CARDIOVASCULAR MEDICINE

Prognostic value of N-terminal pro-B-type natriuretic peptide for conservatively and surgically treated patients with aortic valve stenosis

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Objective: To evaluate the prognostic value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with aortic stenosis being treated conservatively or undergoing aortic valve replacement (AVR).
Methods: 159 patients were followed up for a median of 902 days. 102 patients underwent AVR and 57 were treated conservatively. NT-proBNP at baseline was raised in association with the degree of severity and of functional status.
Results: During follow up 21 patients (13%) died of cardiac causes or required rehospitalisation for decompensated heart failure. NT-proBNP at baseline was higher in patients with an adverse outcome than in event-free survivors (median 623 (interquartile range 204–1854) pg/ml *v* 1054 (687–2960) pg/ml, p = 0.028). This difference was even more obvious in conservatively treated patients (331 (129–881) pg/ml *v* 1102 (796–2960) pg/ml, p = 0.002). Baseline NT-proBNP independently predicted an adverse outcome in the entire study group and in particular in conservatively treated patients (area under the curve (AUC) = 0.65, p = 0.028 and AUC = 0.82, p = 0.002, respectively) but not in patients undergoing AVR (AUC = 0.544). At a cut-off value of 640 pg/ml, baseline NT-proBNP was discriminative for an adverse outcome.
Conclusion: NT-proBNP concentration is related to severity of aortic stenosis and provides independent prognostic information for an adverse outcome. However, this predictive value is limited to conservatively treated patients. Thus, the data suggest that assessing NT-proBNP may have incremental value for selecting the optimal timing of valve replacement.

Aortic valve diseases, namely aortic stenosis (AS) and aortic regurgitation, are common in developed countries, with AS being the most common valvular heart disease.[1 2] Symptomatic status and echocardiography are the most important clinical factors used to confirm the diagnosis, asses severity and monitor progression of AS. Aortic valve replacement (AVR) is indicated for symptomatic patients with severe AS[3 4] but whether asymptomatic patients should undergo AVR or should be treated conservatively is controversial.[5 6] For patients with moderate AS surgical treatment is generally not recommended.

B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are neurohormones synthesised and secreted mainly by the ventricular myocardium. Their release is stimulated by an increase in ventricular wall stress.[7] In patients with AS, BNP and NT-proBNP rise in correlation with severity and functional status as assessed by the New York Heart Association (NYHA) classification.[8–11] Furthermore, a correlation with the progression of AS has been documented.[12] Recently, two studies have been published showing a predictive value for BNP and NT-proBNP in patients with severe AS, most of whom underwent AVR.[13 14] Both studies showed that BNP and NT-proBNP provided independent prognostic information for postoperative outcome.

Therefore, we aimed at evaluating the prognostic value of NT-proBNP in patients with valvular AS who are treated conservatively compared with patients undergoing valve replacement.

METHODS

Patients

We included 159 consecutive patients who were referred to our institution for further evaluation of valvular AS from April 2002 to November 2003. All patients had an ejection fraction above 45% documented by echocardiography. Patients with concomitant relevant aortic regurgitation (> II°) and mitral regurgitation (> II°) were not included in this study. Functional status was evaluated and graded according to the NYHA classification by physicians blinded to NT-proBNP values. The medical history was assessed as the patients reported it or based on their medical records, if available. The indication for valve surgery was left to the discretion of the treating physicians, who were blinded to NT-proBNP values and who were encouraged to decide in accordance with the current guidelines.[3 4] A first follow up visit was attended personally by 109 patients 329 (219–347) days after study entry and a second follow up by 123 patients 902 (861–952) days after study entry. The follow up time did not differ between surgically treated and conservatively treated patients (901 (98) *v* 892 (95), p = 0.551). At study entry and at follow up, medical history and functional status were assessed and echocardiography and blood sampling were performed. The remaining 36 patients who did not attend a follow up visit were interviewed by telephone or their treating home physicians were contacted. Cardiac death, rehospitalisation for acute decompensated heart failure and the combination of cardiac death and rehospitalisation for acute decompensated heart failure were regarded as adverse events. Death was considered to be cardiovascular if no other obvious causes of death had been identified.

Abbreviations: AS, aortic stenosis; AUC, area under the curve; AVR, aortic valve replacement; BNP, B-type natriuretic peptide; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; ROC, receiver operating characteristic

Echocardiography

A comprehensive transthoracic echocardiography study was performed with an Agilent Sonos 1.75–3.5 MHz scanner (Phillips Medical Ultrasound) with the use of harmonic imaging at study entry and at follow up. All examinations were done by an experienced echocardiographer, blinded to NT-proBNP measurements. Left ventricular diameter was assessed by M mode in the left parasternal view. Left ventricular function was visually assessed and quantified as shortening fraction, and ejection fraction was calculated according to Teichholz. Maximum and mean aortic velocities were measured by continuous-wave Doppler echocardiography from the apical or right parasternal view. In sinus rhythm transaortic velocity was averaged over three cycles and in patients with atrial fibrillation over seven cycles. Maximum and mean pressure gradients were calculated by the built-in software. Aortic valve area was calculated from mean velocities. Severity of AS was graded according to the mean transvalvular pressure gradient obtained echocardiographically. A mean transvalvular pressure gradient below 30 mm Hg was considered mild AS (AS I), from 30 and 50 mm Hg moderate AS (AS II) and above 50 mm Hg severe AS (AS III). Left ventricular mass was calculated by the formula of Devereux.[15]

NT-proBNP measurement

From all patients blood samples were taken at study entry and at follow up from an antecubital vein in gel-filled tubes without anticoagulants. The specimens were centrifuged within 1 h and serum was frozen at −80℃ until analysis. NT-proBNP was measured by an electrochemiluminescence immunoassay (Elecsys proBNP; Roche Diagnostics, Mannheim, Germany).

Statistics

Values of NT-proBNP are expressed as median and interquartile range and of all other variables as mean (SD). For statistical comparison of NT-proBNP values the Mann–Whitney test (two groups) and Kruskal–Wallis test (n groups) were applied. For analyses of patients' baseline characteristics Student's t test (two groups) or analysis of variance (n groups) was used for continuous variables and the χ^2 test or Fischer's exact test for categorical variables. The correlation between NT-proBNP and clinical parameters was analysed by Spearmen's correlation coefficient (r_s). Receiver operating characteristic (ROC) curve analysis was performed for NT-proBNP at baseline as a predictor for an adverse event and the area under the curve (AUC) from the ROC curves was calculated. An optimised cut-off value was derived from the ROC curve as the value providing the optimal test accuracy. Event rates according to NT-proBNP values were plotted as Kaplan–Meier curves and for statistical analysis the log rank test was applied. For multivariate estimation of the hazard ratio for the occurrence of the end points Cox regression analysis was performed. All tests were performed two sided and $p < 0.05$ was considered to indicate significance. For all statistical analysis the statistical software SPSS V.10.0 (SPSS Inc, Chicago, Illinois, USA) for Windows was used.

Table 1 Baseline characteristics of all patients according to therapeutic strategy

	Conservative treatment	Aortic valve replacement	p Value
Number	57	102	
Women	29 (51%)	50 (50%)	0.822
Age (years)	69 (13)	69 (10)	0.971
NYHA class			
I	22	12	
II	26	34	<0.001
III	7	41	
IV	2	15	
Atrial fibrillation	6 (11%)	15 (15%)	0.455
Coronary artery disease	19 (33%)	30 (29%)	0.608
Creatinine (μmol/l)	84 (17)	80 (19)	0.265
Body mass index (kg/m^2)	28.4 (3.2)	27.3 (3.6)	0.073
Ejection fraction (%)	59 (4)	56 (9)	0.022
LVMI (g/m^2)	118 (38)	140 (37)	0.002
Mean pressure gradient (mm Hg)	32 (21)	60 (17)	<0.001
Aortic valve area (cm^2)	0.96 (0.33)	0.69 (0.17)	<0.001
NT-proBNP (pg/ml)			
Baseline	423 (163–1145) (n = 57)	832 (364–2752) (n = 102)	0.001
First follow up	456 (166–1664) (n = 39)	501 (229–892) (n = 70)	0.940
Second follow up	498 (165–1918) (n = 40)	493 (225–996) (n = 83)	0.842

Values are expressed as number (%), mean (SD) or median (interquartile range).
LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

RESULTS

A total of 159 patients were enrolled. According to the above mentioned definitions, 26 patients were classified as having mild AS (AS I), 31 patients as having moderate AS (AS II) and 102 patients as having severe AS (AS III). Aortic valves were replaced in 102 patients and 57 patients were treated conservatively. Table 1 details the patients' baseline characteristics. Conservatively treated and surgical patients did not differ in sex distribution, age, serum creatinine and frequency of atrial fibrillation. Coronary artery disease defined as a history of coronary artery bypass grafting, percutaneous intervention, acute myocardial infarction or presence of relevant coronary artery stenosis at angiography was present in 49 patients. There was no difference in frequency of coronary artery disease between conservatively treated patients and patients undergoing valve replacement. Patients scheduled for valve replacement had lower ejection fraction, higher left ventricular mass index, smaller aortic valve area and higher mean pressure gradient than patients for whom a conservative strategy was recommended.

NT-proBNP at baseline

NT-proBNP at baseline was raised in association with the degree of severity (AS I, 301 (135–472) pg/ml; II, 466 (145–1054) pg/ml; and III, 1035 (473–2980) pg/ml; $p < 0.001$) and functional status (NYHA I, 235 (114–1187) pg/ml; II, 623 (308–1425) pg/ml; III, 733 (313–3033) pg/ml; and IV, 4269 (1446–6857) pg/ml; $p < 0.001$). Baseline NT-proBNP in female patients was not different from that in male patients (715 (293–1872) *v* 673 (225–2207) pg/ml, $p = 0.589$). Patients with atrial fibrillation ($n = 21$) had higher values than patients in sinus rhythm (2100 (920–5782) *v* 608 (215–1615) pg/ml, $p = 0.001$). NT-proBNP at baseline was moderately correlated with ejection fraction (−0.419, $p < 0.001$) and left ventricular mass index (0.434, $p < 0.001$) and was weakly but significantly correlated with mean pressure gradient (0.351, $p < 0.001$), aortic valve area ($r_s = 0.380$, $p < 0.001$), age ($r_s = 0.302$, $p < 0.001$) and creatinine ($r_s = 0.171$, $p = 0.037$). Baseline NT-proBNP was higher in patients undergoing AVR than in patients who were treated conservatively.

Association between NT-proBNP and clinical outcome

In the entire study population 18 patients (11%) died during the follow up period. Thirteen patients (8%) died of cardiac causes and five of non-cardiac causes (Wegner's disease with glomerulonephritis, ileus, pulmonary embolism, cerebral stroke and gastric cancer). Ten patients (6%) required rehospitalisation for acute decompensated heart failure. The

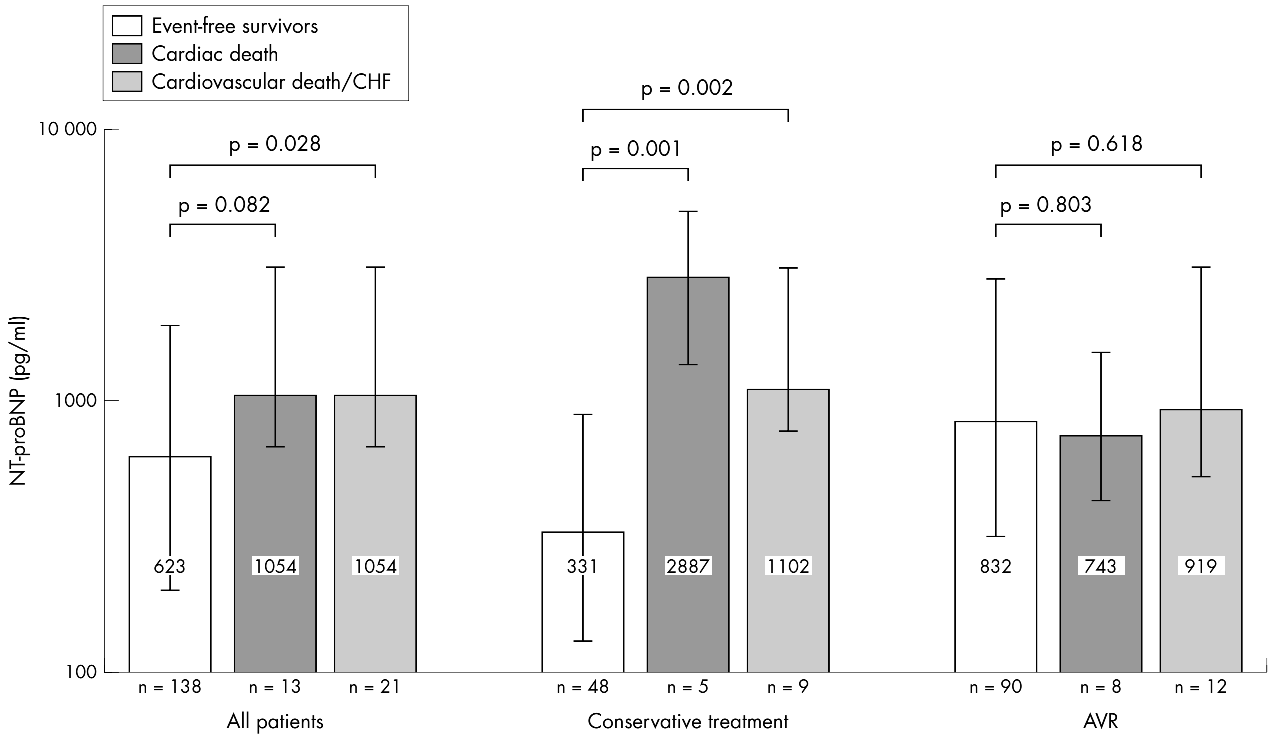

Figure 1 N-terminal pro-B-type natriuretic peptide (NT-proBNP) at study entry (baseline) in relation to clinical outcome and therapeutic strategy. Values are expressed as median (interquartile range). AVR, aortic valve replacement; CHF, decompensated heart failure.

combined end point of cardiac death and rehospitalisation for acute heart failure was reached by 21 patients (13%). There was a slight trend towards a higher rate of rehospitalisation in the conservative group than in the surgical group (6 (11%) *v* 4 (4%), p = 0.169). However, this difference was not significant.

In the entire study population baseline NT-proBNP concentrations were lower in patients without an adverse event during the follow up period than in patients who died of cardiac causes or who were readmitted for decompensated heart failure (623 (204–1854) *v* 1054 (687–2960) pg/ml, p = 0.028). If only patients with cardiac death were compared with survivors, there was a strong trend towards higher baseline NT-proBNP values, but this difference did not reach significance (1054 (687–2969) *v* 646 (218–1930) pg/ml, p = 0.082). In the conservatively treated group, baseline NT-proBNP concentrations differed notably between survivors and those who died of cardiac causes (362 (133–913) *v* 2887 (1617–4032) pg/ml, p = 0.001) and between event-free survivors and patients experiencing the combined end point of cardiac death or rehospitalisation for decompensated heart failure (331 (129–881) *v* 1102 (796–2960) pg/ml, p = 0.002). In contrast, among patients who underwent AVR baseline NT-proBNP values did not differ between event-free survivors and those with an adverse outcome (865 (331–2840) *v* 743 (434–1482) pg/ml, p = 0.803 for patients with cardiac death and 832 (318–2752) *v* 919 (519–2998) pg/ml, p = 0.618 for the combined end point) (fig 1). The AUC of the ROC curve for baseline NT-proBNP as a predictor for the combination of cardiac death or rehospitalisation for decompensated heart failure was 0.649 (p = 0.028) for the entire study group. If the ROC curves were plotted separately for conservatively treated patients and for patients undergoing valve surgery, test accuracy improved for the conservatively treated patients with an AUC of 0.822 (p = 0.002), whereas baseline NT-proBNP had no predictive value for patients undergoing valve surgery (AUC = 0.544, p = 0.618) (fig 2). From the ROC analysis a cut-off value providing optimal test accuracy for the prediction of cardiac death or rehospitalisation for decompensated heart failure of 640 pg/ml was calculated. In applying this cut-off value to the entire study population, sensitivity was 81%, specificity 51%, positive predictive value 20% and negative predictive value 95%. However, for the subgroup of conservatively treated patients test accuracy was noticeably better, with a sensitivity of 89%, specificity 73%, positive predictive value 38% and negative predictive value 97%. Consequently, in Kaplan–Meier analysis baseline NT-proBNP values dichotomised at this cut off discriminated patients with an adverse outcome in the entire study group (hazard ratio (HR) 3.70, 95% confidence interval (CI) 1.46 to 9.36, log rank test p = 0.006) and even better in the conservative group (HR 13.71, 95% CI 3.48 to 54.03, log rank test $p < 0.001$). However, for surgically treated patients baseline NT-proBNP did no discriminate patients at high risk (HR 1.78, 95% CI 0.55 to 5.76, log rank test p = 0.335) (fig 3).

Conservatively treated patients with an adverse outcome had a lower left ventricular ejection fraction (53 (9)% *v* 60 (4)%, p = 0.049) than the event-free survivors. Other parameters such as age, left ventricular mass, valve area and pressure gradient, however, were not different between the two groups (table 2). In multivariate Cox regression analysis for the entire study population and for the subgroup of conservatively treated patients, baseline NT-proBNP was an independent predictor for cardiac death or rehospitalisation for decompensated heart failure. On the contrary, in surgically treated patients only the presence of atrial fibrillation, but not baseline NT-proBNP, was an independent predictor for an adverse outcome (table 3).

Among conservatively treated patients, 11 underwent unscheduled AVR because of disease progression. NT-proBNP values at baseline did not differ between patients who progressed to AVR and those who did not (463 (114–715) *v* 409 (172–1145) pg/ml, p = 0.994). The frequency of

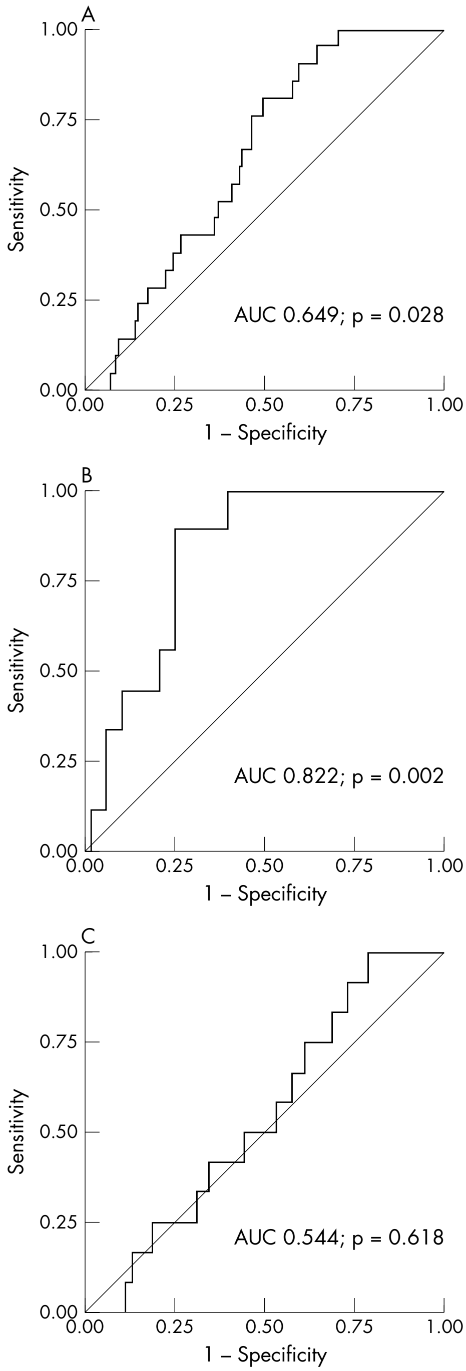

Figure 2 Receiver operating characteristic curves for N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a predictor of cardiac death or rehospitalisation for decompensated heart failure. (A) All patients. (B) Only conservatively treated patients. (C) Only surgically treated patients.

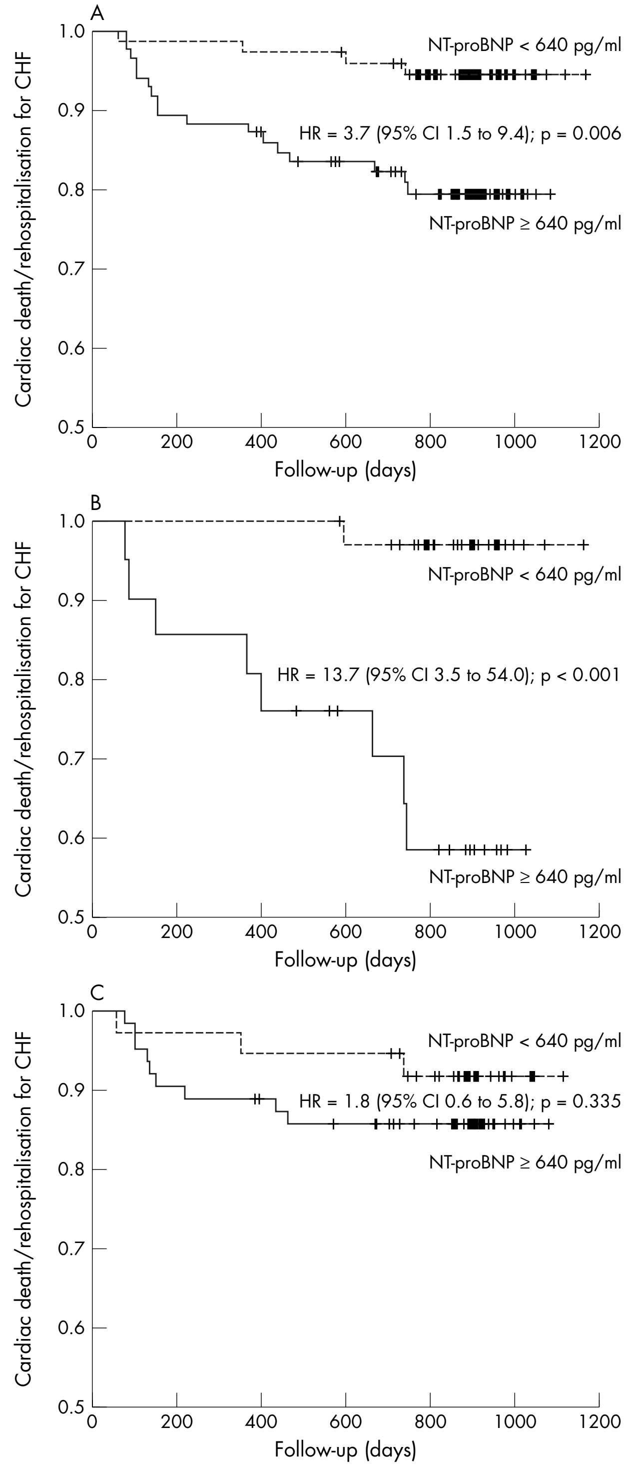

Figure 3 Kaplan–Meier curves of event-free survival (freedom from cardiac death or rehospitalisation for decompensated heart failure (CHF)) of patients according to N-terminal pro-B-type natriuretic peptide (NT-proBNP) values above (solid line) and below (dotted line) a cut-off value of 640 pg/ml. (A) All patients. (B) Only conservatively treated patients. (C) Only surgically treated patients. CI, confidence interval; HR, hazard ratio.

adverse events was not different between patients who underwent unscheduled AVR and those who did not ($p = 0.354$).

DISCUSSION

In this study we aimed at analysing the diagnostic value of NT-proBNP for patients with valvular AS of all degrees of severity. Patients were either treated conservatively or underwent AVR if indicated. The major finding was that NT-proBNP value was related to disease severity and provided independent prognostic information for an adverse outcome in the entire study population. However, subgroup analyses showed that the prognostic value of NT-proBNP was limited to patients who were treated conservatively. For patients undergoing valve surgery NT-proBNP had no prognostic value.

Table 2 Clinical data of conservatively treated patients

	Event-free survivors	Cardiovascular death/readmission for CHF	p Value
Number	48	9	
Women	25 (52%)	4 (44%)	0.730
Atrial fibrillation	4 (8%)	2 (22%)	0.237
Coronary artery disease	14 (30%)	5 (56%)	0.143
Moderate aortic stenosis	38 (79%)	6 (67%)	0.412
Severe aortic stenosis	9 (21%)	3 (33%)	
Age (years)	69 (13)	73 (8)	0.416
Ejection fraction (%)	60 (4)	53 (9)	0.049
LVMI (g/m^2)	116 (37)	131 (45)	0.317
Mean pressure gradient (mm Hg)	31 (22)	38 (13)	0.385
Aortic valve area (cm^2)	0.98 (0.33)	0.87 (0.07)	0.140
NT-proBNP at baseline (pg/ml)	331 (129–881)	1102 (796–2966)	0.002

Values are expressed as number (%), mean (SD) or median (interquartile range).
CHF, decompensated heart failure; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

To date two studies have investigated the predictive value of BNP or NT-proBNP in AS. Bergler-Klein and colleagues[13] reported an independent prognostic value of NT-proBNP for postoperative survival in 79 symptomatic patients with severe AS. Furthermore, they found a predictive value of BNP and NT-proBNP for symptom deterioration of 43 initially asymptomatic patients with severe AS. In another study Lim *et al*[14] described their finding of a predictive value of BNP for survival in 70 patients with severe AS. Although both studies included patients who did not undergo valve surgery and thus were treated conservatively, nothing has been reported on the predictive value of BNP or NT-proBNP in this subgroup. Thus, our data confirm these previous reports and, more importantly, they extend present knowledge. In contrast to the above mentioned studies in which only patients with severe AS were included, we also included patients with mild and moderate AS. In this cohort we obtained a predictive value for an unfavourable outcome for the entire study population. However, and this finding is new, in our study the predictive value of NT-proBNP was limited to the group of patients who were treated conservatively. This finding is of clinical interest, as our data suggest that NT-proBNP assessment provides important additional information about patients not undergoing valve replacement. From our data it can be concluded that NT-proBNP assessment improves risk stratification and may contribute to deciding on the optimal timing of valve replacement. However, this hypothesis needs to be tested in further prospective studies. Conversely, NT-proBNP value does not provide any incremental prognostic information about patients undergoing valve replacement. Therefore, NT-proBNP assessment is not of diagnostic value in this setting.

We were able to calculate an optimised cut-off value of NT-proBNP for the prediction of an adverse outcome of 640 pg/ml. Applying this cut-off, NT-proBNP values discriminate patients at high risk. Notably, the calculated cut-off value in our study was almost identical to the cut-off value for NT-proBNP of 80 pmol/ml (or 592 pg/ml) that Bergler-Klein *et al*[13] applied in their study.

Limitations

Although this study included a high number of patients relative to previously published studies, it is limited by the small number of patients in the conservatively treated group. Our study must therefore be regarded as a pilot study. Although our data suggest that NT-proBNP may contribute to deciding on the optimal timing of valve replacement, admittedly our data do not provide evidence that patients with high NT-proBNP would have benefited from valve surgery. NT-proBNP was assessed at baseline and at follow up while patients were taking standard drugs including β blocker, angiotensin-converting enzyme inhibitors and diuretics. All of these drugs are known to influence natriuretic peptide concentration and an impact of NT-proBNP in the present study has to be considered. We did not perform exercise testing in this study. Especially in asymptomatic patients with severe AS, exercise testing might have distinguished more patients with an indication for valve surgery.

Table 3 Multivariate analysis of predictors of an adverse outcome

	All patients		Conservative group		AVR	
	Wald	p Value	Wald	p Value	Wald	p Value
NT-proBNP ⩾640 pg/ml	4.45*	0.035*	5.24*	0.022*	0.09	0.766
Rhythm	3.83*	0.050*	0.82	0.364	6.37*	0.012*
Age	1.08	0.299	1.99	0.158	2.48	0.116
Mean pressure gradient	0.96	0.326	0.00	0.949	0.11	0.741
Sex	0.39	0.533	0.19	0.659	0.16	0.685
NYHA class III or IV	0.39	0.533	0.05	0.823	0.89	0.345
Ejection fraction	0.28	0.596	7.27*	0.007*	0.00	0.964
Coronary artery disease	0.15	0.697	1.91	0.167	0.45	0.501

*Significant predictor.
Multivariate Cox regression analysis for predictors of an adverse outcome (cardiac death and rehospitalisation for decompensated heart failure) for the entire study group, conservatively treated patients and patients who underwent valve surgery.
AVR, aortic valve replacement; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Conclusion

NT-proBNP is related to severity of valvular AS and provides independent prognostic information for an adverse outcome. However, this predictive value is limited to conservatively treated patients. Thus, our data suggest that NT-proBNP assessment may be of incremental value in deciding on the optimal timing of valve replacement. In contrast, NT-proBNP assessment provides no additional prognostic information for patients undergoing valve replacement.

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IMAGES IN CARDIOLOGY

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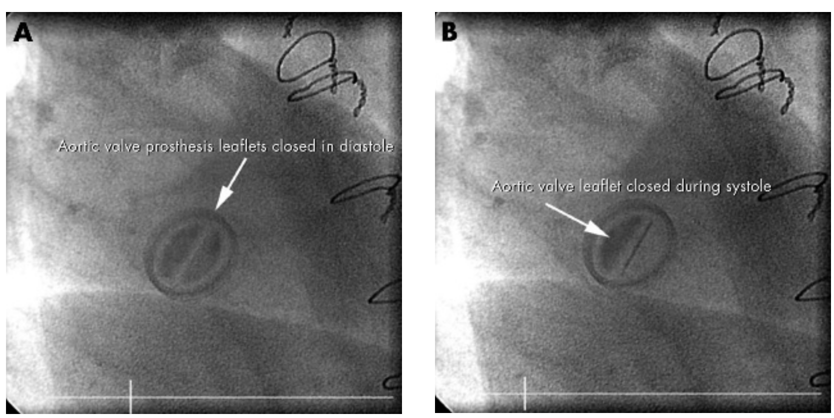
Carbomedics bi-leaflet aortic valve prosthesis: a sticky problem

A 46-year-old Asian woman was under regular follow up for an aortic valve replacement in 2002 for aortic stenosis. The valve was a Carbomedics 19 mm bi-leaflet aortic valve prosthesis for which she had adequate anticoagulation since implantation. She had a past history of end stage renal failure, type 2 diabetes, hypertension, cerebrovascular disease, and systemic lupus erythematosus. She was asymptomatic and had a routine transthoracic echocardiogram performed which revealed her aortic valve prosthesis was well seated with an elevated velocity across the valve; the aortic valve leaflets were poorly visualised but appeared to be mobile. A transoesophageal echocardiogram confirmed the notably increased forward velocity across the aortic valve (maximum velocity 4.6 m/s) with small aortic root, raising the possibility of pressure recovery phenomenon. Once again the leaflets were not clearly seen but appeared mobile. The patient had cineradiography which demonstrated that one of the leaflets of the Carbomedics valve was stuck in the closed position (panels A and B). The most likely cause of this was pannus formation causing the leaflet to stick in the closed position.



Prosthetic valve dysfunction caused by pannus formation has been reported for St Jude Medical aortic valves; the sewing cuff of the Carbomedics valve is coated in biolite carbon, which is an anti-thrombotic agent that prevents adhesion of thrombus or pannus on the sewing cuff. There are a few reports of Carbomedics valve dysfunction by pannus formation in the mitral position, but none in the aortic position.

Prosthetic valve dysfunction caused by a stuck valve leaflet can be more easily visualised by cineradiography and can provide additional information on prosthetic valve function, thereby complementing data obtained from echocardiography.

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