signs. When this is the case, support of a cardiac etiology can be obtained by the use of biomarkers, improving assessment and speeding up treatment [3].

Despite various applications, it's important to consider that, there are some factors that may affect the plasma concentrations of these neuropeptides, and therefore measured levels should be adapted to each situation. Likewise, its pathophysiological mechanisms are not yet fully clarified [4].

The aim of this study was to determine the usefulness of BNP/NTproBNP as a biological marker, for the prediction, diagnosis, monitoring and treatment of situations other than acute and chronic heart failure and eventual role in providing risk stratification. Thus, we intend to document the possible role of these biomarkers as an important additional diagnostic tool, leading to a better outcome in a new spectrum of diseases [1]. However, understanding their contribution implies knowing the pathophysiology behind these disease states, something that also be briefly covered.

Methods

A search to evaluate the clinical application of BNP or NTproBNP, was performed in PubMed, using the following keywords: "BNP", "NTproBNP" and "clinical applications", from October 2012 to December 2012.

The search provided 561 results, among which 4 described biology and function of these biomarkers and 41 were related with other diseases besides heart failure. An additional 11 articles were retrieved from the reference list of the aforementioned articles and 19 articles from manual searches related with specific subjects associated with BNP/NTproBNP.

A total of 75 articles were used in this review article comprising mostly papers published between 2005 and 2012 (figure 1).

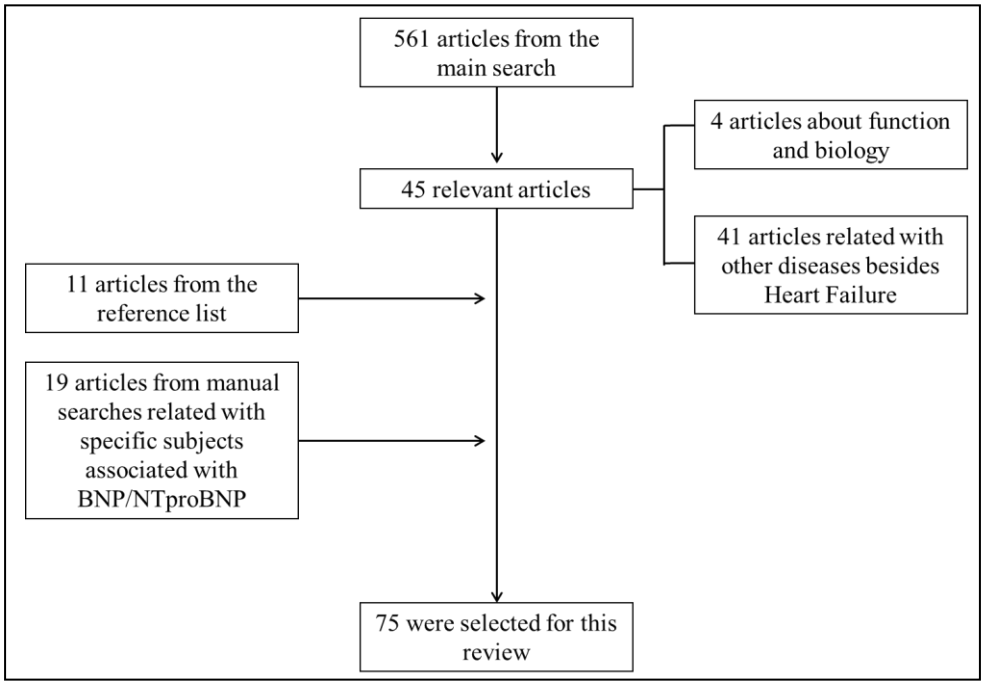

Figure 1. Flowchart illustrating the article(s) selection process.

1. BNP/NTproBNP: Biology

Brain natriuretic peptide (BNP) is a neurohormone secreted by cardiomyocites in response to hemodynamic stress. The BNP gene, located in chromosome 1, encodes 134 amino acid preprohormone (BNP) that is cleaved into a 108 amino acid, proBNP. This

hormone is then cleaved again, by a proteolytic enzyme, into the biologically active prohormone called NTproBNP [3]. Both of these hormones (BNP and NTproBNP) are produced at equimolar levels by ventricular myocites, but NTproBNP has a longer half-life (3), rendering it useful for improving the diagnostic threshold of some diseases [5].

These biomarker levels reflect the hemodynamic status [4], because they are secreted as a response to ventricular volume expansion and electrolytic imbalance, which causes increased intraventricular pressure or stretch and resultant increased wall tension [2,3]. However, when a patient has atrial dysfunction, such as in atrial fibrillation (AF), the main source of brain natriuretic peptide is the atrium [6]. The hormones are released in these circumstances as a way of attenuating these hemodynamic changes, since they have a natriuretic, diuretic and vasodilator effect. They decrease the preload and afterload and consequently decrease pressure, smooth muscle and fibroblast proliferation (preventing fibrosis), and reduce the antidiuretic hormone and aldosterone synthesis to reduce salt and water retention [4].

Despite their hemodynamic effects, the concentration of the hormones may vary between patients, which can be explained by a few factors. One of the most frequent, positively correlated with BNP levels is age, which increases alongside with myocardial mass. Conversely, aging leads to the reduction of the renal clearance [4, 7]. Gender is also a part of the equation: women have higher BNP levels than men, probably because of the influence of sex hormones on gene expression [4, 7]. Even obesity has an important part, and has been shown to have an inverse correlation with peptide levels [4].

Despite these different interactions and limitations, BNP/NTproBNP can be seen as quantitative markers, useful in triage of patients.

2. Clinical applications

In general, in most cardiac diseases that have been associated with an increase in the B-type natriuretic peptides [7] focus has been placed in the presence of left ventricular dysfunction [4]. However, several studies have shown that several other conditions may be associated with an increase in BNP/NTproBNP.

2.1. Ischemic Stroke:

Nowadays, the diagnosis of stroke is based on neuroimaging assessment and clinical symptoms. However, other methods may be important to early differentiate between hemorrhagic and ischemic stroke, or exclude other pathologies, allowing to promptly initiate therapy [1].

Shibazaki K and co-workers assessed 227 patients with atrial fibrillation within 24 hours of onset of transient ischemic attack (TIA) or stroke. Plasma BNP levels were measured on admission and were lower in TIA than in stroke. These authors suggested an optimal cutoff level of 120pg/ml, with values above this threshold being associated with stroke and neurological severity. They also proposed that plasma BNP levels can be used to predict embolic source independently, with a cutoff point of 140 pg/ml [8].

Montaner and co-workers, confirmed that BNP levels were higher in patients suffering from acute cardioembolic stroke (CE) than in other etiologies. They suggested a cutoff level of BNP>76 pg/mL associated with D-dimer >0,96 mg/mL to predict this event [9].

Santamarina and colleagues, evaluating 294 patients with ischemic stroke, of which 89 had an unknown origin, BNP >64pg/mL and CK-MB >1,5 mg/ml were independent predictors of embolic source [10].

However, *Tamura et al* measured plasma BNP levels in 223 patients in 7 days after ischemic stroke, without history of heart failure and found a cutoff point of 90pg/ml, over

which cardiogenic stroke was more likely than cryptogenic stroke [6]. In other stroke types, there was a release of BNP, albeit less pronounced.

Concerning NT-proBNP, *Fonseca et al*, conducted a study that showed a positive association between this peptide and cardioembolic stroke. They estimated a best cut-off point of NT-proBNP discriminating an embolic source was > 265.5 pg/ml. When restricted to patients with AF, sensitivity increased from 71.4 to 94.4% while maintaining a similar specificity. (73.7 to 72.9%, respectively) [11].

Despite the possibility of using BNP plasma levels to elucidate stroke etiology, this neuropeptide can also be used to predict the prevalence of cardiac abnormalities like arrhythmia, coronary or valvular diseases. These diseases states affect ventricular and atrial cardiomyocites leading to the release of the neuropeptides [12].

Chen and co-workers have shown that NTproBNP plasma level alongside with the NIHSS scale (National Institutes of Health Stroke Scale) allowed a combined risk stratification and prognostication of patients. NIHSS is a 15-item neurologic examination stroke scale used to objectively quantify the initial stroke severity/neurologic deficit and predict mortality. They also suggested cut-off points of 1,583.50 pg/ml for NTproBNP, and NIHSS score on admission > 12.5 to detect the group of patients with a higher mortality rate [13].

Among patients with cerebral infarction, the association is more pronounced in those without angiographic vasospasm, suggesting that BNP adequately detects patients with ischemic stroke where large vessel vasospasm was not the main mechanism [14].

Plasma BNP levels seem to have promising applications in stroke (figure 2), and it would be wise to confirm and externally validate optimal cut-off points, allowing the differentiation of the different associated conditions and optimization of treatment.

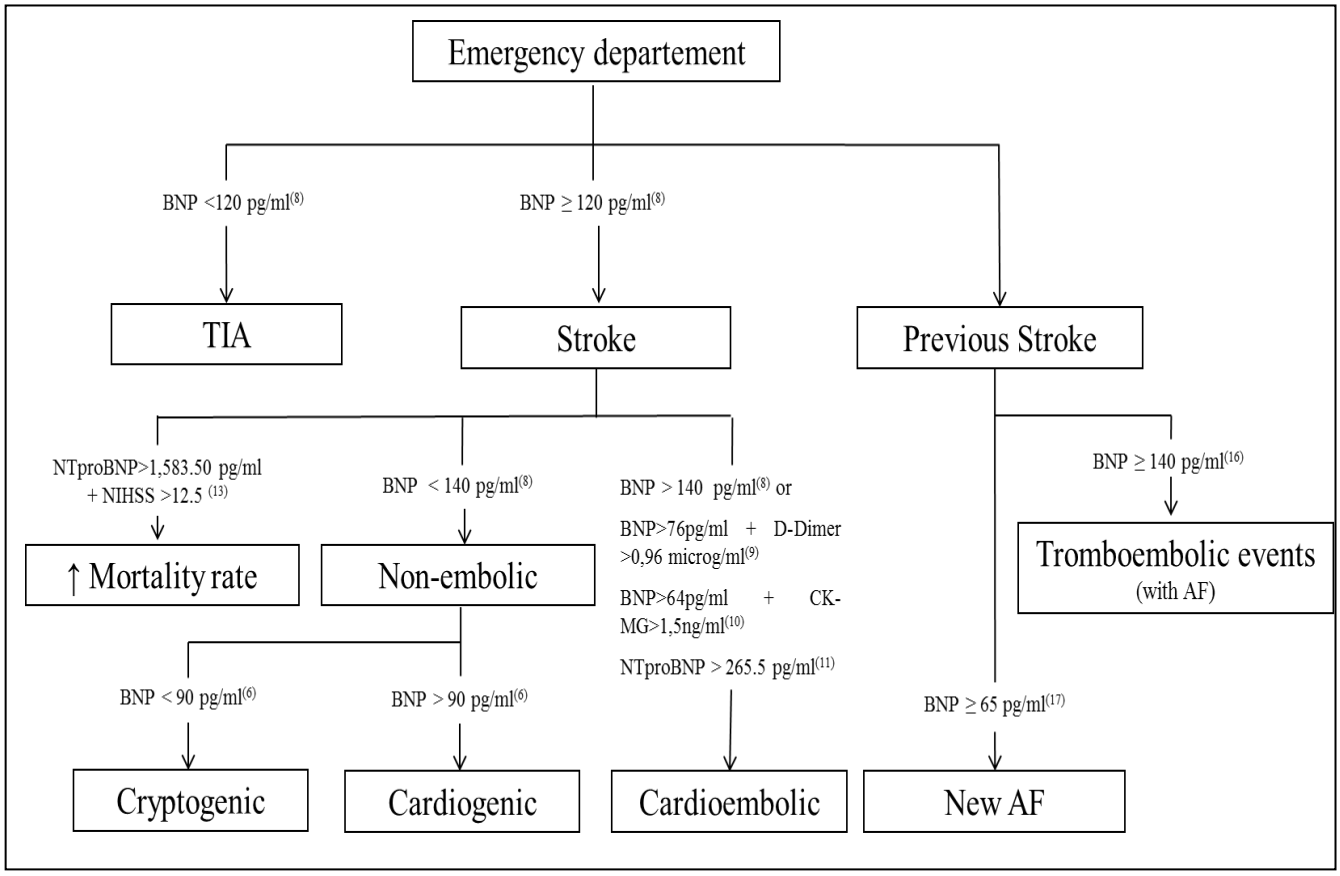

Figure 2: Proposal of a diagnostic approach (and likelihood of cardiac diseases) to the patient with cerebral ischemic event according to BNP/NTproBNP levels. Cutoff values are presented as examples based on presented investigations, but are yet lacking external validation. AF – atrial fibrillation; BNP – brain natriuretic peptide; TIA- transient ischemic attack.

2.2. Atrial Fibrillation (AF):

I. Predictor of changes in patients with AF:

A study conducted by, *Tamura et al*, described a strong association between increased BNP levels, independently of AF or sinus rhythm, and the presence of left atrial appendage (LAA) dysfunction [6]. Another retrospective study supported this association, with an increase in the BNP levels being related to a decreased LAA flow velocity (i.e. LAA dysfunction) [15].

Furthermore, in a group of AF patients with and previous stroke, BNP levels have been identified as a marker of left atrial thrombus: levels higher than 140pg/ml were a predictor of atrial thrombus, but with low sensitivity and specificity (76,5% and 62%, respectively) [16].

According to *Shibazaki* and colleagues, in 584 patients with previous stroke and without previously known AF, 40 patients were diagnosed with AF during follow-up. It was observed that the incidence of the arrhythmia increased alongside with BNP levels: 2% in patients with <50pg/ml, 4% in 50 to 100pg/ml, 12% in 100 to 200 pg/ml, 26% in 200 to 400 and 38% with above 400 pg/ml. They also established a cutoff point of > 65pg/ml that categorized patients according to their risk to develop AF [17].

II. Predictor of stroke and mortality in patients with AF:

The strongest evidence in favor of the association of these peptides with stroke and thromboembolism in AF derives from the RE-LY trial biomarker sub-analysis. In this post-hoc analysis, in 6,189 patients with AF under anticoagulant therapy, troponin I and NTproBNP levels were assessed at baseline. These were found to positively correlate with the risk of stroke and short and long-term mortality [18]. Usually the $CHADS_2$ score is used for risk stratification in patients with AF, and in this study it was possible to observe the additive value of troponin I and NTproBNP to this scale. e.g., In patients with low risk (classification of 0 to 1), an increase in biomarkers (troponin I ≥ 0,020 ug / l and NTproBNP <387 ng/L) doubled the risk of thromboembolism and high levels (troponin I≥ 0,040 ug / l and and NTproBNP >1402 ng/L) increased the risk approximately five times [18].

This confirms the preliminary results by *Kurl* and co-workers suggesting that NTproBNP might help identifying subjects at risk for stroke and AF [19].

In a small cohort study, a similar association was found for BNP. It predicted thromboembolic events in AF patients under anticoagulant therapy, and an optimal cut-off value of 218 pg / ml was established [20].

III. Predictor of atrial fibrillation incidence, type and duration:

Several studies have related the presence of AF with NTproBNP levels. It was suggested that, in patients without structural cardiac disease, those with AF, showed increased NTproBNP levels [21]. This was confirmed in the Cardiovascular Health Study [22] and in Prevention of Renal and Vascular Endstage Disease (PREVEND) [23] cohorts, where this biomarker was a predictor of the incidence of AF.

In 5,187 individuals from the Malmö Diet and Cancer Study (MDCS) NTproBNP modestly improved the discrimination of AF during a mean follow-up of 14 years when added to conventional risk factors [24].

However this was not confirmed by *Tayfun Shain et al,* in a small case-control study of patients with permanent AF of different etiologies and assessed through measurement of BNP levels and transesophageal echocardiography [25]. These authors concluded that BNP levels were higher in mitral stenosis than in other etiologies of AF. No association was found between BNP levels and left atrial function in patients with AF due to the probable lack of statistical power of the sample (84 patients with AF) [25].

A recent study, demonstrated a correlation NTproBNP levels and AF duration, differentiating recent AF (<48 h –960 pg/ml; $CI_{95\%}$ = 236–1328) and progressive AF (>48h – 3695 pg/ml; $CI_{95\%}$ =1255-8062). Therefore, NTproBNP levels can be used as negative predictive value, with lower values meaning low probability of progressive AF. NTproBNP levels were also found to associate with different types of AF: paroxysmal AF with an

average value of 1030 pg/ml ($CI_{95\%}$ =589-1546), persistent with 3658 pg/ml ($CI_{95\%}$ = 3112-5241) and long-standing with 4350 pg/ml ($CI_{95\%}$ = 743-8510) (figure 3) [26].

However, *Deftereos* and co-workers, showed different results, which NTproBNP levels increases progressively during the first 24 hours and falls rapidly thereafter [27]. Given these results, the authors suggested that the NTproBNP levels, could predict the presence of LAA thrombus: lower values were associated with LAA thrombus formation, contradicting previous results [28].

In a cross sectional study of patients with preserved left ventricular (LV) systolic function, NTproBNP levels were higher in patients with AF than controls. Higher values were found in persistent and permanent AF. This increase may be explained due to structural changes, such as atrial enlargement and their loss of contractile function, and ventricular and atrial asynchrony [29].

IV. Predictor of recurrence post-atrial fibrillation ablation:

Fan and colleagues have shown that NTproBNP values are higher in paroxysmal AF (when compared with healthy controls) and normalize 3 months after pulmonary vein isolation. Furthermore, NTproBNP levels predicted recurrence of AF, with an optimum cutoff value of ≥ 423.20 pg / ml [30]. These results have been confirmed by other groups [31, 32].

Nilson and co-workers, found that patients with unsuccessful AF ablation displayed higher NTproBNP levels after an exercise test on a cycle ergometer. The authors suggested that lowers values to predict ablation success (<15 pmol/L) (figure 3) [32].

V. Predictor of atrial fibrillation after surgery:

According to *Iskesen*, elevated NTproBNP before coronary artery bypass grafting, may be predictive of the occurrence of postoperative AF [33]. Similar results were found by

Gasparovic concerning higher values of preoperative and postoperative NTproBNP [34] and *Gibson* regarding BNP levels [35]. In a previous study, NTproBNP was found to be a predictor of AF after coronary bypass surgery on univariate, but not on multivariate analysis [36]. This was also shown by *Samy* and colleagues with NTproBNP cutoff levels of 353 pg/mL and 307 pg/mL (0 hour and 4 hours, respectively) (figure 3) [37].

After lung surgery, it was found that patients who develop AF showed higher values of this neuropeptide [38]. In postoperative patients with esophageal carcinoma, *Hou* and co-workers described a correlation between increased hormone that the presence of AF [39]. Similar findings have also been observed in patients with lung cancer [40].

VI. Predictor of recurrence of atrial fibrillation post-cardioversion:

Freynhofer and collegues established that NTproBNP levels are not useful for predicting the stability of cardiac rhythm after cardioversion (CV), because baseline levels and changes in this neuropeptide after CV were similar irrespective of the presence of relapse. Although NTproBNP levels decreased after CV in all patients and increased solely in the AF recurrence group at 6 weeks, interpretation of these results is difficult as these patients were already in AF at the time of blood sampling [41].

Lack of association of NTproBNP with relapse after AF CV was also described *Psychari* and colleagues [42].

Wozakowska-Kapłon et al. have shown that both BNP and NTproBNP had no role for predicting AF relapse after cardioversion [43].

Conversely, positive results have also been described: baseline NTproBNP values below 450 pg/ml predict successful CV, and values greater than 1800 pg/ml, predict AF recurrence. Intermediate values provide no information towards this endpoint [44].

Likewise, *Beck-Da-Silva et al*, in patients with persistent AF, BNP levels were associated with successful CV. After two weeks of CV, patients who had lower BNP levels, maintained a normal sinus rhythm. Although patients with valvular disease or left ventricular dysfunction were excluded, the study analyzed only 20 patients [45]. Plasma BNP as a predictor of the recurrence of AF, was also described by *Lellouche* and c-workers (table 1) [46].

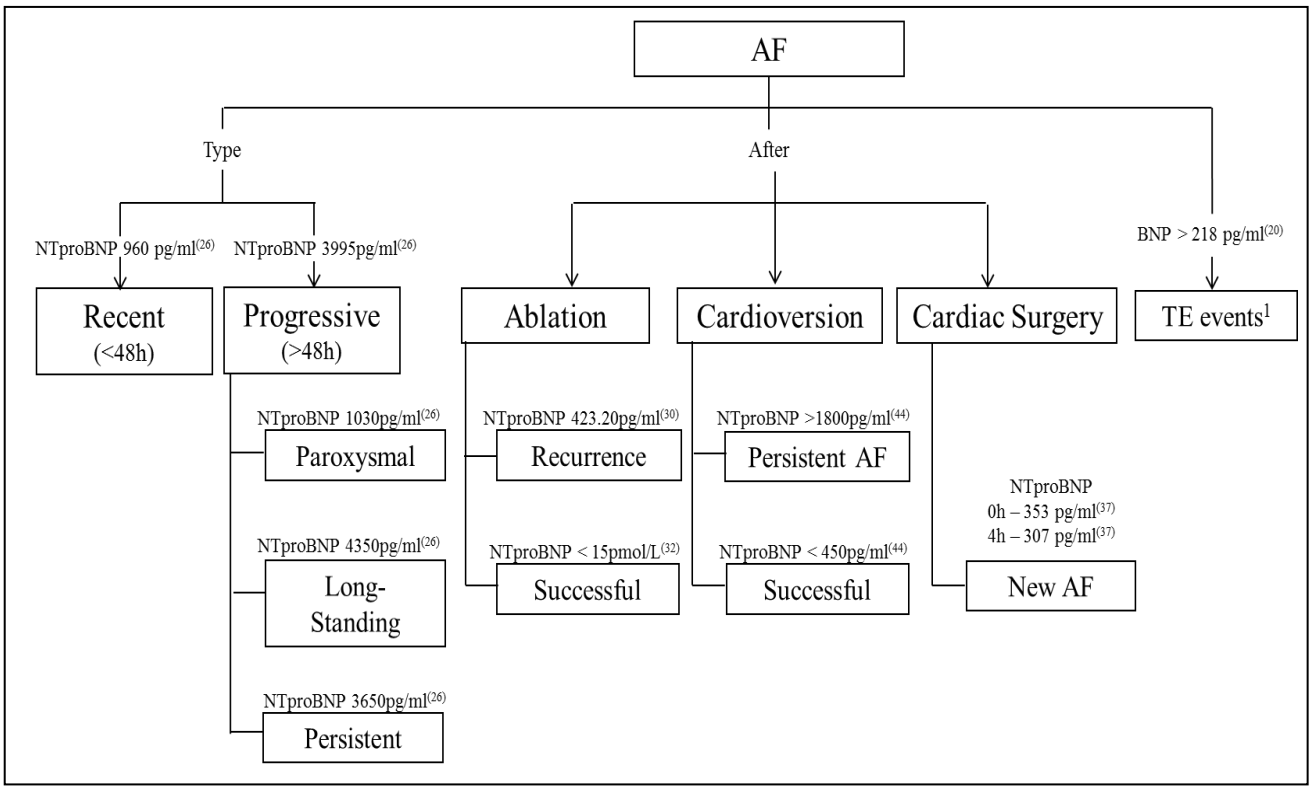

Figure 3: Proposal of a diagnostic approach to the patient with atrial fibrillation according to BNP/NTptoBNP levels. Cutoff values are presented as a form of illustrating possible cutoff values base in presented study results, but an overall flowchart validation is still warranted. AF – Atrial Fibrillation; BNP – brain natriuretic peptide; NTproBNP – N-terminal pro brain natriuretic peptide; TE – tromboembolic events.

[1] with anticoagulant therapy

2.3. Atherosclerotic Disease:

In a case-control study, *Zhou W. et al* analysed 227 pre-dialysis patients with Chronic Kidney Disease (CKD) to relate BNP levels with carotid plaques and atherosclerosis. The study showed higher BNP levels in CKD patients, which were positively related with the intima-media thickness of common carotid artery and left ventricular mass and was significantly higher in patients with carotid plaques [12].

The hormone may have protective effects on the cardiovascular system, and increased BNP concentration may be a response to atherosclerosis in carotid artery stenosis (CAS) patients. This may occur through potent peptide induced inhibition of vascular smooth muscle cell proliferation and generation of Cyclic Guanosine Monophosphate. Relaxation of the atherosclerotic aorta has also been proposed as an adaptive mechanism induced by this peptide [47].

In a recent nonrandomized clinical trial, *Duschek* and co-workers, assessed long term mortality of 205 patients with asymptomatic high-grade internal carotid artery stenosis after carotid endarterectomy using NTproBNP as a stratification tool. They concluded that the increased mortality risk was more pronounced in male patients with higher levels of preoperative NTproBNP. When NTproBNP levels were low, the same survival rate was observed after surgery independently of age [48].

It is thought that the predictive role of this neuropeptide reflects its assessment of cardiac function, namely hemodynamic stress and pressure load, factors that may render patients vulnerable to post-operative events (figure 4) [48].

An experimental study, evaluated 311 patients undergoing coronary angiography to study the relation between BNP levels and the formation of collateral circulation. The authors showed that BNP levels were higher in patients with good collaterals, and suggested that this may be due to potential stimulation of angiogenesis and arteriogenesis [49]. Furthermore,

BNP preconditioning has also been previously shown to decrease myocardial apoptosis induced by ischemia-reperfusion injury [12]. However, the main cause of coronary artery disease (CAD) is atherosclerosis, which also can increase BNP levels, by mechanisms already referred. Therefore, the results may be misinterpreted.

It has also been shown that NTproBNP levels may present minor increases in CAD patients, without myocardial damage, after exercise [4]. This can be explained by the cardiac effort during exercise, with a mismatch in oxygen supply than can cause hemodynamic stress and thereby the release of this neuropeptide.

2.4. Aortic valve stenosis (AVS):

According to *Maréchaux* and colleagues, plasma BNP level reflects LV size, systolic function, disease severity, and NYHA class in patients with AVS. These authors also suggested that, in patients with normal LV ejection fraction, plasma BNP levels predominantly reflect the consequences of the afterload burden faced by the LV rather than the severity of valve stenosis [50]. It is thought that the elevated afterload increases LV systolic wall stress, acting as a stimulus for hypertrophy of myocytes, worsening diastolic dysfunction and increasing the expression of natriuretic peptides. [51].

It has been suggested that higher BNP levels, in conjunction with clinical and echocardiographic parameters, might be important for the risk stratification of patients. Furthermore, preoperative BNP levels can predict the occurrence of perioperative complications, and therefore may be considered when selecting the most adequate patients for surgery [52]. BNP can also be useful after valve replacement, because it correlate the heart function and future postoperative complications, such as, congestive heart failure, renal insufficiency, ischemic stroke, and increased rates of rehospitalisation [52]. Similar results supporting the role of BNP as a predictor of outcome have been presented by *Antonini-*

Canterin et al. (table 1) [53]. The association of elevated BNP levels with a worse outcome, reinforces the need of an early detection and referral of severe aortic stenosis for valve replacement.

2.5. Cardiomyopathy:

2.5.1. Hypertrophic cardiomyopathy(HCM):

Recent studies, have tried to evaluate the prognostic role of BNP/NTproBNP on hypertrophic cardiomyopathy. According to *Kubo T. et al*, BNP levels along with troponin I, are useful for predicting cardiovascular events and clinical deterioration [5]. Patients with higher BNP levels have more dilated left atria, thicker LV walls, higher prevalence of HCM with obstruction and AF. However patients with apical HCM and NYHA functional class I can also present with low BNP values.

In a study by *Kitaoka H. et al*, BNP was associated with the occurrence of cardiovascular events on univariate analysis, but on multivariate logistic regression it was not significantly associated with prognosis, since it did not add predictive information to the variables that were included in the model: high spetal E/e' ratio, history of syncope and documentation of AF [54].

Several mechanisms have been proposed for the release of BNP in this disease: the presence of a dynamic gradient and associated LV dysfunction, either systolic or diastolic, LV hypertrophy and histologic abnormalities that further aggravate diastolic dysfunction and abnormal calcium kinetics and subendocardial ischemia. [54]

2.5.2. Tachycardia-mediated cardiomyopathy (TMC):

In patients with suspected Tachycardia-mediated cardiomyopathy it is necessary to accurately confirm if the tachycardia is the primary cause of the patient's cardiomyopathy, or

if the tachycardia is secondary to a cardiomyopathy of different etiology. Besides, there exists no specific test or exam to elucidate this problem.

Nia and colleagues, in a case-control study, including 40 patients with supraventricular tachycardia (rest heart rate ≥ 100bpm) and a impaired LV ejection fraction (LV ejection fraction < 40%) who underwent successful cardioversion, reported that raised baseline levels of NTproBNP followed by a pronounced decrease in the following weeks favoured the diagnosis of TMC. A ratio of basal to 1-week after cardioversion NTproBNP of ≥2.3 was highly accurate for diagnosing TMC (sensitivity of 84% and specificity of 95%) [55].

It is crucial to quantify NTproBNP levels after cardioversion [55], when compared with structural heart disease. In TMC, the cardioversion eliminates the atrial tachyarrhythmias, during a time period, allowing recovery of LV systolic dysfunction and decrease of NTproBNP levels. Conversely, in patients with structural heart disease, the underlying conditions remain constant leading to less pronounced changes in the peptides.

In the long term, TMC may lead to persistent LV dilatation, diffuse LV fibrosis, and LV systolic dysfunction [56] which may alter the previously suggested interpretation of the evolution of BNP or NTproBNP levels. Despite this limitation, it seems to be an important parameter to differentiate between these two conditions at an early stage (table 1).

2.5.3. Takotsubo cardiomyopathy (TTC):

Fröhlich and co-workers used the ratios of NTproBNP/myoglobin, NTproBNP/troponin T and NTproBNP/creatinekinase-MB to differentiate between TTC (n=39) and ST elevation myocardial infarction (STEMI) (n=48) and with non-ST myocardial infarction (NSTEMI) (n=34). The best differentiation was attained with the ratio of peak levels of NTproBNP/troponin T: a cut-off point of 2889 differentiated TTC from STEMI (sensitivity 91% and specificity 95%) and a ratio of 5000 distinguished TTC from NSTEMI (sensitivity

83% and specificity 95%) [57]. All 3 disease states increase BNP and NTproBNP levels mainly due to myocardial stretch and heart failure (figure 4). However, the severity of myocardial damage can separate the entities since necrosis markers are elevated specially in CAD or other heart diseases causing myocardial necrosis. Contrary to CAD, TTC is characterized by reversible damage without necrosis [57].

Nguyen et al, have also evaluated NTproBNP/BNP levels in 56 patients with TTC that were followed during 3 months. TTC was associated with persistent elevation of NTproBNP levels in the first 24hours after symptom onset, which correlated with the severity of LV systolic dysfunction (assessed by LV ejection fraction and LV wall motion score index). A slow but incomplete resolution during the 3 months thereafter was observed [58].

2.6.Evaluation of surgical patients:

Plasma NTproBNP levels were proven to be useful for assessing pre-operative NYHA and LV ejection fraction and for monitoring haemodynamic status after valve replacement surgery. It has been suggested that an evaluation at 1, 7 and 14 days would be more accurate than a single measurement, since the peak of biomarker occurs at the 7^{th} day and is then followed by a subsequent decrease. [59]. *Scachener* and colleagues evaluated 819 patients undergoing coronary artery bypass grafting and concluded that besides the usually evaluated risk factors, NTproBNP was related to higher mortality and more postoperative complications. The authors observed that a value of NTproBNP greater than 502 ng / ml predicted a higher mid-term mortality and perioperative complications [60].

Similar results were obtained by *Lukasz et al*, who verified that NTproBNP levels can be used to predict postoperative complications in coronary surgery, namely pulmonary outcomes, haemodynamic support and the use of inotropic drugs, length of intensive care unit stay and total hospitalization duration [61].

BNP and NTproBNP have also shown a prognostic role or to be predictors of AF after non-cardiac surgery. In a meta-analysis of 9 studies, *Karthikeyan* and colleagues found that both pre-operative BNP and NTproBNP were powerful and independent predictors of cardiac events within 30 days after non-cardiac surgery [62].

A recent study has shown that BNP might have a role in the screening of patients that might benefit from an echocardiogram before orthopaedic surgery, since elevated BNP levels predicted structural cardiac disease detectable in that examination [63]. Two investigations in the orthopaedic setting [64, 65] confirm the findings of the previously mentioned meta-analysis.

2.7.Kawasaki disease:

BNP plasma levels significantly increase, despite well-preserved global left ventricular function, in Kawasaki disease, namely in the acute phase [66]. The suggested trigger for the release of the neuropeptide in this setting is thought to be coronary artery inflammation.

2.8.Central Sleep Apnea (CSA):

CSA is associated with obstructive sleep apnea syndromes or is caused by an underlying medical condition, namely heart failure (HF). Moreover, the risk of CSA is higher according to the severity of HF. Accordingly, higher levels of BNP are associated with higher risk for CSA in men (table 1) [67]. This association may be triggered by pulmonary congestion, through vagal receptors that lead to intermittent hyperventilation and hypocapnia (figure 4) [68].

2.9. Sepsis:

Both BNP and NTproBNP levels increase alongside with sepsis severity, which is correlated with early systolic dysfunction [4, 69]. Using this marker in early sepsis, it is possible to identify occult systolic dysfunction and provide a chance for timely treatment. Moreover, BNP levels are positively correlated to the risk of mortality, which renders this biomarker a promising prognostic tool for these patients [69]. These neuropeptides may, therefore, used to target patients with higher risk of complications, and who may benefit from a more aggressive treatment (table 1).

4.10.Chronic kidney disease (CKD):

As *Duali S. et al* suggested, in children with CKD, BNP is a powerful tool to predict adverse events related to the progression of disease, namely cardiovascular complications and mortality [70]. However, it is necessary to adjust the threshold in these patients, since renal dysfunction itself can influence these values. NTproBNP and BNP levels were inversely correlated with glomerular filtration rate, and consequently CKD increased the concentrations of both peptides, influencing the cut-off points. Nevertheless, NTproBNP is slightly more influenced than BNP, probably due to the different pathways for clearance: BNP is cleaved by neutral endopeptidase before undergoing renal elimination. NTproBNP does not share this metabolic step and depends more of of renal elimination [3,4].

4.11. Pleural effusions:

Measuring plasma and pleural fluid BNP can help in accurately diagnosing the etiology of pleural effusions. It was reported that a cut-off point of 132pg/ml for plasma BNP (sensitivity 97.1% and specificity 97.4%) and 127pg/ml for pleural fluid BNP (sensitivity

97.1% and specificity 87.8%) was highly suggestive of pleural effusion due to heart failure [71].

4.12. Alcoholism:

Hofer and co-workers evaluated 83 alcohol-dependent patients, with an average consumption of 170 g / day, without cardiac disease or liver disease. Elevated NTproBNP levels on admission were observed in 52% despite a normal LV ejection fraction. This could be explained by either the presence of subclinical cardiac damage not translated in changes of LV ejection fraction (figure 4), adrenergic activation, alterations in volume state due to alcohol intake or interaction in hepatic metabolism of the biomarker [72]. After treatment of alcohol dependence, NTproBNP values decreased despite unchanged LV ejection fraction, establishing a cause-effect relationship between alcohol intake and NTproBNP levels (table 1) [72].

4.13. Chronic Obstructive Pulmonary Disease (COPD):

A prospective study, by *Sanchez*, evaluated 99 patients with an acute exarcebation of chronic obstructive pulmonary disease (COPD) and no history of cardiac disease. They observed that during acute exacerbation of COPD, elevated NTproBNP levels were frequently found and seemed to identify patients at risk of a worse clinical evolution [73].

Gale and colleagues, reported that the NTproBNP was a predictor of survival of these patients. However, NTproBNP values were associated with the length of stay in hospital [74]. *Medina et al* evaluated 192 patients admitted due to acute exacerbations of COPD and measured NTproBNP at 72 hours after admission and 12 months later. NTproBNP levels correlated with the number of hospitalization days and adverse outcomes at 12-months. Values over 587.9pg/ml were associated with a 4-fold higher one year mortality (table 1) [75].

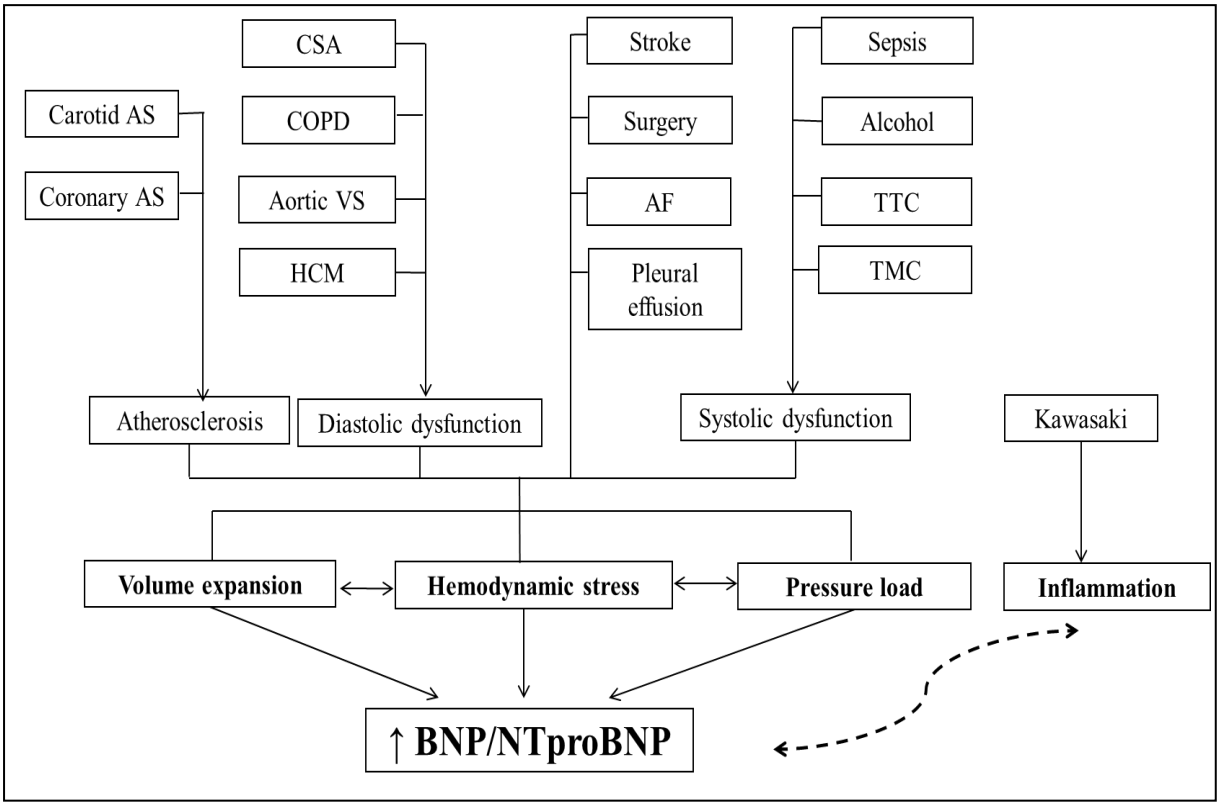

Figure 4 - Discussion of the relationship between different diseases and NTproBNP/BNP. AF – atrial fibrillation; AS – artery stenosis; BNP – brain natriuretic peptide; COPD – chronic obstructive pulmonary disease; CSA – central sleep apnea; HCM – hypertrophic cardiomyopathy; NTproBNP – N-terminal pro brain natriuretic peptide; TMC – tachycardia-mediated cardiomyopathy; TTC - takotsubo cardiomyopathy.

Table 1 – Key ideas about role of BNP/NTproBNP in diverse diseases.

Disease	BNP	NTproBNP	Role	Ref.
Ischemic Stroke	↑↑	↑	- BNP: Elevated in Stroke and TIA; - Predictor of CE stroke; - Higher in patients without angiographic vasospasm; - NTproBNP: Alongside with the NIHHS scale allows risk stratification and prognostication of patients; - Predictor of CE stroke;	1,6, 8-14
Atrial Fibrillation	↑	↑↑	- BNP: Predictor of LAA dysfunction and LA thrombus; - Predictor of AF incidence after stroke; - Predictor of thromboembolic events (under anticoagulant therapy); - Predictor of AF recurrence after cardiac surgery and cardioversion; - NTproBNP: Predictor of AF incidence or AF type; - Predictor of AF duration; - Predictor of stroke and mortality rate; - Predictor of AF recurrence after ablation, cardiac and non-cardiac surgery[a] and cardioversion;	6, 14-45
Atherosclerotic Disease	↑	↑	Carotid Artery Stenosis - BNP is correlated with atherosclerosis; - Higher NTproBNP levels associated with long term mortality; - Low levels identify patients with low surgical risk, even among elderly. Coronary Artery Disease - Patients with good collaterals have higher BNP level; - NTproBNP may increase after exercise.	4, 12, 46-48
Aortic valve stenosis	↑		- Plasma BNP level reflects LV size, systolic function, disease severity, and NYHA class; - Higher levels associate more with LV afterload than with stenosis severity; - Risk stratification after valve replacement.	49-52
Hypertrophic cardiomyopathy	↑		- BNP alongside with other markers (troponin I) can predict progression of disease, but not when isolated; - Predict cardiovascular events.	5, 53
Tachycardia-mediated cardiomyopathy		↑	- Early diagnosis of TMC before and after cardioversion; - Differentiate from structural heart disease.	54, 55
Takotsubo cardiomyopathy	↑	↑	- Aid in distinguishing TTC from acute coronary syndrome (associated with necrosis markers); - TTC is correlated with the severity of LV systolic dysfunction.	56, 57
Evaluation of surgical patients	↑	↑	- BNP: Risk of perioperative event and cardiac mortality, in patients undergoing major non-cardiac surgery; - NTproBNP: Useful for assessing cardiac function and post operative dynamics in valve replacement and coronary surgery; - Predict postoperative complications (e.g. pulmonary outcomes, need of haemodynamic support);	58-65
Kawasaki disease	↑		-In the acute phase, BNP levels increase, despite well-preserved global LV function;	66
CSA	↑		-Risk of CSA is related to higher concentrations of BNP levels;	67, 68
Sepsis	↑	↑	- BNP/NTproBNP levels are associated with sepsis severity; - Higher BNP levels are correlated with higher levels of mortality;	4, 69
CKD	↑	↑	-BNP is useful to predict adverse events and mortality in patients with CKD[b];	3, 4, 12, 70
Pleural effusions	↑		-Plasma and pleural fluid BNP can aid in the diagnosis of pleural effusions due to heart failure;	71
Alcoholism		↑	-Alcohol consumption leads to an increase of NTproBNP, independent of ejection fraction; -After treatment of alcohol dependence, NTproBNP values decreased despite ejection fraction remain constants;	72
COPD		↑	-NTproBNP is a prognostic factor in acute exacerbation; - Associated with hospital stay; - Lower NTproBNP levels are correlated with best prognostic in a year.	73-75

Legend: AF – atrial fibrillation; BNP – brain natriuretic peptide; CAD – coronary artery disease; CE – cardioembolic; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; CSA – central sleep apnea; ; ICU – intensive care unit; NIHSS - National Institutes of Health Stroke Scale; NTproBNP – N-terminal pro brain natriuretic peptide; LAA - left atrial appendage; LV – left ventricle; TIA – transient ischemic attack; TMC – tachycardia-mediated cardiomyopathy; TTC – takotsubo cardiomyopathy.

[a] lung and esophageal surgery.

[b] Both peptides are affected to renal clearance, especially NTproBNP, and their cut-off points must be adjusted to other pathologies, when simultaneous with CKD.

Conclusion

The purpose of this study was to assess the usefulness of BNP/NTproBNP levels among different diseases beyond heart failure. Both peptides levels have been correlated with several diseases, which may affected their release to the bloodstream and eliminations. Therefore, it is crucial to be aware of these interferences, in order to achieve and adjust optimal cut-off points to each disease.

In disease states other than heart failure, BNP and NTproBNP are reliable biomarkers to detect early stages and for the evaluation of severity as prognosis.

Further studies are needed to better define the clinical applications of BNP and NTproBNP, to evaluate the relevance of serial assessment for optimal clinical decision. Due to the variety of existing laboratory tests and reference values, external validation of results may be an issue to deal before implementing decision trees based on peptide levels.

References

1. Berrocoso TG, Cadenas IF, Delgado P, Rosell A, Montaner J. Blood Biomarkers in Cardioembolic Stroke. *Curr Cardiol Rev.* 2010; 6:194-201

2. Ganem F, Serrano CV, Fernandes JL, Blotta MHSL, Souza JA, Nicolau JC, Ramires JAF, Hueb WA. Preoperative B-type natriuretic peptide, and not the inflammation status, predicts an adverse outcome for patients undergoing heart surgery. *Interact Cardiovasc Thorac Surg.* 2011;12(5):778-83.

3. Gobeaux CC, Claessens YE, Voyer S, Desmoulins D, Ekindjian OGJC. Influence of renal function on N-terminal pro-brain natriuretic peptide (NTproBNP) in patients admitted for dyspnea in the Emergency Department: Comparison with brain natriurectis peptide (BNP). *Clinica Chimica Acta*. 2005; 361:167-175.

4. Steiner J, Guglin M. BNP or NTproBNP? A clinician's perspective. *International Journal of Cardiology* 2008;129:5-14.

5. Kubo T, Kitaoka H, Okawa M, Yamanaka S, Hirota T, Baba Y, Hayato K, Yamasaki N, Matsumura Y, Yasuda N, Sugiura T, Doi YL. Combined Measurements of Cardiac Troponin I and Brain Natriuretic Peptide Are Useful for Predicting Adverse Outcomes in Hypertrofic Cardiomyopathy. *Cir J* 2011; 919-926.

6. Tamura H, Watanabe T, Nishiyama S, Sasaki S, Wanezaki M, Arimoto T, Takahashi H, Shishido T, Miyashita T, Miyamoto T, Hirono O, Kayama T, Kubota I. Elevated plasma brain natriuretic peptide levels predict left atrial appendage dysfunction in patients with acute ischemic stroke. *J Cardiol.* 2012.

7. Balion CM, Santaguida P, McKelvie R, Hill SA, McQueen MJ, Worster A, Raina PS. Physiological, pathological, pharmacological, biochemical and hematological factors affecting BNP and NTproBNP. *Clinical Biochemistry.* 2008; 41:231-239.

8. Shibazaki K, Kimura K, Iguchi Y, Aoki J, Sakai K, Kobayashi K. Differences in brain natriuretic peptide value between transient ischemic attack and stroke patients with atrial fibrillation. *Eur Neurol.* 2011;66(5):271-6

9. Montaner J, Perea-Gainza M, Delgado P, Ribó M, Chacón P, Rosell A, Quintana M, Palacios ME, Molina CA, Alvarez-Sabín J. Etiologic diagnosis of ischemic stroke subtypes with plasma biomarkers. Stroke. 2008;39(8):2280-7.

10. Santamarina E, Penalba A, García-Berrocoso T, Delgado P, Quintana M, González-Alujas T, Ribó M, Maisterra O, Molina CA, Evangelista A, Alvarez-Sabín J, Montaner J. Biomarker level improves the diagnosis of embolic source in ischemic stroke of unknown origin. *J Neurol.* 2012; 259

11. Fonseca AC, Matias JS, Pinho e Melo T, Falcão F, Canhão P, Ferro JM. N-terminal probrain natriuretic peptide as a biomarker of cardioembolic stroke. Int J Stroke. 2011;6(5):398-403.

12. Zhou W, Ni Z, Yu Z, Shi B, Wang Q, Divisio R. Brain natriuretic peptide is related to carotid plaques and predicts atherosclerosis in pre-dialysis patients with chronic kidney disease. *European Journal of Internal Medicine*. 2012; 23(6):539–544.

13. Chen X, Zhan X, Chen M, Lei H, Wang Y, Wei D, Jiang X. The Prognostic Value of Combined NT-pro-BNP Levels and NIHSS Scores in Patients with Acute Ischemic Stroke. *Intern Med.* 2012;51(20):2887-92.

14. Taub PR, Fields JD, Wu AH, Miss JC, Lawton MT, Smith WS, Young WL, Zaroff JG, Ko NU. Elevated BNP is associated with vasospasm-independent cerebral infarction following aneurysmal subarachnoid hemorrhage. *Neurocrit Care.* 2011;15(1):13-8.

15. Shimizu H, Murakami Y, Inoue S, Ohta Y, Nakamura K, Katoh H, Sakne T, Takahashi N, Ohata S, Sugamori T, Ishibashi Y, Shimada T (2002) High plasma brain natriuretic polypeptide level as a marker of risk for thromboembolism in patients with nonvalvular atrial fibrillation. Stroke. 33(4):1005-10.

16. Okada Y, Shibazaki K, Kimura K, Matsumoto N, Iguchi Y, Aoki J, Kobayashi K, Sakai K. Brain natriuretic peptide is a marker associated with thrombus in stroke patients with atrial fibrillation. Journal of the Neurological Sciences. 2011;301(1–2):86–89.

17. Shibazaki K, Kimura K, Fujii S, Sakai K, Iguchi Y. Brain natriuretic Peptide levels as a predictor for new atrial fibrillation during hospitalization in patients with acute ischemic stroke. *Am J Cardiol.* 2012;109(9):1303-7.

18. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, Reilly PA, Vinereanu D, Siegbahn A, Yusuf S, Wallentin L. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. *Circulation.* 2012;125(13):1605-16.

19. Kurl S, Ala-Kopsala M, Ruskoaho H, Mäkikallio T, Nyyssönen K, Vuolteenaho O, Sivenius J, Salonen JT, Laukkanen JA. Plasma N-terminal fragments of natriuretic peptides predict the risk of stroke and atrial fibrillation in men. *Heart.* 2009 ;95(13):1067-71.

20. Sadanaga T, Kohsaka S, Mitamura H, Ogawa S. Elevated B-type natriuretic peptide level as a marker of subsequent thromboembolic events in patients with atrial fibrillation. *Heart Vessels.* 2011;26(5):530-5.

21. Bai M, Yang J, Li Y. Serum N-terminal-pro-brain natriuretic peptide level and its clinical implications in patients with atrial fibrillation. *Clin Cardiol.* 2009 ;32(12):E1-5.

22. Patton KK, Ellinor PT, Heckbert SR, Christenson RH, DeFilippi C, Gottdiener JS, Kronmal RA. N-terminal pro-B-type natriuretic peptide is a major predictor of the development of atrial fibrillation: the Cardiovascular Health Study. *Circulation.* 2009 ;120(18):1768-74.

23. Asselbergs FW, van den Berg MP, Bakker SJ, Signorovitch JE, Hillege HL, van Gilst WH, van Veldhuisen DJ. N-terminal pro B-type natriuretic peptide levels predict newly detected atrial fibrillation in a population-based cohort. *Neth Heart J.* 2008;16(3):73-8.

24. Smith JG, Newton-Cheh C, Almgren P, Struck J, Morgenthaler NG, Bergmann A, Platonov PG, Hedblad B, Engström G, Wang TJ, Melander O. Assessment of conventional cardiovascular risk factors and multiple biomarkers for the prediction of incident heart failure and atrial fibrillation. *J Am Coll Cardiol.* 2010;56(21):1712-9.

25. Sahin T, Acar E, Celikyurt U, Killic T, Kozdag G, Yilmaz I, Agacdiken A, Ural D. Relation of hs-CRP and BNP levels with the atrial spontaneous echo contrast and thrombi in permanent atrial fibrillation patients with different etiologies. *Med Sci Monit*. 2012;18(2):CR78-87.

26. Meune C, Wahbi K, Vermillet A, Guerin S, Aelion H, Weber S, Chenevier-Gobeaux C. N-Terminal-proBrain natriuretic peptide measurement at presentation to identify patients with recent onset of atrial fibrillation. *Int J Cardiol.* 2012;154(2):208-9.

27. Deftereos S, Giannopoulos G, Kossyvakis C, Raisakis K, Theodorakis A, Kaoukis A, Toli K, Panagopoulou V, Driva M, Mantas I, Pyrgakis V, Alpert MA. Short-term fluctuations of plasma NTproBNP levels in patients with new-onset atrial fibrillation: a way to assess time of onset? *Heart.* 2010;96(13):1033-6.

28. Deftereos S, Giannopoulos G, Kossyvakis C, Raisakis K, Kaoukis A, Aggeli C, Toli K, Theodorakis A, Panagopoulou V, Driva M, Mantas I, Pyrgakis V, Rentoukas I, Stefanadis C. Estimation of atrial fibrillation recency of onset and safety of cardioversion using NTproBNP levels in patients with unknown time of onset. *Heart.* 2011;97(11):914-7.

29. Doğan A, Gedikli O, Ozaydin M, Acar G. Plasma renin activity and pro-B-type natriuretic peptide levels in different atrial fibrillation types. *Anadolu Kardiyol Derg.* 2010;10(4):317-22.

30. Fan J, Cao H, Su L, Ling Z, Liu Z, Lan X, Xu Y, Chen W, Yin Y. NTproBNP, but not ANP and C-reactive protein, is predictive of paroxysmal atrial fibrillation in patients undergoing pulmonary vein isolation. *J Interv Card Electrophysiol.* 2012;33(1):93-100.

31. Den Uijl DW, Delgado V, Tops LF, Ng AC, Boersma E, Trines SA, Zeppenfeld K, Schalij MJ, van der Laarse A, Bax JJ. Natriuretic peptide levels predict recurrence of atrial fibrillation after radiofrequency catheter ablation. *Am Heart J.* 2011 ;161(1):197-203.

32. Nilsson B, Goetze JP, Chen X, Pehrson S, Svendsen JH. Increased NT-pro-B-type natriuretic peptide independently predicts outcome following catheter ablation of atrial fibrillation. *Scand J Clin Lab Invest.* 2009;69(8):843-50.

33. Iskesen I, Eserdag M, Kurdal AT, Cerrahoglu M, Sirin BH. Preoperative NTproBNP levels: a reliable parameter to estimate postoperative atrial fibrillation in coronary artery bypass patients.*Thorac Cardiovasc Surg*. 2011;59(4):213-6.

34. Gasparovic H, Burcar I, Kopjar T, Vojkovic J, Gabelica R, Biocina B, Jelic I. NT-pro-BNP, but not C-reactive protein, is predictive of atrial fibrillation in patients undergoing coronary artery bypass surgery. *Eur J Cardiothorac Surg.* 2010 ;37(1):100-5.

35. Gibson PH, Croal BL, Cuthbertson BH, Rae D, McNeilly JD, Gibson G, Jeffrey RR, Buchan KG, El-Shafei H, Hillis GS. Use of preoperative natriuretic peptides and echocardiographic parameters in predicting new-onsetatrial fibrillation after coronary artery bypass grafting: a prospective comparative study. *Am Heart J.* 2009;158(2):244-51.

36. Dogan SM, Buyukates M, Kandemir O, Aydin M, Gursurer M, Acikgoz S, Yavuzer R, Cam F, Dursun A. Predictors of atrial fibrillation after coronary artery bypass surgery. *Coron Artery Dis*. 2007;18(5):327-31.

37. Samy K, Anouar J, Mnif E, Imed F, Fatma A, Abdelhamid K. N-terminal pro-brain natriuretic peptide identifies patients at risk for occurence of postoperative atrial fibrillation in cardiac surgery with cardiopulmonary bypass. *Ann Card Anaesth.* 2012;15(3):199-205.

38. Gurgo AM, Ciccone AM, D'Andrilli A, Ibrahim M, Musumeci B, Quarta G, Saponaro A, Rendina EA, Volpe M. Plasma NTproBNP levels and the risk of atrial fibrillation after major lung resection. *Minerva Cardioangiol.* 2008;56(6):581-5.

39. Hou JL, Gao K, Li M, Ma JY, Shi YK, Wang Y, Zhao YF. Increased N-terminal pro-brain natriuretic peptide level predicts atrial fibrillation after surgery for esophageal carcinoma. *World J Gastroenterol.* 2008;14(16):2582-5.

40. Salvatici M, Cardinale D, Spaggiari L, Veglia F, Tedesco CC, Solli P, Cipolla CM, Zorzino L, Passerini R, Riggio D, Cassatella MC, Sandri MT. Atrial fibrillation after thoracic surgery for lung cancer: use of a single cut-off value of N-terminal pro-B type natriuretic peptide to identify patients at risk. *Biomarkers.* 2010;15(3):259-65.

41. Freynhofer MK, Jarai R, Höchtl T, Bruno V, Vogel B, Aydinkoc K, Nürnberg M, Wojta J, Huber K. Predictive value of plasma NTproBNP and body mass index for recurrence of atrial fibrillation after cardioversion. *Int J Cardiol.* 2011;149(2):257-9.

42. Psychari SN, Chatzopoulos D, Iliodromitis EK, Apostolou TS, Kremastinos DT. C-reactive protein, interleukin 6, and N-terminal pro-brain natriuretic peptide following cardioversion of atrial fibrillation: is there a role of biomarkers in arrhythmia recurrence? *Angiology.* 2011;62(4):310-6.

43. Wozakowska-Kapłon B, Bartkowiak R, Grabowska U, Janiszewska G. B-type natriuretic peptide level after sinus rhythm restoration in patients with persistent atrial fibrillation - clinical significance. *Kardiol Pol.* 2010;68(7):781-6.

44. Buccelletti F, Gilardi E, Marsiliani D, Carroccia A, Silveri NG, Franceschi F. Predictive value of NTproBNP for cardioversion in a new onset atrial fibrillation. *Eur J Emerg Med.* 2011;18(3):157-61.

45. Beck-da-Silva L, de Bold A, Fraser M, Williams K, Haddad H. Brain natriuretic peptide predicts successful cardioversion in patients with atrial fibrillation and maintenance of sinus rhythm. Can J Cardiol 2004;20:1245–8.

46. Lellouche N, Berthier R, Mekontso-Dessap A, et al. Usefulness of plasma B-type natriuretic peptide in predicting recurrence of atrial fibrillation one year after external cardioversion. Am J Cardiol 2005;95:1380–2.

47. Schirger J, Grantham JA, Kullo IJ, Jougasaki M, Wennberg PW, Chen HH, Lisy O, MillerV, Simari R, Burnett JC. Vascular actions of brain natriuretic peptide: modulation by atherosclerosis and neutral endopeptidase inhibition. *Journal of the American College of Cardiology*. 2000; 35(3):796–801.

48. Duschek N, Skrinjar E, Waldhör T, Vutuc C, Daniel G, Hübl W, Assadian A. N-terminal pro B-type natriuretic peptide (NT pro-BNP) is a predictor of long-term survival in male patients of 75 years and older with high-grade asymptomatic internal carotid artery stenosis. *J Vasc Surg.* 2011;53(5):1242-50.

49. Xi WW, Cheng G, Lv S, Gao Q, Bu G, Zhou Y, Xu G. An elevated level of BNP in plasma is related to the development of good collateral circulation in coronary artery disease. *Eur J Cardiovasc Prev Rehabil*. 2011;18(6):797-802.

50. Maréchaux S, Hattabi M, Juthier F, Neicu DV, Richardson M, Carpentier E, Bouabdallaoui N, Delelis F, Banfi C, Breyne J, Jude B, Asseman P, Vincentelli A, Le Tourneau T, Graux P, Pibarot P, Ennezat PV. Clinical and echocardiographic correlates of plasma B-type natriuretic peptide levels in patients with aortic valve stenosis and normal left ventricular ejection fraction. *Echocardiography.* 2011;28(7):695-702.

51. Pibarot P, Dumesnil JG. Improving Assessment of Aortic Stenosis. *Journal of the American College of Cardiology.* 2012; 60(3):169–180.

52. Iwahashi N, Nakatani S, Umemura S, Kimura K, Kitakaze M. Usefulness of Plasma B-Type Natriuretic Peptide in the Assessment of Disease Severity and Prediction of Outcome after Aortic Valve Replacement in Patients with Severe Aortic Stenosis. *Journal of the American Society of Echocardiography.* 2011; 24(9):984–99.

53. Canterina FA, Popescu BA, Beladan CC, Korcovaa R, Piazzaa R, Cappellettia P, Rubina D, Cassin M, Faggiano P, Nicolosi GL. Heart failure in patients with aortic stenosis: Clinical and prognostic significance of carbohydrate antigen 125 and brain natriuretic peptide measurement. *International Journal of Cardiology.* 2008; 128(3):406–412.

54. Kitaoka H, Kubo T, Okawa M, Takenaka N, Sakamoto C, Baba Y, Hayashi K, Yamasaki N, Matsumura Y, Doi YL. Tissue doppler imaging and plasma BNP levels to assess the prognosis in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr*. 2011;24(9):1020-5.

55. Nia AM, Gassanov N, Dahlem KM, Caglayan E, Hellmich M, Erdmann E, Er F. Diagnostic accuracy of NTproBNP ratio (BNP-R) for early diagnosis of tachycardia-mediated cardiomyopathy: a pilot study. *Clin Res Cardiol*. 2011;100(10):887-96.

56. Ling L, Kistler P, Medi C, Ellims A, Iles L, The A, Lee G, Sherratt C, Kaye D, Kalman J, Taylor A. Magnetic Resonance Imaging Identifies Persistent Left Ventricular Dilatation and Diffuse Fibrosis Long After Functional Recovery in Tachycardia-MediatedCardiomyopathy: A Five-Year Follow-up Study. *Heart, Lung and Circulation.* 2012; 21(1): S131.

57. Fröhlich GM, Schoch B, Schmid F, Keller P, Sudano I, Lüscher TF, Noll G, Ruschitzka F, Enseleit F. Takotsubo cardiomyopathy has a unique cardiac biomarker profile: NTproBNP/myoglobin and NTproBNP/troponin T ratios for the differential diagnosis of acute coronary syndromes and stress induced cardiomyopathy. *International Journal of Cardiology*. 2012;154(3): 328–332.

58. Nguyen TH, Neil CJ, Sverdlov AL, Mahadavan G, Chirkov YY, Kucia AM, Stansborough J, Beltrame JF, Selvanayagam JB, Zeitz CJ, Struthers AD, Frenneaux MP, Horowitz JD. N-terminal pro-brain natriuretic protein levels in takotsubo cardiomyopathy. *Am J Cardiol.* 2011;108(9):1316-21.

59. Cai B, Wang L, Liu J, Shi Y, Guo Y. N-terminal pro-Brain natriuretic peptide as a useful biomarker for monitoring prognosis in patients with cardiac valve replacement. J Clin Lab Anal. 2011;25(3):149-55.

60. Schachner T, Wiedemann D, Fetz H, Laufer G, Kocher A, Bonaros N. Influence of preoperative serum N-terminal pro-brain type natriuretic peptide on the postoperative outcome and survival rates of coronary artery bypass patients. *Clinics (Sao Paulo).* 2010;65(12):1239-45.

61. Krzych ŁJ, Szurlej D, Kołodziej T, Machej L, Węglarzy A, Błach A, Wilczyński M, Woś S, Bochenek A. Diagnostic accuracy of pre-operative NTproBNP level in predicting short-term outcomes in coronary surgery: a pilot study. *Kardiol Pol.* 2011;69(11):1121-7

62. Karthikeyan G, Moncur RA, Levine O, Heels-Ansdell D, Chan MT, Alonso-Coello P, Yusuf S, Sessler D, Villar JC, Berwanger O, McQueen M, Mathew A, Hill S, Gibson S, Berry C, Yeh HM, Devereaux PJ. Is a pre-operative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. *J Am Coll Cardiol.* 2009 20;54(17):1599-606.

63. Flourya SP, Gineta M, Sauniera L, Bescha G, Bartholina F, Chopardc R, Boillota A, Mebazaae A, Samaina E. Preoperative plasma B-type natriuretic peptide (BNP) identifies abnormal transthoracic echocardiography in elderly patients with traumatic hip fracture. *Injury.* 2012; 43(6): 811–816.

64. Chong CP, Lim WK, Velkoska E, van Gaal WJ, Ryan JE, Savige J, Burrell LM. N-terminal pro-brain natriuretic peptide and angiotensin-converting enzyme-2 levels and their association with postoperative cardiac complications after emergency orthopedic surgery. *Am J Cardiol.* 2012;109(9):1365-73.

65. Chong CP, Ryan JE, van Gaal WJ, Lam QT, Sinnappu RN, Burrell LM, Savige J, Lim WK. Usefulness of N-terminal pro-brain natriuretic peptide to predict postoperative cardiac complications and long-term mortality after emergency lower limb orthopedic surgery. *Am J Cardiol.* 2010;106(6):865-72.

66. Kishimoto S, Suda K, Teramachi Y, Nishino H, Kudo Y, Ishii H, Iemura M, Takahashi T, Okamura H, Matsuishi T. Increased plasma type B natriuretic peptide in the acute phase of Kawasaki disease. *Pediatr Int.* 2011;53(5):736-41.

67. Calvin AD, Somers VK, van der Walt C, Scott CG, Olson LJ. Relation of natriuretic peptide concentrations to central sleep apnea in patients with heart failure. *Chest.* 2011;140(6):1517-23.

68. Carnevalea C, Georgesc M, Rabecc C, Tamisiera R, Levya P, Pépina JL. Effectiveness of Adaptive Servo Ventilation in the treatment of hypocapnic centralsleepapnea of various etiologies. *Sleep Medicine*. 2011; 12(10): 952–958.

69. Turner KL, Moore LJ, Todd SR, Sucher JF, Jones SA, McKinley BA, Valdivia A, Sailors RM, Moore FA. Identification of cardiac dysfunction in sepsis with B-type natriuretic peptide. *J Am Coll Surg.* 2011 ;213(1):139-46.

70. Ouali S, Bougmiza I, Abroug S, Omezzine A, Ben Salem H, Neffeti E, Remedi F, Bouslema A, Harabi A, Boughzela E. Relationship of brain natriuretic peptide concentrations to left ventricular function and adverse outcomes in children with end-stage renal disease undergoing hemodialysis. *Pediatr Cardiol.* 2011;32(5):568-77.

71. Marinho FC, Vargas FS, Fabri J Jr, Acencio MM, Genofre EH, Antonangelo L, Sales RK, Teixeira LR. Clinical usefulness of B-type natriuretic peptide in the diagnosis of pleural effusions due to heart failure. *Respirology*. 2011;16(3):495-9.

72. Höfer P, Syeda B, Bergler-Klein J, Friedrich F, Lesch OM, Vyssoki B, Binder T, Walter H. Amino-terminal pro-B-type brain natriuretic peptide: screening for cardiovascular disease in the setting of alcoholism. *Alcohol Alcohol*. 2011;46(3):247-52.

73. Sánchez-Marteles M, Cecilio-Irazola A, Vañó-Sanchis D, Nuviala-Mateo R, Serrano-Martínez S, Pérez-Calvo JJ. NTproBNP in chronic obstructive pulmonary disease patients. *An Sist Sanit Navar.* 2009;32(2):235-41.

74. Gale CP, White JE, Hunter A, Owen J, Allen J, Watson J, Holbrook I, Durham NP, Pye MP. Predicting mortality and hospital admission in patients with COPD: significance of NT pro-BNP, clinical and echocardiographic assessment. *J Cardiovasc Med (Hagerstown).* 2011;12(9):613-8.

75. Medina AM, Marteles MS, Sáiz EB, Martínez SS, Laiglesia FR, Rodríguez JA, Pérez-Calvo JI. Prognostic utility of NTproBNP in acute exacerbations of chronic pulmonary diseases. *Eur J Intern Med.* 2011;22(2):167-71.