

## Aminoterminal proB-type natriuretic peptide: a key parameter to optimise therapeutic management of low-flow, low-gradient aortic stenosis

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On behalf of TOPAS study

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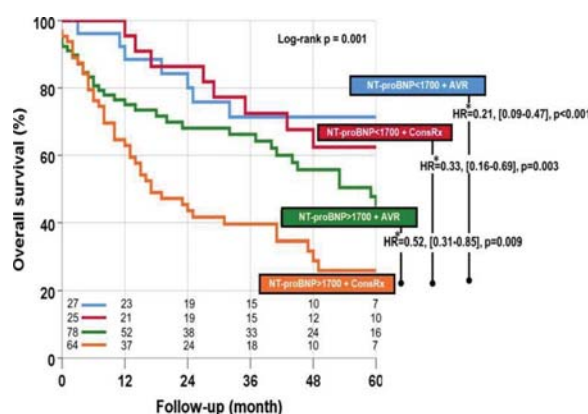
**Background:** B-type natriuretic peptide (BNP) and aminoterminal-proBNP (NT-proBNP) are well established surrogates of LV function impairment. However, data are scarce regarding their prognostic value to risk-stratify patients with classical low-flow, low-gradient aortic stenosis (LFLG-AS, with low left ventricular [LV] ejection fraction).

**Methods:** The TOPAS study is a prospective observational cohort of 240 patients with aortic valve area  $<0.6 \text{ cm}^2/\text{m}^2$ , mean gradient  $<40 \text{ mmHg}$  and LVEF  $<50\%$ . True severe AS was adjudicated using flow independent grading schemes.

**Results:** BNP significantly predicted one-year (area under the receiver operating-characteristic curve [AUC]  $0.62 \pm 0.04$ ,  $p=0.026$ ) but not three-year mortality. After adjustment for the severity of AS, initial treatment (aortic valve replacement [AVR] vs. conservative management [ConsRx]), age, sex and the EuroSCORE (Model#1), BNP-ratio  $>550 \text{ pg/ml}$  had a trend to predict time to death ( $\text{HR}=2.14$  [ $1.00-4.58$ ],  $p=0.05$ ). In contrast, NT-proBNP ratio significantly predicted both one and three-year mortality (AUC  $=0.67 \pm 0.04$  and  $0.66 \pm 0.05$ , both  $p=0.001$ ), and independently predicted time to death ( $\text{HR}=1.39$  per 1 unit of Log transformed NT-proBNP [ $1.11-1.74$ ],  $p=0.004$ ). In a head-to-head comparison (108 patients with both biomarkers), the AUCs to predict one and three-year mortality were

significantly higher with NT-proBNP versus BNP ( $p<0.009$ ). NT-proBNP but not BNP independently predicted mortality and significantly improved Model#1 (Likelihood ratio test  $\chi^2=15.95$ ,  $p<0.001$ ). The category-free net reclassification index of NT-proBNP was  $0.71$  ( $p=0.008$ ) versus  $0.38$  ( $p=0.15$ ) for BNP. Furthermore, there was a marked survival benefit associated with AVR in patients with NT-proBNP  $\geq 1700 \text{ pg/ml}$  (adjusted hazard ratio (aHR) associated to AVR vs conservative management  $=0.52$  [ $0.31-0.85$ ],  $p=0.009$ ), while those  $<1700 \text{ pg/ml}$  had excellent one-year survival under ConsRx (only one death [ $4.5 \pm 4.4\%$ ] at one year as compared to 23 [ $37 \pm 6.2\%$ ] for ConsRx-NTproBNP  $>1700$ , aHR  $=0.11$  [ $0.01-0.83$ ],  $p=0.033$ ). The survival benefit associated with AVR interacted with NT-proBNP ( $p<0.001$ ) but not with true or pseudosevere AS ( $p=0.53$  for interaction), suggesting that NT-proBNP might identify moderate AS patients but sufficiently severe valvulo-ventricular disease to justify AVR.

**Conclusion:** NT-proBNP appears to be an excellent biomarker for the clinical purpose of risk-stratifying classical LFLG-AS. A threshold of  $1700 \text{ pg/ml}$  i.e. close to the diagnostic threshold for heart failure in acute dyspnea, was a strong independent determinant of the survival benefit associated with aortic valve replacement. Our findings suggest that NT-proBNP should be preferred over BNP.



\*HR: hazard ratio of death adjusted for age, sex, true aortic AS severity and the EuroSCORE

Survival according to NT-proBNP and AVR