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Natriuretic Peptides in Severe Aortic Stenosis - Role in Predicting Outcomes and Assessment for Early Aortic Valve Replacement

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1. Introduction

The natriuretic peptides are a group of endogenous, structurally related hormones with natriuretic, diuretic and peripheral vasodilatory actions. (Hunt, 1997; Yandle, 1986; Yandle, 1993) They serve an important regulatory role in response to acute increases in ventricular wall stress. A large number of cardiac conditions may cause an elevation of plasma levels of natriuretic peptides. Clinically, natriuretic peptides are of value in ruling out heart failure in patients presenting acutely to the emergency department with dyspnoea. (Maisel et al., 2002). Natriuretic peptides could also be useful in evaluating the severity and prognosis of patients with aortic stenosis (AS). Severe AS causes an increase in afterload and end-systolic left ventricular (LV) wall stress that, over time, leads to concentric myocardial hypertrophy. (Wachtell, 2008) This anatomical change of the LV is characterized at the molecular level by the re-expression of fetal isogenes, including increased gene expression of natriuretic peptides in the ventricular cardiomyocytes. (Sadoshima, 1992; Cameron, 1996)
This chapter reviews the existing data on natriuretic peptide measurement in AS, to summarize how these biomarkers can be utilized in clinical practice, and to explore their therapeutic implication concerning the optimal timing of aortic valve replacement in the setting of severe AS.

2. Management of severe Aortic Stenosis

2.1 Difficulty in determining the timing of valvular surgery

AS is a slowly progressive disease and current guidelines recommend that surgery is delayed until symptoms develop or LV function decreases. (Bonow et al., 2006) Initial symptoms experienced by patients with AS are often subtle and insidious and can be difficult to evaluate clinically. However, once significant symptoms develop, there is a dramatic change in patients' outlook with a reported average survival on medical therapy of less than 3 years. (Ross Jr, 1968; Frank, 1973) The risk of rapid clinical deterioration and poorer prognosis after symptom onset in some AS patients emphasizes the importance of early and accurate detection of AS related symptoms and timely referral for valvular surgery to avoid adverse cardiovascular outcomes in these patients.

Echocardiography is currently the gold standard for the non-invasive assessment of AS. The most widely used echocardiographic measures of AS severity in clinical practice are peak aortic velocity and aortic valve area determined by the continuity equation. (Otto, 1998) However, according to the current American College of Cardiology/American Heart Association guidelines, there is no single clinical, haemodynamic, or echocardiographic measure that has been adopted as a class I recommendation for valve replacement in the absence of symptoms in patients with isolated AS. (Bonow et al., 2006) This is because of the wide overlaps in haemodynamic and echocardiographic measures of severity between the symptomatic and asymptomatic patients, consistent with the known heterogeneous response to the pressure load of AS. (Otto, 2000)

There is also the problem of evaluating symptoms. Patients may not realize gradual onset of symptoms is due to disease progression. Also some patients may be unable to exercise because of non-cardiac comorbidities, or do not develop the classic symptoms of AS. This makes the determination of the optimal timing of aortic valve replacement (AVR) more challenging.

There is reluctance to perform surgery earlier than necessary because of a mortality rate for aortic valve surgery of approximately 3% to 5%, even in patients younger than 70 years, (Edwards et al., 2001) and prosthetic valve-related long-term morbidity. Conversely, patients who become symptomatic are at significant risk of developing adverse cardiac events while waiting for surgery, and peri-operative risk increases significantly with the severity of symptoms. (Rosenhek et al., 2002) These factors contribute to the controversy on the optimal timing of AVR in asymptomatic severe AS, because the risk of potential adverse cardiac complications from AS must be weighed against the risk of surgery in truly asymptomatic patients.

A non-invasive marker of early cardiac decompensation could be useful to risk stratify asymptomatic AS patients into those likely to derive benefit from surgery before the development of symptoms or irreversible LV impairment, from those who have a low risk of adverse events during follow-up.

2.2 Non-invasive biomarkers

Cardiac biomarkers are one solution to this dilemma. In recent years, biomarkers have become important tools for diagnosis, risk stratification and therapeutic decision making in cardiovascular diseases. To serve as markers of cardiac function, the biomarkers need to predict clinical and echocardiographic progression of disease. Echocardiographic assessment of AS requires trained and experienced sonographers with meticulous attention to the technical details of imaging and Doppler flow recording and accurate interpretation of findings. In contrast the introduction of fully automated assays with proven excellent test precision means that measurement of plasma levels of biomarkers is simple, reliable, not operator-dependent, relatively inexpensive, and reproducible.

Several biomarkers have been studied for this purpose. They include atrial natriuretic peptide (also known A-type natriuretic peptide, or ANP), brain natriuretic peptide (also known as B-type natriuretic peptide, or BNP), N-terminal BNP (the amino terminal part of BNP, or NT-BNP), N-terminal-proBNP (the amino terminal part of the BNP prohormone, or NT-proBNP), urodilatin, cardiotrophin-1, tumour necrosis factor-a (TNF-a) and TNF receptors 1 and 2. Of these the natriuretic peptides BNP and NT-proBNP predict adverse outcomes across a broad range of cardiac diseases in a great number of different clinical settings.

2.3 Natriuretic peptides

BNP was initially identified and described in 1988 after isolation from porcine brain. It was later recognised that BNP is predominately synthesized and secreted from the LV in response to increased ventricular wall stress. In the setting of volume and pressure overload, the increased wall stress initiates synthesis of the prehormone, pre-proBNP which is cleaved first to pro-BNP, then to the biologically active BNP and the inactive NT-proBNP fragments upon release into the circulation (Figure 1 and 2).

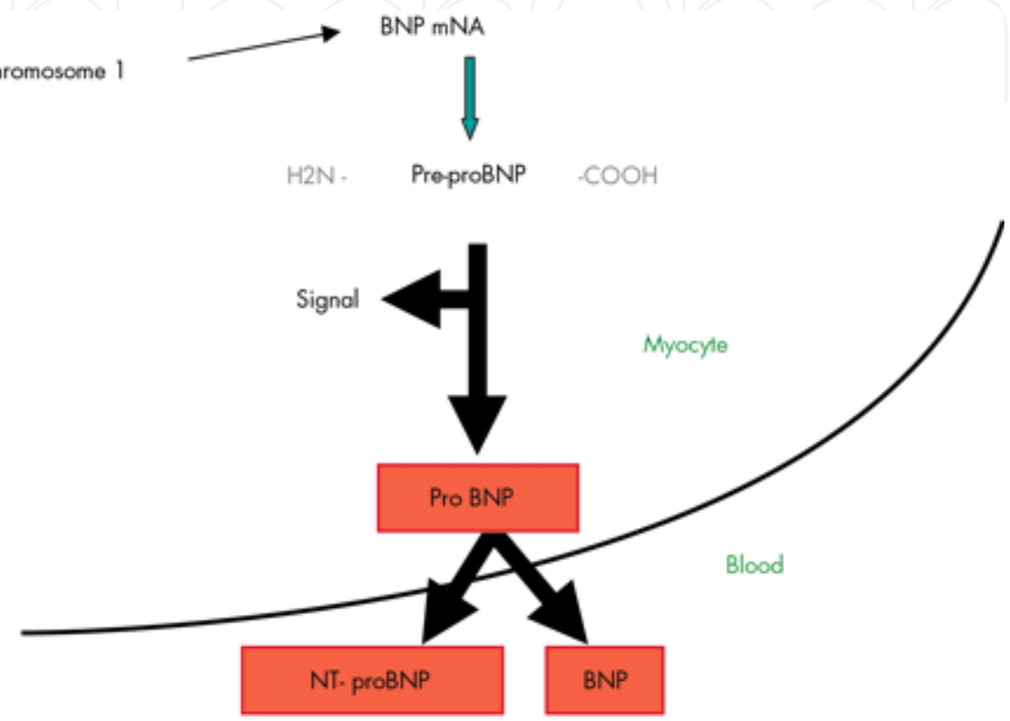


Fig. 1. Synthesis and secretion of B-type natriuretic peptide. (adapted from Bettencourt et al., 2005)

In contrast to BNP, ANP which is stored in granules within the atria and is released immediately after atrial stretch. (Yasue et al., 1994) Only small amounts of BNP are stored in granules. Rapid gene expression with de novo synthesis seems to be the underlying mechanism for the regulation of BNP secretion. (Yoshimura et al., 1993) However, the exact signalling pathways of natriuretic peptide secretion remain poorly defined. During the development of LV hypertrophy, gradual disappearance of natriuretic peptide clearance receptor mRNA had been found in the rat heart (Brown et al., 1993) and down-regulation of membrane-bound natriuretic peptide clearance receptor may, therefore, be a contributing factor to increased plasma natriuretic peptide levels.

As shown in Figure 3, in patients with normal LV systolic function and normal LA pressure, BNP and NT-proBNP levels correlate more significantly with LV mass index than ANP irrespective of aetiology. (Qi et al., 2001)

Because of differences in the excretion of BNP and NT-proBNP the absolute levels are not linearly correlated. BNP is cleared from plasma mostly by binding to the natriuretic peptide receptor type-C and through proteolysis by neutral endopeptidases. Direct renal filtration

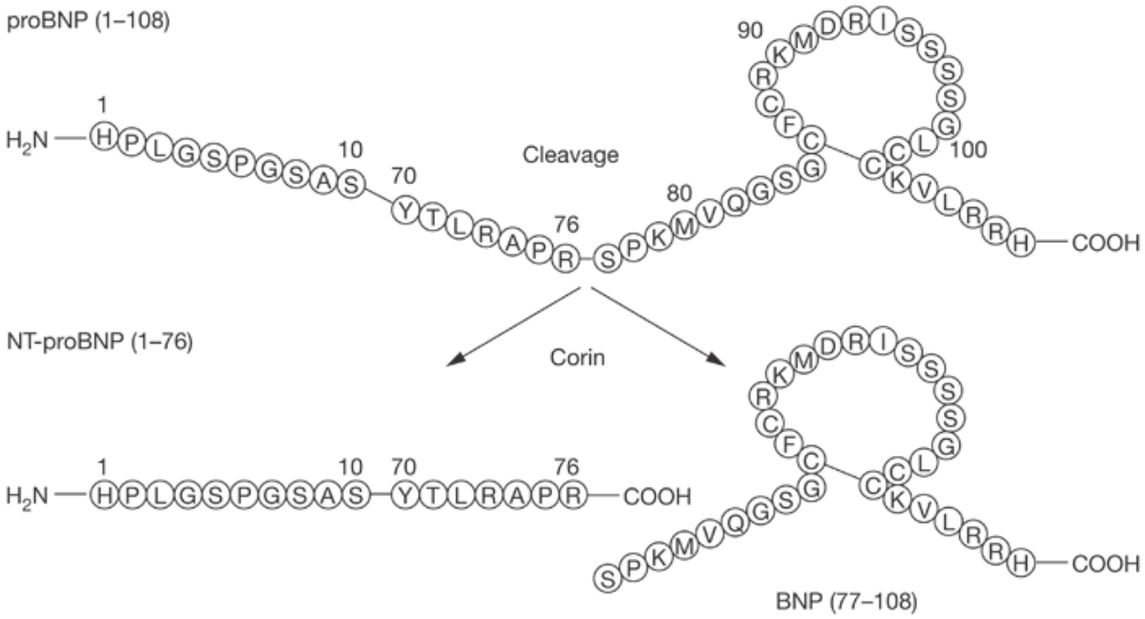


Fig. 2. Diagrammatic representation of the cleavage of the B-type natriuretic peptide prohormone. (adapted from Costello-Boerrigter et al., 2005)

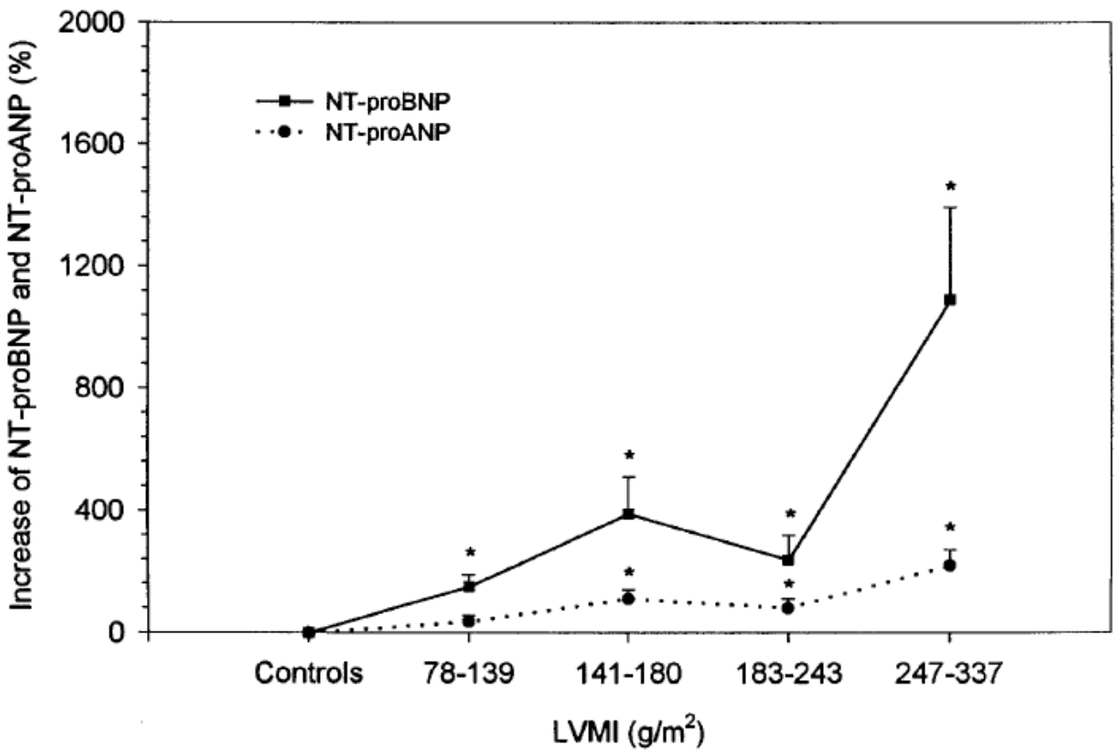


Fig. 3. Plot showing relation of NT-proBNP and NT-proANP to LVMI. *P < .05 vs control subjects. (adapted from Qi et al., 2001)

and passive excretion may also be responsible for some BNP clearance. In contrast, NT-proBNP has no specific clearance receptors and is mainly cleared by renal excretion. As a result, NT-proBNP has a longer half-life and circulates in higher concentrations in plasma. NT-proBNP is less influenced by short bursts of secretion, even though both molecules are released in equimolar proportions. (Qi, 2001; Boomsma, 2001)
ANP and NT-proANP are most closely associated with left atrial (LA) pressure as represented by pulmonary capillary wedge pressure (Qi et al., 2001) and the levels may result from increased LA pressure caused by LV systolic dysfunction and decompensation.

3. Natriuretic peptide levels in other cardiac and non-cardiac states

A number of cardiac and non-cardiac co-morbidities may influence natriuretic peptide levels. Cardiac examples include acute coronary syndromes, (de Lemos et al., 2001) mitral regurgitation, (Sutton et al., 2003) hypertrophic cardiomyopathy, (Hasegawa et al., 1993) advanced LV diastolic dysfunction, (Iwanaga et al., 2006) atrial fibrillation, (Iwanaga et al., 2006) and heart failure. Non-cardiac examples include severe respiratory disease, (Jensen et al., 1997) renal failure, (Jensen et al., 1997) fluid overload, and obesity. In patients with chronic kidney disease, decreased estimated glomerular filtration rate (GFR) is associated with increased plasma BNP and even greater elevation in NT-proBNP concentrations. Higher cut-off values for those with GFR <60mL/min/1.7m² have been suggested. (McCullough, 2003; Anwaruddin, 2006)
On average, obese patients tend to have lower plasma BNP and NT-proBNP levels than non-obese patients. (Das, 2005; Wang, 2005; Horwich, 2006) An inverse relationship between body mass index (BMI) and natriuretic peptides has been observed in patients both with and without heart failure. The underlying mechanism remains to be elucidated. Higher plasma BNP values within any body mass index category are associated with worse outcomes, (Horwich, 2006) although lower cut-offs are needed for diagnosing heart failure in obese patients.
It is unclear whether a single cut-point for the natriuretic peptides, as used for BNP in the diagnosis of heart failure (100 pg/mL), (Maisel et al., 2002) is appropriate for patients of all ages and both genders. Natriuretic peptide levels increase with aging in normal subjects and values are higher in women than in men with no cardiac disease after adjustment for age. (Wang, 2002; Gerber, 2003; Redfield, 2002) Some studies suggest BNP levels are related to oestrogen and/or testosterone levels, although results have been inconsistent. (Redfield, 2002; Costello-Boerrigter, 2006; Chang, 2007) These observations suggest the use of an age- and sex-specific threshold in different clinical settings could improve the diagnostic accuracy of natriuretic peptide levels and the clinical cut-off level should be elucidated in further studies. The specific assay used can also affect natriuretic peptide levels and contribute to different "normal" values.

4. Natriuretic peptides in aortic stenosis

Natriuretic peptide levels increase with the severity of aortic disease. (Gerber, 2003; Weber, 2005; Bergler-Klein, 2004; Weber, 2004) BNP and NT-proBNP levels correlate with peak-to-peak aortic valve and mean aortic gradient, and the correlation coefficients were stronger for BNP than for ANP. (Qi, 2001; Poulsen, 2007) Elevated BNP is also associated with lower AVA, (Gerber, 2003; Lim, 2004; Qi, 2001; Weber, 2003) although the correlation is lower than

with other echocardiographic parameters. The plasma level of BNP also increases with decrease in LV systolic function. These observations suggest serial measurements of BNP may be useful for monitoring patients with asymptomatic AS.

In the natural history of AS, a latent stage may exist during which LV hypertrophy compensates for the rise in afterload without producing a concomitant elevation of mean atrial pressure. As disease progresses, decompensation may occur with a reduction in the ratio between wall thickness and LV cavity size and a rise in atrial and pulmonary capillary wedge pressures.

4.1 Natriuretic peptides and functional status of AS patients

The transition from compensated to decompensated LV function may not be reliably detected by current echocardiographic measures such as ejection fraction, stroke volume, and transvalvular flow. In contrast, levels of natriuretic peptides correlate with the New York Heart Association (NYHA) symptom class and echocardiographic measures of LV dysfunction and therefore may be useful in indicating subtle LV pathology in asymptomatic patients. (Lim, 2004; Van Pelt, 2008; Weber, 2005; Gerber, 2005) Importantly, natriuretic peptide levels are on average higher in patients with NYHA class II symptoms than in patients with class I symptoms. This supports the notion that natriuretic peptide levels could be used to discriminate between early heart failure symptoms and normal effort tolerance (Figure 4). Interestingly, AVA is poorly correlated with the presence of symptoms. (Lim et al., 2004)

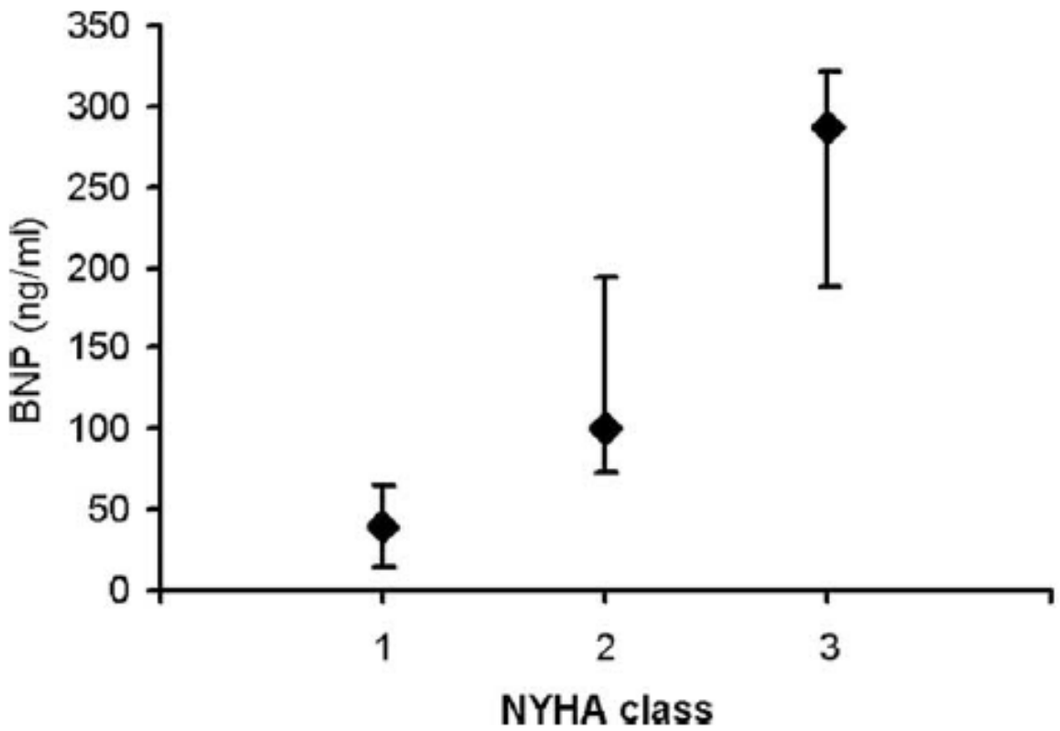


Fig. 4. Association between BNP levels (indicated as median and quartiles) and NYHA functional class (trend test, $p < 0.01$). (adapted from Lim et al., 2004)

In a study by Gerber et al and colleagues, 74 patients with severe AS were sub-grouped according to their AVA, symptom status, and LV EF. BNP and NT-proBNP levels were consistently higher in symptomatic patients referred for surgery whereas asymptomatic patients had lower natriuretic peptide levels (Figure 5). (Gerber et al., 2003)

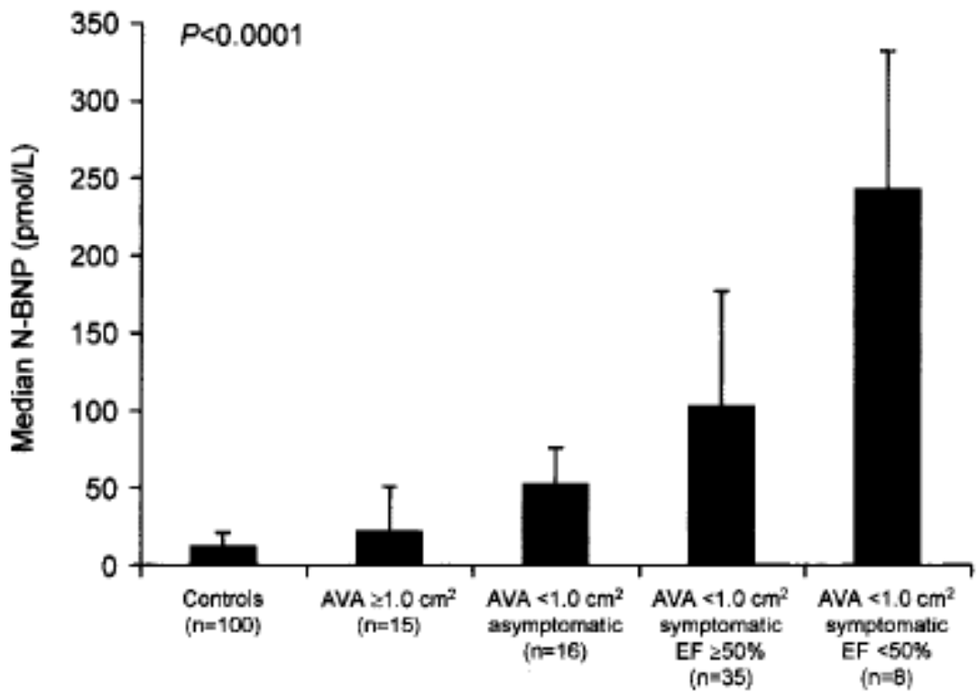


Fig. 5. Association between N-BNP levels and severity of aortic stenosis. The N-BNP levels (median [upper quartile]) in normal control subjects and in subgroups of patients with aortic stenosis by aortic valve area, symptoms, and LV systolic function are shown. AVA indicates aortic valve area; EF, ejection fraction. (adapted from Gerber et al., 2003)

Within each NYHA class, natriuretic peptide levels were not higher in patients with angina or syncope than in those without these symptoms, suggesting different pathophysiologies for these symptoms.

In a separate study, Gerber et al followed 29 asymptomatic patients with AS for an average of eighteen months. (Gerber et al., 2005) Patients with a plasma level of NT-proBNP that exceeded normal limits (>50 pmol/L) at baseline were more likely to develop symptoms earlier and significantly more often than those whose NT-proBNP levels were within normal limits. The average increase in NT-proBNP per year was also greater in patients who developed symptoms compared with those who remained asymptomatic. AVA, peak aortic velocity, and the ejection fraction were less reliable predictors of symptom onset. Similar findings were observed by Bergler-Klein et al in a group of 43 initially asymptomatic patients. (Bergler-Klein et al., 2004)

An abnormal blood pressure response to exercise is generally considered an indication for AVR in patients with asymptomatic AS. (Bonow et al., 2006) Exercise testing is

recommended to assess AS patients with equivocal symptoms. However, there is sometimes reluctance to undertake an exercise test, or the patient may not be able to perform the test due to co-morbidities. A rise in plasma BNP may reflect early systolic dysfunction which results in a decrease in exercise capacity. Van Pelt et al demonstrated that AS patients with an increase in systolic BP of ≤20 mmHg during exercise had higher plasma levels of BNP than patients with an increase in systolic BP >20 mmHg. (Van Pelt et al., 2008) BNP was a superior predictor of abnormal blood pressure response than AVA, LV EF, diastolic function, and LV mass index. These observations support the use of BNP for monitoring asymptomatic patients or patients with equivocal symptoms, as well as patients who are unable to exercise. Newer echocardiographic methods such as tissue Doppler or speckle tracking methods which detect early deterioration of LV function also correlate with BNP levels. (Poulsen, 2007; Van Pelt, 2007)

4.2 Natriuretic peptides to predict outcome in asymptomatic severe AS

Echocardiography is the primary investigation for the assessment and monitoring of patients with AS, and the degree of aortic valve calcification, (Rosenhek et al., 2000) aortic valve area, parameters of LV function and LV hypertrophy each predict outcome in this group of patients, (Otto et al., 1997) although the severity of AS is the most important predictor. (Stewart et al., 2010) However, these echocardiographic parameters have only modest value in predicting individual risk. BNP levels have been shown to be independently prognostic of cardiovascular outcomes in patients with aortic stenosis who are treated without surgery (Figure 6). (Nessmith, 2005; Weber, 2006) BNP level is also an independent predictor for cardiovascular death in asymptomatic patients. (Lim et al., 2004) This may be explained if BNP is a more sensitive marker of early LV dysfunction than symptoms.

The risk of sudden cardiac death, (Pellikka, 2005; Rosenhek, 2000) as well as the risk of irreversible myocardial damage due to LV hypertrophy, (Lund et al., 2004) make risk stratification of patients with AS important. A comprehensive and objective approach that will facilitate decision making would, therefore, be of value.

A scoring system to predict adverse outcomes has been created by Monin et al for patients with asymptomatic severe aortic stenosis based on risk score including gender, BNP and peak aortic jet velocity at baseline. (Monin et al., 2009) These variables were chosen because each was independently associated with midterm adverse outcome. As no single value is an absolute criterion to define haemodynamic severity or to predict the development of symptoms, a continuous score integrating valve and ventricular related parameters may be more appropriate in selecting patients likely to benefit from early surgery. Independent predictors of outcome were female sex, peak aortic-jet velocity, and BNP at baseline. Accordingly, the score could be calculated as follows: Score = [peak velocity (m/s)×2]+(natural logarithm of BNP×1.5)+1.5 (if female sex). The use of aortic valve velocity and BNP emphasizes the haemodynamic effects at a valve level as well as the impact on the ventricle. Event-free survival after 20 months was 80% for patients within the first score quartile compared with only 7% for the fourth quartile. Areas under the receiver operating characteristic curves showed excellent performance of their risk score calculation. Future studies will also be needed to validate this strategy before implementing it as a risk calculator for bedside use.

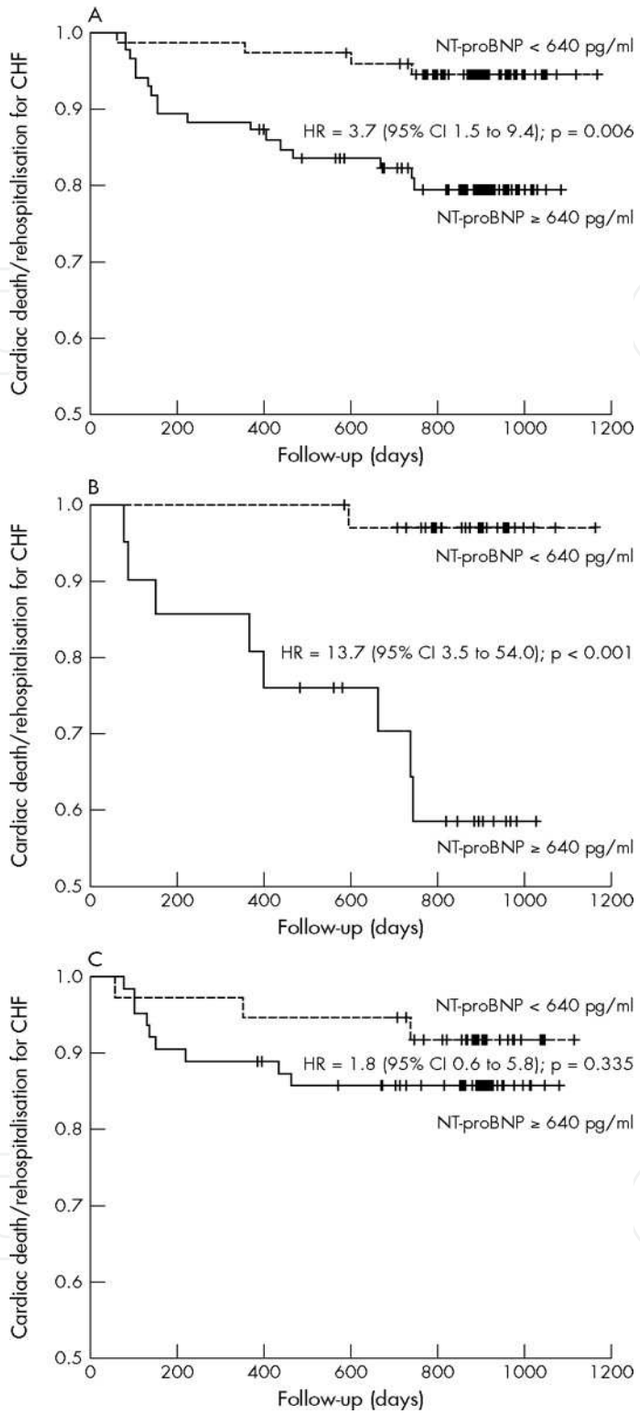


Fig. 6. Kaplan–Meier curves of event-free survival (freedom from cardiac death or rehospitalisation for decompensated heart failure (CHF)) of patients according to N-terminal pro-B-type natriuretic peptide (NT-proBNP) values above (solid line) and below (dotted line) a cut-off value of 640 pg/ml. (A) All patients. (B) Only conservatively treated patients. (C) Only surgically treated patients. CI, confidence interval; HR, hazard ratio. (adapted from Weber et al., 2006)

4.3 Natriuretic peptides and outcomes after aortic valve replacement

Preoperative NT-proBNP independently predicts perioperative and postoperative survival, necessity of intra-aortic balloon pump, postoperative symptomatic status, postoperative hospital stay, and postoperative LV function in patients undergoing heart surgery of various aetiologies. (Hutfless, 2004; Provenchere, 2006) Persistently elevated postoperative BNP levels are also associated with poorer outcomes and higher mortality after heart surgery. (Hutfless et al., 2004)

In symptomatic severe AS patients referred for AVR, preoperative natriuretic peptides were correlated with postoperative NYHA symptom class, LV function, and mortality. (Bergler-Klein, 2004; Predrazzini, 2008) Following AVR, BNP and NT-proBNP levels decrease over time, consistent with the expected haemodynamic improvement after valve replacement with relief of the LV afterload followed by reverse remodelling with gradual regression of LV hypertrophy. (Qi, 2002; Poulsen, 2007) The largest reduction is seen in patients with the largest postoperative valve area index. The postoperative decrease of NT-proBNP had also been demonstrated in some patients to be independently related to improvement of LV myocardial systolic longitudinal strain in echocardiography. (Van Pelt, 2007) However, BNP levels do not decrease in some patients. This may be due to persistent LV dysfunction or aortic prosthesis mismatch with a persistent residual LV outflow gradient from a small prosthetic valve orifice area. Patients who did not derive a symptomatic improvement from AVR were in lower NYHA class at baseline and had a tendency towards lower levels of NT-proBNP at study entry. (Weber et al., 2005)

5. BNP in low-flow, low-gradient aortic stenosis

The prognostic value of BNP in the particularly challenging subset of patients who have low-flow and low-gradient AS has also been studied. It is critical from the perspective of therapeutic decisions to make the distinction between severe AS and pseudo-severe AS who have a high operative mortality (Monin, 2003; Connolly, 2000) and a poor prognosis. It remains unclear which patients would derive benefit from AVR and which could be treated medically. In severe AS, the LV systolic dysfunction is related to the duration and severity of AS. In pseudo-severe AS, LV dysfunction from other causes results in low forward flow and reduced valve opening which overestimates the severity of AS. Dobutamine stress echocardiography (DSE) is potentially useful in distinguishing the two conditions (Blais, 2006; De Filippi, 1995) by assessing the response of valve area and gradient to a dobutamine-induced flow increase. Nonetheless, this differentiation remains difficult and it is uncertain whether DSE can reliably predict the outcome with surgery. (Monin, 2003; Quere, 2006)

Bergler-Klein and colleagues reported on 69 low-flow, low-gradient patients who underwent inotropic challenge and related the outcome to their BNP levels (Figure 7). (Bergler-Klein et al., 2007) The study included 29 patients with severe AS and 40 patients with pseudo-severe AS. BNP levels were higher in patients with true AS when compared with pseudo-AS, a finding consistent with the concept that BNP is elevated in AS due to the effect on wall tension and ventricular stretch associated with the increased after-load in addition to the failing LV. Nonetheless, a significant overlap of BNP values was observed between groups.

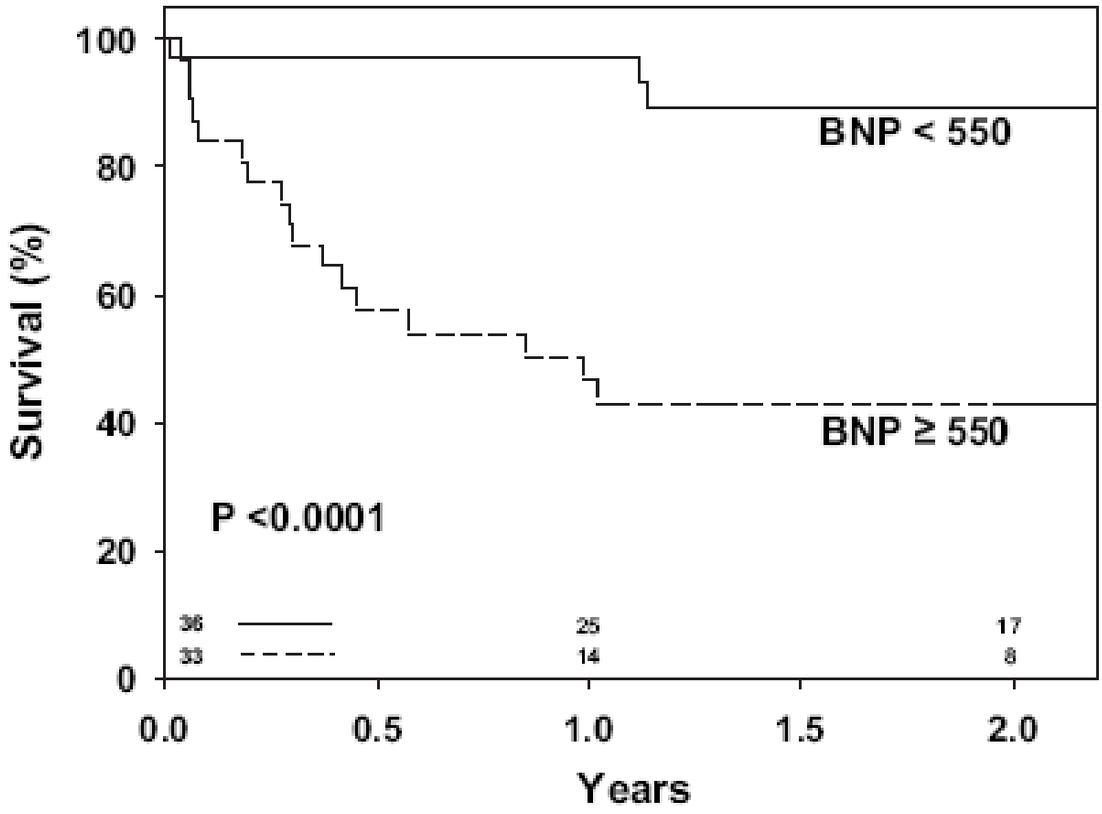


Fig. 7. **K**aplan-Meier survival curve for the entire study population according to baseline BNP<550 or ≥550 pg/mL. A BNP of >550 pg/mL was found to be associated with a poor outcome for both groups, with only 47% of such patients surviving for 1 year compared with 97% survival in patients with lower BNP values. (adapted from Bergler-Klein et al., 2007))

BNP level >550 pg/mL remained the strongest independent predictor of survival when factors such as New York Heart Association functional class, LV EF, contractile reserve, the status of true or pseudo-AS, medical versus surgical therapy, and other clinical variables such as coronary artery disease or diabetes were considered. Therefore, BNP could potentially be used to improve risk stratification and management of this group of patients. However, BNP is non-specific with plasma levels increasing with heart failure due to many causes. More data will be required before BNP can be formally used for therapeutic recommendations.

6. Conclusion

Together with clinical and echocardiographic parameters, measurement of BNP may improve risk stratification and management of patients with AS. BNP and NT-proBNP are important prognostic markers and predictors of symptom-free survival in patients with severe AS. A patient with severe AS and a high plasma level of BNP is likely to carry a high

risk of adverse events, and aortic valve replacement should be considered. Measurement of BNP may complement clinical and echocardiographic evaluation, allow more reliable follow-up, and improve the optimal timing of AVR surgery by early identification of the transition from compensated to decompensated LV function. Serially rising levels could also be helpful in identifying patients with LV dysfunction, but current evidence for such use is limited. Clinical judgment will be needed to interpret the significance of a BNP measurement in patients with AS.

7. Acknowledgements

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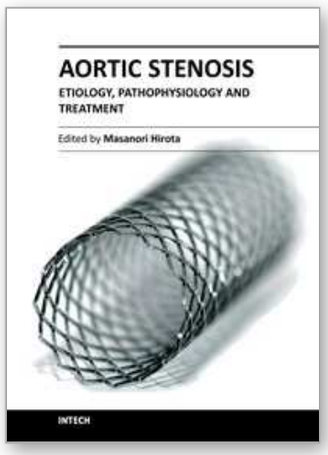
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Currently, aortic stenosis (AS) is the most prevalent valvular disease in developed countries. Pathological and molecular mechanisms of AS have been investigated in many aspects. And new therapeutic devices such as transcatheter aortic valve implantation have been developed as a less invasive treatment for high-risk patients. Due to advanced prevalent age of AS, further discovery and technology are required to treat elderly patients for longer life expectancy. This book is an effort to present an up-to-date account of existing knowledge, involving recent development in this field. Various opinion leaders described details of established knowledge or newly recognized advances associated with diagnosis, treatment and mechanism. Thus, this book will enable close intercommunication to another field and collaboration technology for new devices. We hope that it will be an important source, not only for clinicians, but also for general practitioners, contributing to development of better therapeutic adjuncts in the future.

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