Long-Term Prognostic Value of High-Sensitivity Troponin T Added to N-Terminal Pro Brain Natriuretic Peptide Plasma Levels Before Valve Replacement for Severe Aortic Stenosis

Fabian Barbieri, MD[a], Thomas Senoner, MD[a], Agne Adukauskaite, MD[a], Stephan Dobner, MD, PhD[b], Johannes Holfeld, MD[c], Severin Semsroth, MD[c], Thomas Lambert, MD[d], David Zweiker, MD[e], Thomas Theurl, MD[f], Peter Paul Rainer, MD, PhD[e], Albrecht Schmidt, MD[e], Gudrun Maria Feuchtner, MD[g], Clemens Steinwender, MD[d], Uta Charlotte Hoppe, MD, PhD[f], Florian Hintringer, MD[a], Axel Bauer, MD[a], Silvana Müller, MD[a], Michael Grimm, MD[c], Bernhard Erich Pfeifer, PhD[h,i], and Wolfgang Dichtl, MD, PhD[a,*]

Natriuretic peptide plasma levels help to manage patients with severe aortic stenosis (AS). The role of troponin plasma levels in this patient cohort remains speculative. A consortium of 4 university hospital centers in Austria analyzed retrospectively 3,595 patients admitted for valve replacement because of severe AS since 2007. The aim was to compare the additive preprocedural value of high-sensitivity troponin T (hsTnT) to N-terminal pro brain natriuretic peptide (NT-proBNP) plasma levels in predicting postoperative long-term survival in a large cohort undergoing either surgical (57.8%) or transcatheter (42.2%) aortic valve replacement. During a median follow-up of 2.93 (1.91 to 4.92) years, 919 patients (25.6%) died, in them 556 (15.5%) due to cardiovascular causes. Both normal hsTnT (<14 ng/l) and NT-proBNP (within age- and sex-corrected normal range) plasma levels were found in 481 patients (14.3%, group 1). Normal hsTnT but elevated NT-proBNP plasma levels were found in 748 patients (22.3%, group 2). Elevated hsTnT but normal NT-proBNP plasma levels were found in 258 patients (7.7%, group 3). Both elevated hsTnT and elevated NT-proBNP plasma levels were found in 1,869 patients (55.7%, group 4). Using Log Rank tests for comparison there was a highly significant difference in both cardiovascular mortality (p <0.0001) and all-cause mortality (p <0.0001). All-cause mortality rates after 1, 3, and 5 years were 2.1%, 5.4%, 7.7% in group 1; 4.0%, 7.5%, 11.5% in group 2; 5.8%, 8.9%, 14.0% in group 3; and 12.3%, 22.6%, 28.4% in group 4. In conclusion, hsTnT adds additional impact to NT-proBNP as a routinely available biomarker for risk stratification concerning postoperative survival in patients with severe AS admitted for valve replacement. The present study supports the concept to integrate hsTnT plasma levels in the management of severe AS. **(Am J Cardiol 2019;124:1932−1939)**

Biomarkers used in clinical routine such as natriuretic peptides[1−3] or troponins[4−6] may play a role in the risk stratification of patients with severe aortic stenosis (AS). Small studies indicate that in particular natriuretic peptides plasma levels predict symptom onset in previously asymptomatic patients and postoperative outcome in high-risk patients.[1−3] Accordingly, the use of B-type natriuretic peptide (BNP) plasma levels has been introduced in American and European recommendations using a qualitative description corrected for age, sex, and renal function.[7,8] Whereas the American appropriate use criteria distinguish between normal versus elevated BNP plasma levels, European guidelines set the BNP cut-off at a threefold increase of normal range by repeated measures without other explanations. High-sensitivity troponin T (hsTnT) plasma levels are not mentioned in current recommendations. As recently shown in a small study of 98 patients with low flow, low gradient AS, a combined measure of natriuretic peptides and troponins plasma levels may enhance biomarker based risk stratification.[9]

[a]University Clinic of Internal Medicine III, Medical University Innsbruck, Innsbruck, Austria; [b]Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [c]University Clinic of Heart Surgery, Medical University Innsbruck, Innsbruck, Austria; [d]Department of Cardiology, Kepler University Hospital, Medical Faculty, Johannes Kepler University Linz, Austria; [e]Department of Internal Medicine, Division of Cardiology, Medical University Graz, Graz, Austria; [f]University Clinic of Internal Medicine II, Paracelsus Medical University, Salzburg, Austria; [g]University Clinic of Radiology, Medical University Innsbruck, Innsbruck, Austria; [h]Institute of Clinical Epidemiology, Tirol Kliniken, Innsbruck, Austria; and [i]Institute of Electrical and Biomedical Engineering, University for Health Sciences, Medical Informatics and Technology (UMIT), Hall in Tirol, Austria. Manuscript received June 26, 2019; revised manuscript received and accepted September 12, 2019.

Grant support: Tiroler Wissenschaftsförderung (Innsbruck, Austria): TWF-2017-1-5, GZ: UNI-0404-2104 to WD.

See page 1938 for disclosure information.

*Corresponding author: Tel: (43) 5-1250481388; fax: (43) 5-1250422767.

E-mail addresses: dichtl@me.com; wolfgang.dichtl@i-med.ac.at (W. Dichtl).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.09.014

Methods

The Tyrolean Aortic Stenosis Study-2 (TASS-2) was established at the leading center Medical University Innsbruck in collaboration with 3 Austrian university hospitals (Medical University Graz, Johannes Kepler University Linz, Paracelsus Medical University Salzburg). Data were collected in accordance with regulations set forth by institutional review boards. Records from patients diagnosed with severe AS undergoing valve replacement between 2007 and 2017 were reviewed from 2013 to 2018. The TASS-2 group screened 4,516 consecutive patients who underwent aortic valve replacement. At Medical University Graz and Paracelsus Medical University Salzburg only patients receiving transcatheter aortic valve replacement (TAVR) were enrolled. Exclusion criteria were aortic valve replacement due to nonsevere AS and/or ongoing or previous endocarditis, acute coronary syndrome or cardiopulmonary resuscitation within 2 months before valve intervention, redo aortic valve intervention, Ross procedure surgery, subvalvular severe AS, aortic balloon valvuloplasty for bridging, unknown coronary anatomy, conversion of TAVR to surgical aortic valve replacement (SAVR) during the procedure and other valve pathologies considered as the main clinical problem. Accordingly, 3,595 patients with severe AS—defined by an aortic valve area (AVA) equal/below 1 cm^2 and/or 0.6 cm^2/m^2 body surface area—were enrolled. AVA was calculated using the continuity equation according to the

Table 1
Baseline characteristics of patients with severe aortic stenosis undergoing valve replacement

Variable	All patients (n = 3,595)	SAVR (n = 2,078)	TAVR (n = 1,517)
Age (years)	77 (70−82)	72 (66−78)	82 (78−85)
Total cholesterol (mg/dl)	175 (145−207)	180 (151−213)	168 (140−197)
LDL cholesterol (mg/dl)	100 (78-127)	108 (85−136)	92 (71−117)
Triglycerides (mg/dl)	103 (76−141)	106 (77−148)	99 (75−131)
HsTnT (ng/l)	18.0 (10.7−32.0)	14 (8.4−22)	27 (17−50)
<14	1235 (36.5%)	1023 (49.7%)	212 (16.0%)
≥14	2146 (63.5%)	1037 (50.3%)	1109 (84.0%)
NTproBNP (ng/l)	1342.5 (516.9−3221.0)	855.9 (363.0−2121.5)	2357.5 (979.4−4878.3)
Normal	763 (21.4%)	543 (26.3%)	220 (14.7%)
Elevated	2799 (78.6%)	1519 (73.7%)	1280 (85.3%)
Creatinine (mg/dl)	1.00 (0.83−1.20)	0.97 (0.82−1.13)	1.05 (0.86−1.31)
eGFR (ml/min/1.73 m^2)	80.8 (65.0−92.3)	85.6 (74.0−98.6)	73.1 (53.9−82.5)
No. of coronary arteries narrowed			
None	2,190 (61.0%)	1,416 (68.1%)	776 (51.2%)
1	622 (17.3%)	319 (15.4%)	303 (20.0%)
2	337 (9.4%)	161 (7.7%)	176 (11.6%)
3	310 (8.6%)	132 (6.4%)	178 (11.7%)
Left main	133 (3.7%)	50 (2.4%)	83 (5.5%)
STS PROM			
<3%	2,031 (57.3%)	1,537 (74.6%)	494 (33.3%)
3−<8%	1,372 (38.7%)	496 (24.1%)	876 (59.1%)
8-<15%	131 (3.7%)	26 (1.3%)	105 (7.1%)
≥15%	8 (0.2%)	0 (0%)	8 (0.5%)
Arterial hypertension	2,913 (81.1%)	1,668 (80.3%)	1,245 (82.2%)
Diabetes mellitus	862 (24.0%)	461 (22.2%)	401 (26.5%)
Hypercholesterolemia	1,758 (57.9%)	1,233 (59.3%)	525 (54.7%)
Chronic obstructive pulmonary disease	508 (16.1%)	345 (16.6%)	235 (15.5%)
Significant carotid stenosis	391 (10.9%)	159 (7.7%)	232 (15.5%)
Stroke/transient ischemic attack	336 (9.4%)	155 (7.5%)	181 (12.0%)
Echocardiography			
AVA (cm^2)	0.68 (0.53−0.80)	0.70 (0.60−0.85)	0.60 (0.50−0.75)
AVA/BSA [DuBois]	0.36 (0.30−0.44)	0.37 (0.31−0.45)	0.35 (0.29−0.42)
AV mean pressure gradient (mm Hg)	49 (41−60)	50 (42−60)	49 (40−60)
LVEF (%)	59 (50−63)	60 (52−65)	55 (45−62)
Electrocardiogram			
Resting heart rate (beats/min)	71 (63−80)	70 (62−79)	72 (64−82)
Atrial fibrillation	1,013 (28.2%)	449 (21.6%)	564 (37.2%)
AV block I°	527 (15.1%)	297 (14.5%)	230 (15.9%)
Bundle branch block	739 (20.9%)	380 (18.5%)	359 (24.2%)

Numbers are presented as median (interquartile range) or number of patients (percentage).

AV = aortic valve; AVA = aortic valve area; BSA = body surface area; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; hsTnT = high sensitivity troponin T; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro brain natriuretic peptide; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging.[10] Echocardiographic imaging of the heart was performed/supervised by level III observers. Patients were subjected to coronary angiography to identify any significant coronary artery disease before aortic valve replacement, along with right heart catheterization to invasively test for concomitant pulmonary hypertension. In selected patients (e.g., poor echocardiographic imaging due to obesity and/or emphysema) invasive assessment of AVA and pressure gradients was performed, according to the operator's discretion.

The concentration of hsTnT in plasma was determined using electrochemiluminescence immunoassay kits according to the manufactureŕs instruction (Roche Diagnostics GmbH, Mannheim, Germany). In human plasma samples, the test has a lower detection limit of 5 ng/l, and the 99th percentile cut-off point has been reported as 14 ng/l in healthy individuals,[11] which is currently defined as a normal cut-off value regardless of gender, age, and renal function.

NT-proBNP concentrations were measured using a commercially available assay with an E170 instrument (proBNP II assay using monoclonal antibodies on a Modular, Roche Diagnostics, Vienna, Austria). The lower analytical limit of detection of NT-proBNP is 5 ng/l. Upper limits of the normal ranges were as follows: <130 ng/l for women aged 18 to 44 years; <85.8 ng/l for men aged 18 to 44 years; <249 ng/l for women aged 45 to 54 years; <121 ng/l for men aged 45 to 54 years; <287 ng/l for women aged 55 to 64 years; <210 ng/l for men aged 55 to 64 years; <301 ng/l for women aged 65 to 74 years; <376 ng/l for men aged 65 to 74 years; <738 ng/l for women aged above 75 years; <486 ng/l for men aged above 75 years.

Clinical variables were obtained through patient chart abstraction. The Society of Thoracic Surgeons predicted risk

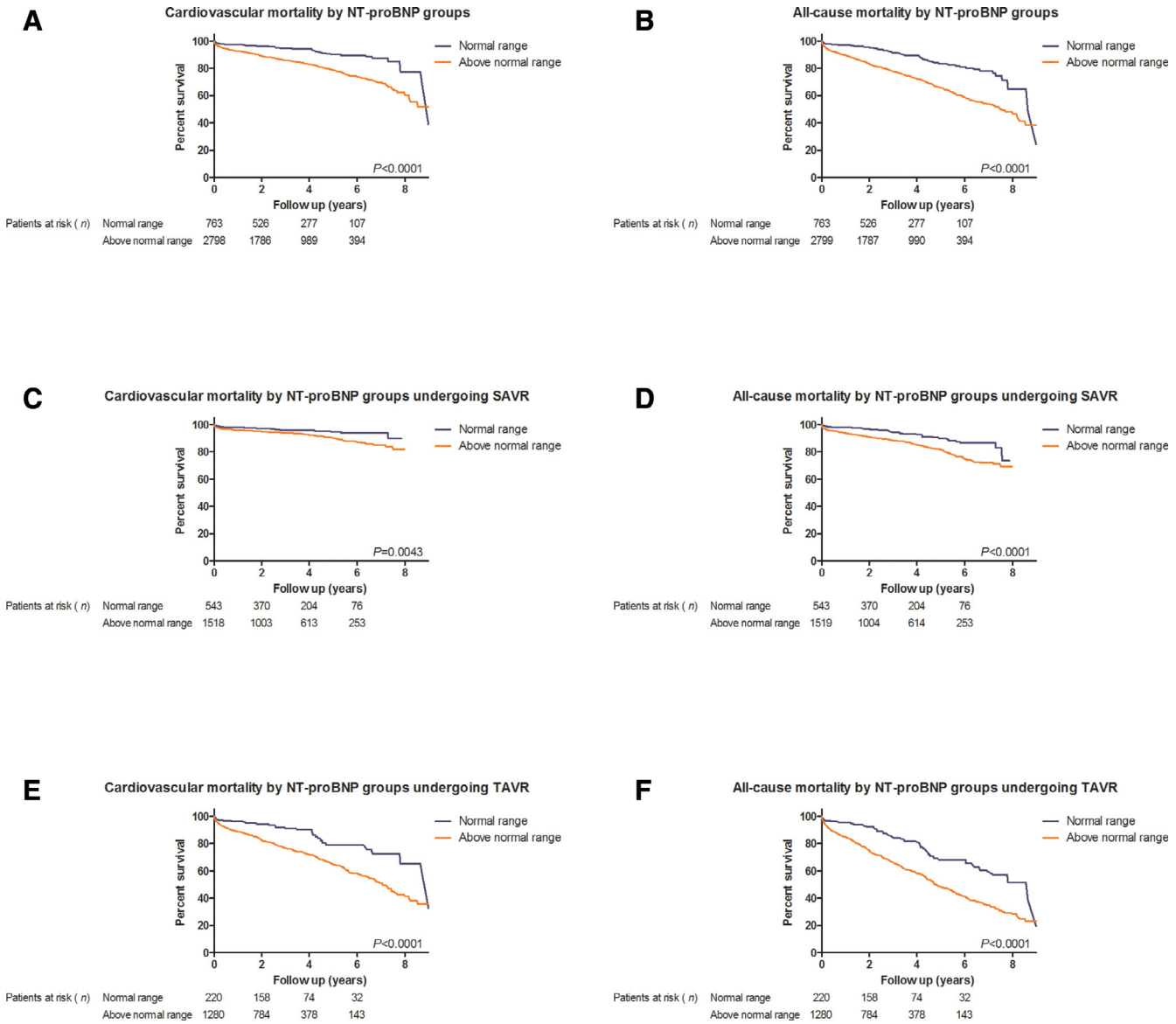

Figure 1. Kaplan-Meier estimates of cardiovascular (*A, C*, and *E*) and all-cause mortality (*B, D,* and *F*) in patients after aortic valve replacement due to severe stenosis, stratified to pre-procedural NT-proBNP plasma levels using a cut-off point within or above age- and sex-corrected normal range. Parts *C* to *F* show Kaplan-Meier estimates in patients divided by type of procedure (SAVR or TAVR).

of mortality score (STS-PROM score) was calculated for each patient. Cardiovascular and total mortality was provided by the Austrian Statistical Office (Statistik Austria). The cause of death was uncertain for a single patient only, therefore he was excluded from analysis of cardiovascular mortality. This study was approved by the local ethical committee and registered at ClinicalTrials.gov (NCT02448485).

Continuous variables are presented as median and interquartile range. Categorical variables were expressed as number and percentages. Patients were divided into groups based on measurements taken to evaluate risk stratification. Survival analyses were estimated with the Kaplan-Meier method and assessed with a log-rank test. Cox proportional hazards regression was performed for multivariate analysis on overall survival by using statistically significant variables from univariate analysis. To assess the Youden index for the prediction of mortality a receiver operating curve was conducted. Calculations were conducted with IBM

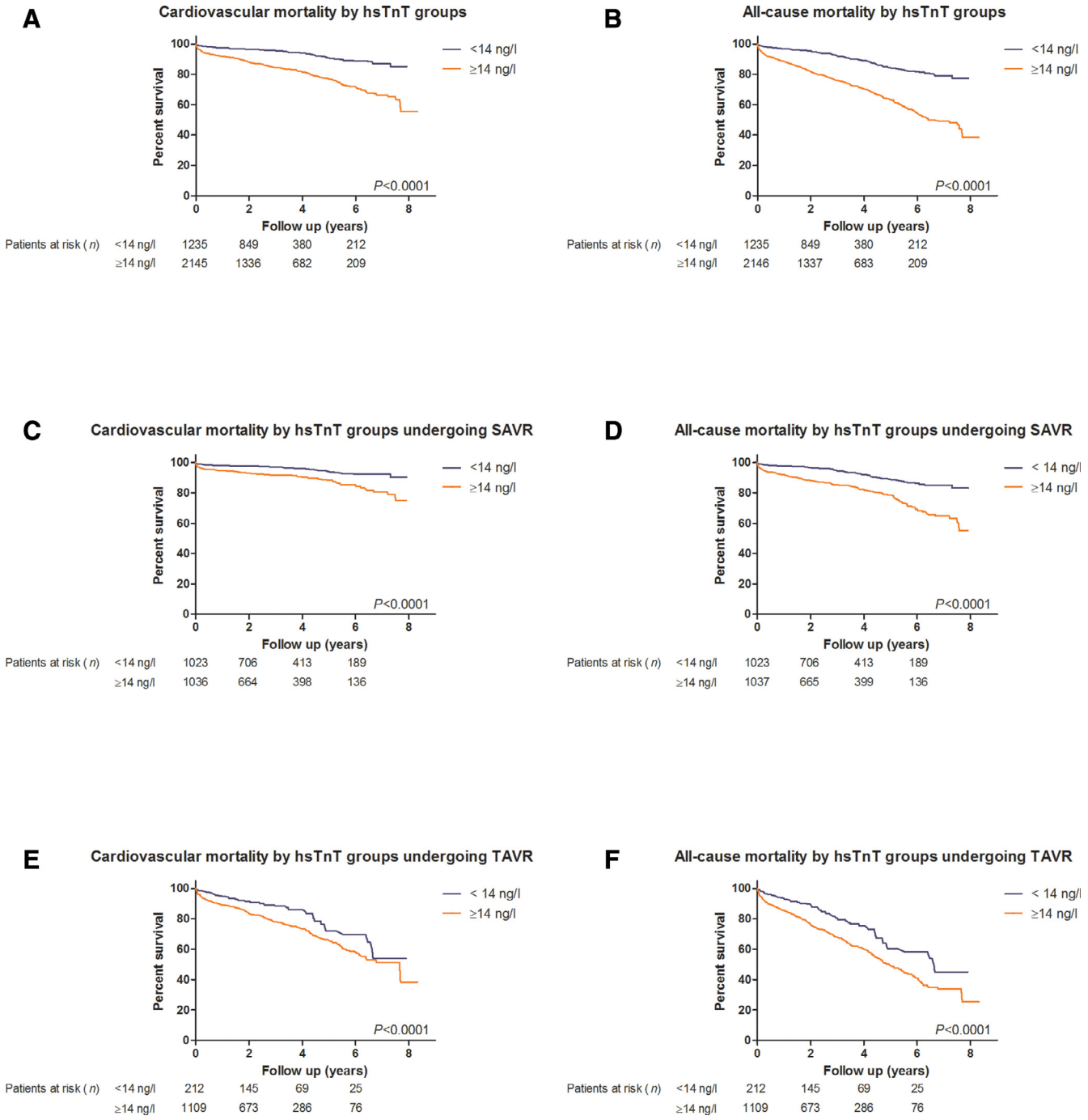

Figure 2. Kaplan-Meier estimates of cardiovascular (*A, C*, and *E*) and all-cause mortality (*B, D*, and *F*) in patients after aortic valve replacement due to severe stenosis, stratified to preprocedural hsTnT plasma levels using a cut-off point at 14 ng/l. Parts *C* to *F* show Kaplan-Meier estimates in patients divided by type of procedure (SAVR or TAVR).

SPSS version 24 (IBM Corporation, Armonk, New York). Graphics were designed by using GraphPad PRISM, version 5 (GraphPad Software, Inc., La Jolla, California). p Values of <0.05 were considered significant.

Results

Baseline characteristics of the cohort (n = 3,595) are summarized in Table 1. Out of 2,078 patients who underwent SAVR, a mechanical prosthesis was implanted in 190 patients (9.1%), a biological prosthesis was implanted in 1,878 patients (90.4%) and a Bentall procedure was performed in 10 patients (0.5%).

Normal NT-proBNP plasma levels were found in 763 (21.4%) patients, 2,799 (78.6%) had elevated NT-proBNP plasma levels. Using Log Rank tests for comparison there was a highly significant difference in both cardiovascular mortality (p <0.0001) and all-cause mortality (p <0.0001), as shown in Figure 1. Patients were then stratified according whether SAVR or TAVR had been performed. Both cardiovascular and all-cause mortality (part D and F) were significantly increased if preprocedural NT-proBNP levels had been above normal range. By using the receiver operating characteristic curve method, we found the most sensitive and specific value of 1,295 ng/l NT-proBNP with an area under the curve of 0.692. Corresponding figure is displayed in a supplementary publication.[12]

Normal (<14 ng/l) hsTnT plasma levels were found in 1,235 (36.5%) patients, whereas 2,146 (63.5%) had pathological values. Using Log Rank tests for comparison of cardiovascular mortality and all-cause mortality between the 2 groups yielded highly significant differences (p <0.0001, Figure 2). Patients were then stratified according whether SAVR or TAVR had been performed. Both cardiovascular and all-cause mortality were significantly increased if preprocedural hsTnT levels had been ≥14 ng/l. By using the receiver operating characteristic curve method we found the most sensitive and specific value of 25 ng/l hsTnT with an area under the curve of 0.703.

In depth analysis of the influence of concomitant CAD on the prognostic value of hsTnT on cardiovascular as well as all-cause mortality is provided in a supplementary publication.[12]

To further evaluate the prognostic value of hsTnT plasma levels, we analyzed predefined subgroups—below detection level of 5 ng/l; 5 to 13.99 ng/l; 14 to 50 ng/l;

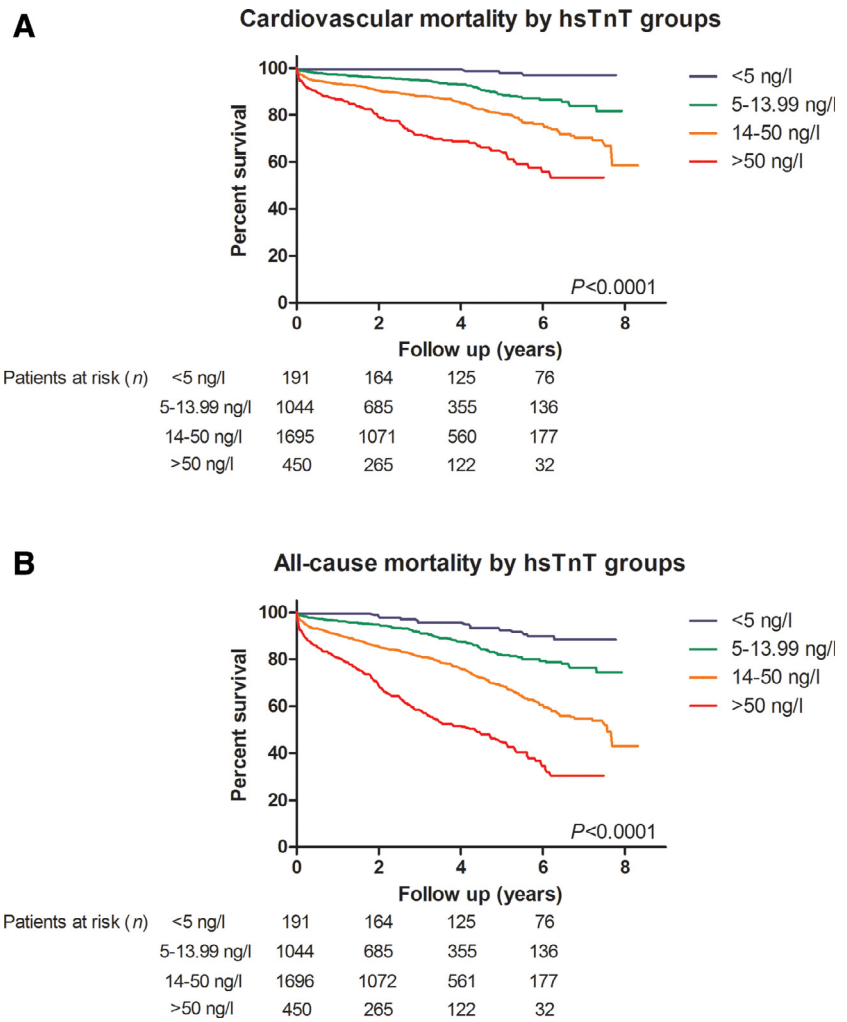

Figure 3. Kaplan-Meier estimates of cardiovascular (*A*) and all-cause mortality (*B*) in patients after aortic valve replacement due to severe stenosis, stratified to pre-procedural hsTnT plasma levels using predefined subgroups.

>50 ng/l. Undetectable hsTnT (<5 ng/l) plasma levels were found in 191 (5.6%) patients, whereas 1,044 (30.9%) had minimally detectable hsTnT plasma levels (5 to 13.99 ng/l), 1,696 (50.2%) had mildly to moderately elevated values (14 to 50 ng/l) and 450 (13.3%) had severely increased hsTnT plasma levels (>50 ng/l). Using Log Rank tests for comparison of cardiovascular mortality and all-cause mortality within all 4 subgroups yielded highly significant differences (p <0.0001, Figure 3).

Both normal hsTnT and NT-proBNP plasma levels (group 1) were measured in 481 (14.3%) patients. Cardiovascular mortality rates after 1, 3, and 5 years were 9 (1.9%), 15 (3.1%), and 21 (4.4%). All-cause mortality rates after 1, 3, and 5 years were 10 (2.1%), 26 (5.4%), and 37 (7.7%).

Normal hsTnT but elevated NT-proBNP plasma levels (group 2) were measured in 748 (22.3%) patients. Cardiovascular mortality rates after 1, 3, and 5 years were 22 (2.9%), 33 (4.4%), and 51 (6.8%). All-cause mortality rates after 1, 3, and 5 years were 30 (4.0%), 56 (7.5%), and 86 (11.5%).

Elevated hsTnT but normal NT-proBNP plasma levels (group 3) were measured in 258 (7.7%) patients. Cardiovascular mortality rates after 1, 3, and 5 years were 14 (5.4%), 19 (7.4%), and 26 (10.1%). All-cause mortality rates after 1, 3, and 5 years were 15 (5.8%), 23 (8.9%), and 36 (14.0%).

Both elevated hsTnT and elevated NT-proBNP plasma levels (group 4) were measured in 1,869 (55.7%) patients. Cardiovascular mortality rates after 1, 3, and 5 years were 161 (8.6%), 264 (14.1%), and 315 (16.9%). All-cause mortality rates after 1, 3, and 5 years were 230 (12.3%), 423 (22.6%), and 531 (28.4%).

Using Log Rank tests for comparison, there was a highly significant difference in both cardiovascular mortality (p <0.0001) and all-cause mortality (p <0.0001), as shown in Figure 4. In multivariate cox regression analysis—including STS PROM score (low risk <3%, intermediate risk 3 - <8%, high risk 8 - <15%, extreme risk ≥15%), degree of left ventricular systolic dysfunction (ejection fraction 30% to 50% and <30%), atrial fibrillation, sex, age, renal function,

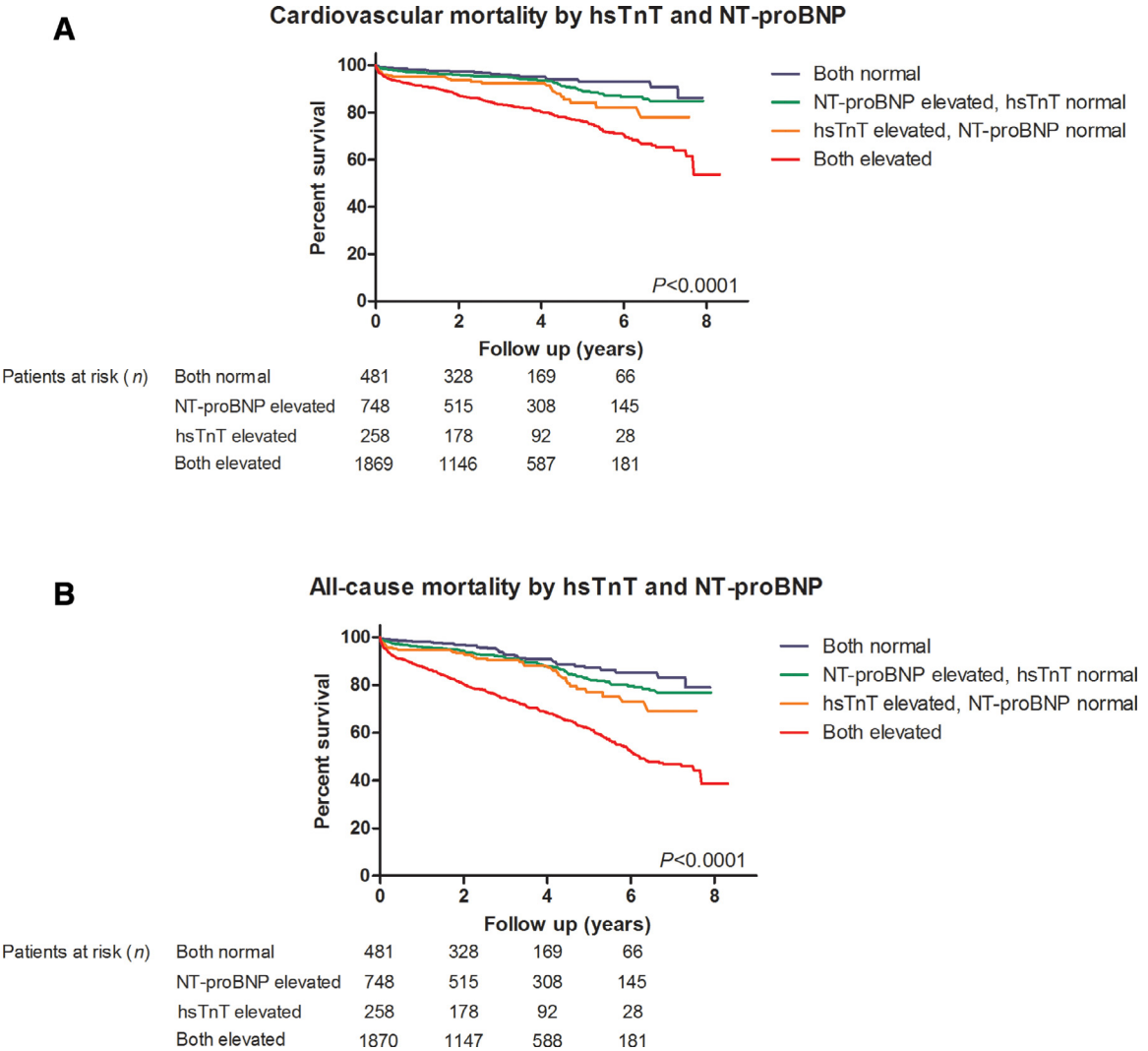

Figure 4. Kaplan-Meier estimates of cardiovascular (*A*) and all-cause mortality (*B*) in patients after aortic valve replacement due to severe stenosis, stratified to combined measures of preprocedural hsTnT and NT-proBNP plasma levels. Cut-off points were 14 ng/l for hsTnT and within or above age- and sex-corrected normal range for NT-proBNP, respectively.

Table 2
Multivariate cox regression analysis for all-cause mortality

Variable	HR (95 % CI)	*p* Value for heterogenity
hsTnT (<14 ng/l as reference)	1.381 (1.087−1.755)	0.008
NT-proBNP (normal range as reference)	1.262 (1.054−1.512)	0.012
LVEF (>50% as reference)		
LVEF (30%−50%)	1.037 (0.865−1.244)	0.691
LVEF (<30%)	1.242 (0.905−1.705)	0.179
Age	1.024 (1.01−1.038)	0.001
CAD	1.103 (0.940−1.294)	0.230
Male gender	0.805 (0.680−0.953)	0.012
Arterial hypertension	1.124 (0.907−1.393)	0.268
Atrial fibrillation	1.625 (1.388−1.903)	<0.001
eGFR	0.992 (0.988−0.996)	<0.001
COPD	1.255 (1.028−1.532)	0.025
Diabetes mellitus	1.037 (0.865−1.244)	0.692
STS-PROM score (<3% as reference)		
3 - <8%	1.166 (0.938−1.448)	0.166
8 - <15%	1.434 (0.998−2.061)	0.051
≥15%	2.166 (0.761−6.162)	0.147
TAVR (SAVR as reference)	1.813 (1.489−2.209)	<0.001

CAD = coronary artery disease; CI = confidence interval; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HR = hazard ratio; hsTnT = high sensitivity troponin T; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro brain natriuretic peptide; SAVR = surgical aortic valve replacement; STS-PROM score = Society of Thoracic Surgeons predicted risk of mortality score; TAVR = transcatheter aortic valve replacement.

chronic obstructive pulmonary disease, diabetes mellitus, concomitant significant coronary artery disease and type of procedure—preprocedural hsTnT and NT-proBNP plasma levels were strong independent predictors for postoperative survival, as shown in Table 2: hazard ratio 1.381, 95% confidence interval, 1.087 to 1.755; p = 0.008 for elevated hsTnT (≥14 ng/l). Age- and sex-corrected elevated NT-proBNP showed a hazard ratio of 1.262, confidence interval 1.054 to 1.512, p = 0.012. The multivariate cox regression model on cardiovascular mortality using identical covariates is displayed in a supplementary publication.[12]

Discussion

Our study demonstrates significant impact of hsTnT in addition to NT-proBNP plasma levels in biomarker-based risk stratification in patients with severe AS undergoing valve replacement. A combined measure of both routinely available biomakers improves risk stratification as patients with elevation of both hsTnT and NT-proBNP had a marked increase in postoperative mortality.

To the best of our knowledge TASS-2 shows real-life data of the largest multicenter study cohort to date consisting of consecutively enrolled patients with biomarkers from both the troponin and natriuretic peptide families. It supports the notion that some patients with severe AS undergo valve replacement at a later than ideal time point. Our results suggest that in particular a combination of subtle myocardial damage − detectable by elevated hsTnT plasma levels − and of intracardiac pressure overload − detectable by elevated NT-proBNP levels − significantly and negatively affect long-term outcome by increasing cardiovascular and all-cause mortality, even after an uneventful peri-interventional course.

Recent advances in imaging techniques such as echocardiographic longitudinal or global strain and/or detection of myocardial fibrosis by late gadolinium cardiac magnetic resonance imaging may play a role in improving risk assessment in the future. However, some of these techniques are expensive, not readily available and/or highly operator-dependent. Therefore, we believe that easily assessable biomarkers will increasingly influence clinical decision making in the near future and our data suggest that hsTnT should be taken into account in addition to NT-proBNP in optimal timing for valve replacement. However, most of our patient cohort had developed symptoms before valve replacement. The predictive value of hsTnT plasma levels in asymptomatic patients thus remains speculative and extrapolation of our results for risk assessment in asymptomatic patients with severe AS should only be done with great caution. Ongoing prospective studies will show whether increased troponin and natriuretic peptides plasma levels favour earlier valve replacement in patients with severe but still asymptomatic AS.

Disclosures

The authors have no conflicts of interest to disclose.

1. Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H, Binder T, Pacher R, Maurer G, Baumgartner H. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation* 2004;109:2302–2308.
2. Dichtl W, Alber HF, Feuchtner GM, Hintringer F, Reinthaler M, Bartel T, Süssenbacher A, Grander W, Ulmer H, Pachinger O, Müller S. Prognosis and risk factors in patients with asymptomatic aortic stenosis and their modulation by atorvastatin treatment. *Am J Cardiol* 2008;102:743–748.
3. Clavel MA, Malouf J, Michelena HI, Suri RM, Jaffe AS, Mahoney DW, Enriquez-Sarano M. B-type natriuretic peptide clinical activation in aortic stenosis: impact on long-term survival. *J Am Coll Cardiol* 2014;63:2016–2025.
4. Røsjø H, Andreassen J, Edvardsen T, Omland T. Prognostic usefulness of circulating high-sensitivity troponin T in aortic stenosis and relation to echocardiographic indexes of cardiac function and anatomy. *Am J Cardiol* 2011;108:88–91.
5. Saito T, Hojo Y, Hirose M, Ikemoto T, Katsuki T, Kario K. High-sensitivity troponin T is a prognostic marker for patients with aortic stenosis after valve replacement surgery. *J Cardiol* 2013;61:342–347.
6. Chin CW, Shah AS, McAllister DA, Cowell J, Alam S, Langrish JP, Strachan FE, Hunter AL, Choy MA, Lang CC, Walker S, Boon NA, Newby DE, Mills NL, Dweck MR. High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis. *Eur Heart J* 2014;35:2312–2321.
7. Bonow RO, Brown AS, Gillam LD, Kapadia SR, Kavinsky CJ, Lindman BR, Mack MJ, Thourani VH. ACC/AATS/AHA/ASE/EACTS/HVS/SCA/SCAI/SCCT/SCMR/STS 2017 appropriate use criteria for the treatment of patients with severe aortic stenosis: a report of the American College of Cardiology appropriate use criteria task force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Valve Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2017;70:2566–2598.
8. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S,

Zamorano JL, ESC Scientific Document Group. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739–2791.

9. Dahou A, Clavel MA, Capoulade R, O'Connor K, Ribeiro HB, Côté N, Le Ven F, Rodés-Cabau J, Dumesnil JG, Mathieu P, Pibarot P. B-type natriuretic peptide and high-sensitivity cardiac troponin for risk stratification in low-flow, low-gradient aortic stenosis: a substudy of the TOPAS study. *JACC Cardiovasc Imag* 2018;11:939–947.
10. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, Lancellotti P, LeFevre M, Miller F Jr, Otto CM. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr* 2017;30:372–392.
11. Giannitsis E, Kurz K, Hallermayer J, Jarausch AS, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem* 2010;56:254–261.
12. Barbieri F, Senoner T, Adukauskaite A, Dobner S, Holfeld J, Semsroth S, Lambert T, Zweiker D, Theurl T, Rainer P, Schmidt A, Feuchtner G, Steinwender C, Hoppe U, Hintringer F, Bauer A, Mueller S, Grimm M, Pfeifer B, Dichtl W. Dataset on the prognostic value of cardiac biomarkers used in clinical routine in patients with severe aortic stenosis undergoing valve replacement. *Data Brief* 2019. in press.