Risk scores and biomarkers for the prediction of 1-year outcome after transcatheter aortic valve replacement

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Background Up to 50% of the patients still die or have to be rehospitalized during the first year after transcatheter aortic valve replacement (TAVR). This emphasizes the need for more strategic patient selection. The aim of this prospective observational cohort study was to compare the prognostic value of risk scores and circulating biomarkers to predict all-cause mortality and rehospitalization in patients undergoing TAVR.

Methods We calculated the hazard ratios and C-statistics (area under the curve [AUC]) of 4 risk scores (logistic European System for Cardiac Operative Risk Evaluation [EuroSCORE], EuroSCORE II, Society of Thoracic Surgeons predicted risk of mortality, and German aortic valve score) and 5 biomarkers of inflammation and/or myocardial dysfunction (high-sensitivity C-reactive protein, growth differentiation factor (GDF)–15, interleukin-6, interleukin-8, and N-terminal pro–B-type natriuretic peptide) for the risk of death (n = 80) and the combination of death or rehospitalization (n = 132) during the first year after TAVR in 310 consecutive TAVR patients.

Results The EuroSCORE II and GDF-15 had the strongest predictive value for 1-year mortality (EuroSCORE II, AUC 0.711; GDF-15, AUC 0.686) and for the composite end point (EuroSCORE II, AUC 0.690; GDF-15, AUC 0.682). When added to the logistic EuroSCORE and EuroSCORE II, GDF-15 enhanced the prognostic performance of the score and enabled substantial reclassification of patients. Combinations of increasing tertiles of the logistic EuroSCORE or EuroSCORE II and GDF-15 allowed the stratification of the patients into subgroups with mortality rates ranging from 4.0% to 49.1% and death/rehospitalization rates ranging from 15.3% to 68.4%.

Conclusions Our study identified GDF-15 in addition to the logistic EuroSCORE and the EuroSCORE II as the most promising predictors of a poor outcome after TAVR. (Am Heart J 2015;170:821-9.)

Transcatheter aortic valve replacement (TAVR) has emerged as an alternative treatment strategy in patients with severe aortic stenosis and a high perioperative risk.[1–3] Although TAVR may lead to substantial reductions in mortality and morbidity in carefully selected individuals, up to 50% of the patients still die or have to be rehospitalized during the first year after the procedure.[1,2] Most of these deaths are not related to periprocedural complications, highlighting that the prognosis after TAVR is predominantly determined by comorbidities and advanced age.[4–7] Identification of patients with a poor outcome despite technically successful TAVR may support medical decision making and enable a judicious allocation of health care resources.[5–8]

Scoring systems such as the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE)[9], EuroSCORE II[10], and Society of Thoracic Surgeons predicted risk of mortality (STS-PROM)[11] were developed to estimate perioperative risk and in-hospital mortality after cardiac surgery. The German aortic valve (GAV) score was the first attempt of an aortic valve–specific predictor of in-hospital mortality.[12] However, none of these scores has been validated to predict long-term outcome in heterogeneous, high-risk patients considered for TAVR.[13] Despite these shortcomings, surgical risk

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scores, especially the logistic EuroSCORE and STS-PROM, have been recommended and are currently used for risk stratification in patients undergoing TAVR.[14,15]

Because risk scores consider only certain disease dimensions that are related to outcome in TAVR, biomarkers, which reflect distinct aspects of cardiovascular or noncardiovascular disease pathophysiology, may provide additional prognostic information, a hypothesis that has not yet been systematically tested in contemporary patients undergoing TAVR. Thus, we compared the prognostic performance of 4 risk scores (logistic EuroSCORE, EuroSCORE II, STS-PROM, GAV score) and 5 circulating biomarkers of inflammation and/or myocardial dysfunction (high-sensitivity C-reactive protein [hsCRP], growth differentiation factor (GDF)–15, interleukin (IL)-6, IL-8, and N-terminal pro–B-type natriuretic peptide [NT-proBNP]), alone and in combination, to predict 1-year mortality and rehospitalization in TAVR patients.

Methods

Patients

From January 2010 to May 2013, 310 consecutive patients underwent TAVR at the Heart Centre Bonn and were included into this prospective observational cohort registry. The decision for TAVR was made by the local heart team. The third-generation Medtronic CoreValve (Medtronic, Minneapolis, MN) was implanted in 249 patients (80.3%), the Edwards-SAPIEN XT valve (Edwards Lifesciences, Irvine, CA) in 45 (14.5%), the Symetis Acurate TF valve (Symetis, Eclubens, Switzerland) in 8 (2.6%), the Direct Flow Medical valve (Direct Flow Medical, Santa Rosa, CA) in 5 (1.6%), and the Edwards Centera valve (Edwards Lifesciences, Irvine, CA) in 3 (1.0%). The study was approved by the local ethics committee of the University of Bonn, and all patients provided written informed consent. Details about patient screening, valve implantation techniques, and adjunctive medication have been described previously.[16]

All-cause mortality during the first year of follow-up after TAVR was the primary end point of our study. The secondary end point was a composite of 1-year death or rehospitalization due to cardiovascular disease and was analyzed as the time to first occurrence of any such event (whichever comes first). *Recurrent rehospitalization* was defined as rehospitalization for symptoms of heart failure, angina, or syncope due to aortic valve disease requiring aortic valve intervention or intensified medical management, and hospitalization for complications from the procedure, such as infection, renal failure, and others. Follow-up data were collected during routine outpatient visits (after 3, 6, and 12 months), from hospital discharge letters, or via telephone interviews with the referring cardiologists or primary care physicians. No patient was lost to follow-up.

All authors vouch for the accuracy and completeness of the data and all analyses and confirm that the study was conducted according to the protocol.

Table I. Baseline characteristics

Clinical parameters	All patients (N = 310)
Age (y)	82.0 (77.0-86.0)
Male gender, n (%)	165 (53.4)
Body mass index (kg/m^2)	25.6 (22.9-28.9)
COPD, n (%)	95 (30.7)
Coronary artery disease, n (%)	202 (65.4)
Extracardiac arteriopathy, n (%)	116 (37.5)
Previous stroke, n (%)	51 (16.5)
Previous MI, n (%)	45 (14.6)
Previous cardiac surgery, n (%)	51 (16.5)
Pulmonary hypertension, n (%)	103 (33.3)
Atrial fibrillation, n (%)	120 (38.8)
Diabetes, n (%)	91 (29.4)
Chronic renal failure,* n (%)	197 (63.5)
eGFR (mL/[min 1.73 m^2])	52.3 (38.5-68.0)
Left ventricular EF (%)	54.0 (40.0-60.0)
NYHA class IV, n (%)	74 (23.9)
Aortic valve area (cm^2)	0.70 (0.60-0.80)
Mean gradient (mm Hg)	40.0 (31.0-51.0)
Low-flow/low-gradient AS, n (%)	68 (21.9)

COPD, chronic obstructive pulmonary disease; *MI*, myocardial infarction; *eGFR*, estimated glomerular filtration rate; *EF*, ejection fraction; *NYHA*, New York Heart Association; *AS*, aortic stenosis.
* *Chronic renal failure* was defined as eGFR <60 mL/(min 1.73m^2).

Risk scores

The logistic EuroSCORE, EuroSCORE II, STS-PROM, and GAV score have been described elsewhere.[9–12] All scores are risk prediction tools for the estimation of in-hospital mortality after cardiac surgery (aortic valve surgery in the case of the GAV score) and are derived from clinical variables that are readily available on admission. Values for these variables were entered into the logistic EuroSCORE calculator (http://www.euroscore.org/calcold.html), the EuroSCORE II calculator (http://www.euroscore.org/calc.html), and the STS-PROM calculator (http://riskcalc.sts.org/STSWebRiskCalc/) to assess the risk of in-hospital mortality. The GAV score was calculated according to the recently published algorithm.[12]

Biomarkers

Serum and lithium-heparin plasma samples were obtained 1 day before TAVR. High-sensitivity C-reactive protein, NT-proBNP, IL-6, and IL-8 were measured in plasma using immunoassays from Siemens Healthcare Diagnostics (hsCRP Flex reagent cartridges, PBNP Flex reagent cartridges, IL-6 and IL-8 Immulite tests). Serum samples were stored at −80°C and thawed once for the measurement of GDF-15. The GDF-15 was measured with an immunoluminometric assay. Values of GDF-15 obtained with this assay correlate closely with the values measured with a previously described immunoradiometric assay[17] and with the precommercial electrochemiluminiscence GDF-15 assay from Roche Diagnostics (r = 0.9915, slope 1.082, intercept −384 ng/L; Roche Diagnostics, data on file).