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ST2 predicts survival in patients undergoing transcatheter aortic valve implantation☆

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ABSTRACT

Objective: To assess soluble suppression of tumorigenicity 2 (sST2) serum concentrations and predict mortality in patients undergoing transcatheter aortic valve implantation (TAVI).
Methods: We prospectively enrolled 74 patients with severe aortic stenosis (AS) who underwent TAVI and matched them to patients without aortic valve disease (n = 74). AS patients underwent comprehensive echocardiographic and cardiac magnetic resonance imaging and laboratory examinations. sST2 levels were determined by enzyme-linked immunosorbent assay (ELISA), their association with post procedural mortality was investigated using logistic and Cox regression analyses, and the prognostic performance compared to established risk scores.
Results: AS patients had substantially higher sST2 levels than controls (39.5 vs. 17.8 ng/mL, $p < 0.001$). sST2 significantly correlated with left and right atrial sizes ($r = 0.25$, $p = 0.033$ and $r = 0.38$, $p = 0.001$). At one and two years, 10 (13.9%) and 18 (25%) patients had died, respectively. sST2 significantly predicted survival in uni- and multivariate Cox regression analyses in our cohort ($p = 0.005$ and $p = 0.025$). sST2 also predicted major adverse cardiovascular events (MACE, $p = 0.046$). Adding sST2 to the established STS score improved prediction of two-year mortality in our cohort ($\Delta AUC = 0.108$; 95% CI −0.066–0.281; continuous NRI = 0.778; 95% CI: 0.277–1.278 and IDI = 0.141; 95% CI: 0.031–0.251), and a model containing both sST2 and the STS score had a negative predictive value of 96.1% and 86.3% regarding one and two-year mortality, respectively.
Conclusions: sST2 is elevated in AS patients and a prognostic marker of survival after TAVI. Implementation of this marker in routine pre-TAVI workup may improve risk prediction and patient selection.

1. Introduction

The prevalence of severe aortic stenosis (AS) is approximately 3.4% in individuals above 75 years and treatment of these patients poses enormous clinical and economic challenges [1]. Transcatheter aortic valve implantation (TAVI) has emerged as a novel treatment option for symptomatic severe AS. It has high procedural success rates, is less invasive than the conventional surgical approach, and recovery time is reduced [2,3]. TAVI is currently mainly performed in high-risk patients who are not deemed suitable for surgery, and many patients who have been treated conservatively in the past are now undergoing TAVI. Thus, the number of candidates for valve interventions has substantially increased. In addition, recent trials demonstrated that TAVI is also safe in patients with intermediate surgical risk [4] and patient numbers are therefore likely to increase further. In some industrialized countries, TAVIs already surpass the number of isolated surgical aortic valve replacements (SAVR) [5]. Current guidelines suggest TAVI should only be performed if life expectancy exceeds one year [6], however, not all patients benefit from TAVI in terms of functional improvement or mortality and some die shortly after the procedure.

Established clinical risk models for short-term procedural outcome such as the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), Society of Thoracic Surgeons (STS) score, or German Aortic Valve (AV) score are generally based on cohorts of patients undergoing cardiac surgery and poorly predict outcome in patients undergoing transcatheter aortic valve interventions [7]. Biomarkers

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that can be easily obtained may improve risk stratification. One of the most commonly used predictive biomarkers in cardiac patients is N-terminal pro brain natriuretic peptide (NT-proBNP), which is prognostic in heart failure and other heart diseases [8]. Another risk factor that has been investigated in TAVI patients is carbohydrate antigen 125 (CA125) [9]. Recently, soluble suppression of tumorigenicity 2 (sST2) has emerged as a promising novel biomarker of myocardial stress [10]. Serum levels of sST2 are elevated and associated with adverse outcomes in patients with ST-elevation myocardial infarction (STEMI) and non-ST-elevation acute coronary syndromes (NSTE-ACS) [11,12], congestive heart failure [10,13], and also in patients with AS [14,15]. ST2 is the receptor protein for the interleukin-1 family alarmin IL-33 [16], and is expressed in two main isoforms: as membrane bound receptor (ST2L), or as soluble form (sST2) that lacks the transmembrane domain. ST2L activates intracellular pathways that result in increased NF-κB activity and transcription of stress response factors [17]. The soluble form, sST2, acts as a decoy receptor that binds free IL-33 thereby reducing IL-33 activity. IL-33 itself exerts anti-hypertrophic and anti-fibrotic effects in experimental heart failure via membrane-bound ST2L [18,19]. Thus, increased sST2 levels may interfere with IL-33′s protective effects via ST2L.

Here, we investigated the role of sST2 as prognostic marker in patients with severe AS undergoing TAVI and establish reference values in a matched control cohort. We demonstrate that sST2 is substantially increased in these patients. sST2 improves the prediction of mortality by established risk scores and is by itself a significant predictor of outcome after TAVI.

2. Methods

2.1. Study cohorts

We included patients with severe AS (aortic valve area <1 cm^2) that underwent TAVI between June 2011 and February 2015 at the Division of Cardiology, Medical University of Graz, who were prospectively recruited for pre-procedural cardiac magnetic resonance imaging (cMR), blood sampling, and echocardiography. Within this time period, 280 patients underwent TAVI, 129 patients were recruited for cMR, and of those 74 had pre-procedural blood samples available. This cohort was representative for patients undergoing TAVI in our centre (Supplementary Table 1), with the exception of renal function, which was slightly higher in our patient sample due to the exclusion of patients with severe renal impairment for contrast-enhanced cMR imaging. In two patients TAVI was not successful (only valvuloplasty or valve dislocation to the aortic arch), these were excluded from survival analyses. All patients received a CoreValve (Medtronic, Minneapolis, Minnesota) prosthesis, which was implanted via transfemoral access. Patients were followed up at our institution for at least two years after the procedure. The study conforms to the Declaration of Helsinki and has been approved by the institutional ethics committee (No. 25-437ex12/13). Patients gave written informed consent.

Control patients without AS were obtained from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, which is a prospective cohort study of patients referred for coronary angiography and was designed to investigate genetic and environmental risk factors of cardiovascular disease [20]. Seventy-four patients were matched for gender and age, excluding patients with significant valve disease or evidence of ongoing myocardial ischemia.

2.2. Outcome and baseline variables

All-cause mortality was used as outcome variable and obtained from the Austrian death records (Statistics Austria), regular follow up visits, medical records, or personal contacts via phone. Two year follow-up was completed in all patients. Cardiovascular death was defined according to the Valve Academic Research Consortium-2 (VARC-2) criteria [21]. Major adverse cardiac events (MACE) were defined as cardiovascular death or readmission for non-fatal myocardial infarction, revascularization, or heart failure. Established risk scores, including EuroSCORE II [22], German AV score [23] and STS score, were determined by means of published formula or the respective online calculators (http://euroscore.org; http://riskcalc.sts.org, database v2.81).

2.3. Laboratory measurements

Blood samples were obtained within one week prior to TAVI and routine laboratory measurements performed. NT-proBNP and high-sensitivity cardiac Troponin T (cTnT) were determined by electrochemiluminescence immunoassays (Roche Diagnostics, Mannheim, Germany). Creatine kinase (CK) was measured enzymatically and C-reactive protein (CRP) by immunoturbidimetry on a Cobas 8000 modular analyser (Roche Diagnostics, Mannheim, Germany). Creatinine was measured using a rate-blanked and compensated modified Jaffé method (Roche Diagnostics, Mannheim, Germany). Estimated glomerular filtration rate (eGFR) was calculated according to the chronic kidney disease (CKD) Epidemiology Collaboration (CKD-EPI) equation [24]. Blood samples were then aliquoted, frozen, and stored until measurement of sST2, which was measured by enzyme-linked immunosorbent assay (Presage, Critical Diagnostics, San Diego, CA) according to the manufacturer's instructions.

2.4. Imaging

Echocardiography and cardiac magnetic resonance (cMR) were performed in all patients within one week before the procedure. Cardiac volumes and function were evaluated from retrospectively ECG-gated steady-state free precession cine images on a 1.5T cMR scanner in 2-chamber, 4-chamber, and short axis orientations. Left atrial (LA) volume was determined with the biplane method, right atrial (RA) area was measured from 4-chamber view [25]. Given reference values are derived from published literature adopted to our age and gender distribution [25,26]. Myocardial late gadolinium enhancement (LGE) images were obtained with inversion-recovery gradient echo imaging sequences with phase sensitive reconstruction. Presence of LGE was evaluated visually and classified according to the American Heart Association 17 segment model and distribution pattern [27].

2.5. Statistical analyses

Statistical calculations were performed using SPSS version 22 (IBM, Armonk, New York, USA) and R (The R Foundation for Statistical Computing, Vienna, Austria; version 3.2.4, Hmisc and pROC packages).

Values are presented as mean ± SD, median [IQR] or percentage (n). A two-sided p-value of <0.05 was considered statistically significant. Normal distribution was assessed visually and with Shapiro-Wilk test; where appropriate variables were log-transformed on the basis 10 (log) or 2 (ld) to achieve normal distribution. Pearson correlation coefficients (r) between sST2 and other baseline parameters were calculated. Baseline parameters were compared between AS and control cohorts using Student's *t*-test or χ^2-test as appropriate. Some parameters were additionally compared by analysis of covariance (ANCOVA) and adjusted for age and eGFR. An sST2 cut-off at the 95th percentile of the control cohort was used to classify patients into groups of elevated and normal sST2. This cut-off was then applied to the AS cohort.

We performed univariate Cox regression analyses for full available follow up. Significant predictors were then included in a multivariate Cox regression model. Survival according to sST2 levels was illustrated with Kaplan Meier curves. Logistic regression was used to test the association of sST2, EuroSCORE II, STS score, and German AV score with one- and two-year mortality. sST2 was added to the respective risk scores and improvement in prediction of two-year mortality was assessed by means of the difference in the area under the receiver operating characteristics (ROC) curve (ΔAUC), continuous net reclassification improvement NRI (>0), and integrated discrimination improvement (IDI) [28]. Confidence intervals of AUC, NRI (>0), IDI, and Harrell's C were determined in a bootstrap procedure (1000 replicates), as were hypothesis tests in logistic regression. The 8% cut-off applied to the STS score is derived from [4].

3. Results

3.1. AS patient characteristics

Patients presenting for TAVI were mostly octogenarians with a mean age of 83 ± 5.3 years, mean aortic valve area (AVA) of 0.65 ± 0.15 cm^2, and a mean transaortic gradient of 56 ± 19.7 mmHg (Table 1). Renal function (eGFR) was moderately impaired, on average corresponding to chronic kidney disease (CKD) stage 3A. Patients had marked left ventricular (LV) hypertrophy with a mean LV mass index of 84 g/m^2 (reference mean for the given gender distribution 66.5 g/m^2). In 31% (23/72) of patients LV ejection fraction (EF) was below the reference limit of 57%, and 12% (9/72) had severely impaired (<40%) EF. Left atria (LA) were considerably enlarged with a mean LA volume of 122 mL (reference mean volume 94 mL), and fibrosis, as reflected by late gadolinium enhancement (LGE), was present in almost 90% of patients. The mean predicted 30-day mortality by established risk scores in these patients ranged from 5.1 (EuroSCORE II) to 12.4% (logistic EuroSCORE) (Table 1).

3.2. sST2 levels in AS patients and controls

Patients without acute myocardial infarction or significant valve disease (n = 1704) were selected from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study [29]. sST2 levels in the LURIC

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