Is B-type Natriuretic Peptide Superior to Contractile Reserve in Predicting Outcome in Low-Flow, Low-Gradient Aortic Stenosis? Results from the Multicenter TOPAS* Study

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ABSTRACT

Background: B-type natriuretic peptide (BNP) and contractile reserve (CR) have been shown to be predictors of outcome in low-flow, low-gradient aortic stenosis (AS). However, it is unknown how they compare in their prognostic value.
Methods: BNP measurements and dobutamine stress echo (DSE) were performed in 69 pts with low-flow AS (indexed orifice area < 0.6 cm^2/m^2, mean gradient ≤ 40 mmHg, LVEF ≤ 40%). Presence of CR was defined by an increase of stroke volume ≥ 20% at DSE. Pts were followed for 411 ± 343 days.
Results: 1-year survival was poor in pts with BNP ≥ 550 pg/ml but favorable in those with BNP < 550 in the entire group (47±9% vs 97±3%; p<0.0001), as well as in the surgically treated group (53±13% vs 92±7%; p=0.02). Even in pts with CR, 1-year survival was significantly lower when BNP was ≥ 550 (48±12% vs 93±6%; p=0.009, Figure D). More importantly, in the subset of pts without CR, survival was only poor when BNP was ≥ 550, but still favorable when it was < 550 (50±14 vs 100%, p=0.014). After adjusting for age, NYHA, LVEF, CR, coronary artery disease, severity of stenosis and type of treatment, BNP ≥ 550 remained an independent predictor of outcome (p=0.0003).
Conclusion: BNP thus appears to add critical information beyond the CR assessment. BNP may help to identify those pts in the difficult subgroup without CR who are likely to benefit from valve replacement.

BACKGROUND

Severe AS carries a dismal prognosis when associated with congestive heart failure, the expected survival is <2 years when treated medically only. Aortic valve replacement (AVR) is the only effective treatment, but the operative risk increases with the development of LV dysfunction. Pts with low-flow low-gradient AS have a high operative mortality between 8-33%.

Dobutamine stress echocardiography (DSE) has been shown to be useful for the stratification of the operative risk and indication of AVR based on the severity of the stenosis and the presence of LV contractile reserve (1-3). Pts with truly severe AS (TS) and concomitant LV dysfunction will generally benefit from AVR, whereas pts with pseudo-severe AS (PS) due to poor LVF but only moderate stenosis will not.

Contractile reserve (CR) has been demonstrated to be a predictor of outcome in low-flow AS. Patients with CR at DSE had a good survival after surgery, whereas outcome was poor in those without CR, regardless of the type of treatment, i.e. medical or surgical (2) . However, in a recent study (3), a substantial proportion of pts without CR appeared to benefit from valve replacement (AVR), although it remained unclear how to identify these patients. Thus, further criteria are necessary to select the appropriate pts for surgery.

BNP has been shown to be a predictor in AS with normal LV function (4,5) and recently also in low-flow AS by our group (6). The present study prospectively evaluates the relationship of BNP on the outcome in pts with low-flow AS and compares the prognostic value to the presence of contractile reserve.

METHODS

A total of 69 consecutive patients with low-flow AS (indexed effective orifice area [IEOA] < 0.6 cm^2/m^2, mean gradient [mG] ≤ 40 mmHg, and LV ejection fraction [EF] ≤ 40%) were included in the study after giving informed consent (baseline characteristics, **Table 1**).

All pts underwent DSE using 8 minutes increments of 2.5 or 5 up to 20 µg/kg/min.
Pts were classified as TS or PS if their projected EOA at normal flow rate (250 mL/s) was ≤ or >1.0 cm^2 as reported recently in the TOPAS study (1): EOAproj= EOArest +VCx(250-Qrest), with valve compliance corresponding to the slope of the EOA-flow relationship and representing the rate of change in EOA in relation to the increase in flow during stress. Contractile reserve (CR) was defined by an increase of stroke volume ≥ 20% at peak DSE.

Plasma BNP was determined by fluorescence immunoassay (Triage, Biosite).
Exclusion criteria were >2+ aortic regurgitation; mitral valve area < 2.0 cm^2 or > 2+ mitral regurgitation caused by intrinsic valve pathology; atrial fibrillation; paced rhythm; unstable angina; acute pulmonary edema; or end-stage renal disease.

The therapeutic decision of AVR or medical treatment was left to the discretion of the treating physician using the baseline results (response to DSE, PET scan, coronary angio etc). Physicians were blinded to BNP results. A follow-up assessment for mortality was scheduled at 1 and 2 years after AVR or after the baseline evaluation when pts remained on medical treatment.

Table 1

Patient Characteristics Baseline	
n=69	
Age, years	70±10
Female, Male	13 / 56
EOA, cm^2	0.94±0.23
IEOA, cm^2	0.51±0.12
MG rest, mmHg	21±8
EF, %	29±10
CO, l/min	4.14±1.22
Mean Q, ml/s	195±52
Syst RR, mmHg	118±20
CAD, n (%)	53 (77)
Hypertension, n (%)	43 (62)
Diabetes, n (%)	24 (35)
BNP, pg/ml	523 (239-971)

Abbreviations:
r_s= Spearman´s correlation coefficient; BNP median (interquartile range); others mean±SD; (I)EOA= (indexed) effective orifice area aortic valve; Valv. Resist.= valve resistance; MG = mean gradient; EF= left ventricular ejection fraction; CO= cardiac output; Q= mean transvalvular flow rate; WMSI= wall motion score index; CAD=coronary artery disease

Table 2

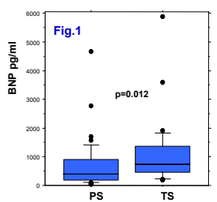
Parameter	BNP r_s	p
EOA		
rest	-0.50	<0.0001
peak stress	-0.46	0.0002
MG		
rest	0.15	0.21
peak stress	0.09	0.47
Valv. Resist.		
rest	0.42	0.0006
peak stress	0.36	0.003
EF		
rest	-0.59	<0.0001
peak stress	-0.51	<0.0001
SV		
rest	-0.33	0.006
peak stress	-0.22	0.07
Mean Q		
rest	-0.31	0.01
peak stress	-0.29	0.02
WMSI		
rest	0.36	0.004
peak stress	0.51	<0.0001
Age	0.12	0.32
CAD	0.07	0.54
number of vessels	0.06	0.61

RESULTS

BNP was markedly elevated in low-flow AS compared to reported AS pts with normal LV function (e.g. 4,5), although levels varied widely (**Table 1**).

BNP was significantly related to EF, EOA, valve resistance, wall motion score index, SV, and mean transvalvular flow rate at rest and peak stress, but not mean gradient, age or gender.

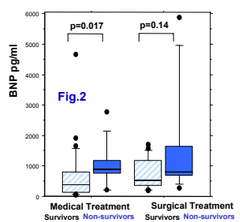
Truly severe vs pseudo-severe AS: BNP was significantly higher in TS (p=0.012), although a wide overlap was found (**Fig.1**).



Outcome (Fig.2):
AVR was performed in 29 pts. Overall, 20 pts died (after 154±142 d), of these 9 pts after AVR (1-269 d postop.).

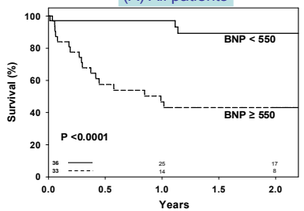
BNP was higher in 20 pts who died compared to 49 survivors: 850 [740 to 1124] vs. 422 [210 to 928] pg/ml, p=0.004.

In 9 pts who died after AVR, BNP tended to be higher compared to the 20 surgical survivors. No difference was found in EF (25±9 vs. 28±8%, n.s.) or age (68±10 vs. 65±11 y, n.s), whereas preop. EOA was lower (0.74±0.14 vs. 0.89±0.18 cm^2, p=0.04).



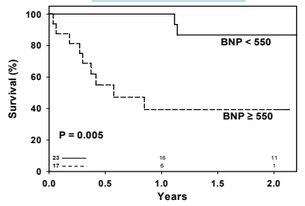
RESULTS: SURVIVAL of pts with BNP ≥ 550 vs BNP < 550

(A) All patients



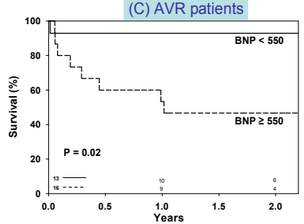
(A): In the **total cohort** survival at 1 year was poor in pts with BNP ≥550 pg/ml (47±9%), however, good in pts with BNP <550 (97±3%, p<0.0001).

(B) No AVR patients



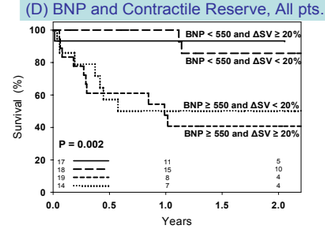
(B): 1-year survival was 39±13% in **medically treated** pts with BNP ≥550 and 100% (p=0.005) with BNP <550.

(C) AVR patients



(C): In pts **with AVR**, 30-day mortality was 19% in pts with BNP ≥550 vs. 8% in pts with BNP <550.
1-year survival was 53±13% vs. 92±7% (p=0.02).

(D) BNP and Contractile Reserve, All pts.



(D): **Contractile reserve** defined by increase of SV ≥20% at peak DSE:

In 36 pts **with CR**, 1-year survival was significantly lower in pts with BNP ≥550 compared to BNP <550:

48±12% vs. 93±6%; p=0.009.

The same pattern was observed in the subset of 32 pts with **no or poor CR**: 50±14% vs. 100%; p=0.014.

By univariate analysis only age ≥70 years (p=0.015), NYHA class ≥2 (p=0.006), resting EOA ≤0.8 cm^2 (p=0.005), poor CR defined by a peak transvalvular flow rate <250 ml/s on DSE (p=0.0017), and BNP ≥550 (p<0.001) were significant predictors of outcome for the total cohort. A trend was observed for diabetes (p=0.05). Gender, coronary artery disease, LV EF, aortic valve replacement and projected indexed EOA were not significantly related to outcome.

After adjusting for age, NYHA class, resting EOA and contractile reserve, **BNP ≥550** remained a strong independent predictor of outcome (p=0.0009; HR 6.1, 95% CI 2.0-26.3).

DISCUSSION

Increased LV wall pressure may lead to higher BNP in truly severe AS compared to pseudo-severe AS. Due to high overlap of levels, however, BNP does not appear useful for clinical differentiation of TS or PS. BNP was the strongest parameter of outcome in all subgroups. Further studies with even larger patient numbers are needed.

Importantly, high BNP ≥550 predicts survival in pts with low-flow AS independently of presence of contractile reserve: Even pts without CR had a better outcome with low BNP.

CONCLUSIONS

High BNP is independently associated with poor survival in pts with low-flow AS.

In patients without contractile reserve, outcome is significantly reduced in patients with BNP ≥550 pg/ml, whereas outcome is good with low BNP.

Thus, BNP adds important information beyond the contractile reserve, and may help to identify pts in the difficult subgroup without CR who are likely to benefit from valve replacement.

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