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Echocardiographic pulmonary hypertension probability is associated with clinical outcomes after transcatheter aortic valve implantation

V.J. Nijenhuis [a,*,1], M.P. Huitema [a,1], V.M.M. Vorselaars [a,1], M.J. Swaans [a,1], T. de Kroon [b,1], J.A.S. van der Heyden [a,1], B.J.W.M. Rensing [a,1], R. Heijmen [b,1], J.M. ten Berg [a,1], M.C. Post [a,1]

[a] Department of Cardiology, St. Antonius Hospital, Nieuwegein, The Netherlands
[b] Department of Cardiothoracic Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands

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ABSTRACT

Aims: Pulmonary hypertension (PH) is associated with mortality after transcatheter aortic valve implantation (TAVI). However, diagnosis based on tricuspid regurgitant velocity (TRV) is often inaccurate and unreliable. The updated PH guidelines introduced a PH probability grading implementing additional PH signs on transthoracic echocardiography (TTE), from which we aimed to analyse its effects on clinical outcomes in patients undergoing TAVI.

Methods and results: We included 591 consecutive patients (mean age 80.2 ± 8.4 years, 58.0% female, mean STS risk score 6.2 ± 3.8%) undergoing TAVI. Patients were divided into "low" ($n = 270$; TRV ≤2.8 m/s without additional PH signs), "intermediate" ($n = 131$; TRV ≤2.8 m/s with additional PH signs, or TRV 2.9–3.4 m/s without additional PH signs), and "high" PH probability ($n = 190$; TRV 2.9–3.4 m/s with additional PH signs, or TRV > 3.4 m/s). The overall 30-day and 2-year mortality rates were 10.2% and 33.8%, respectively. "High" PH probability was an independent predictor of mortality at 30 days (HR 3.68, 95% CI 2.03 to 6.67, $p < 0.01$) and 2 years (HR 2.19, 95% CI 1.57 to 3.04, $p < 0.01$), compared to "low" PH probability. The "intermediate" group did not show an increased risk. The presence of additional PH signs resulted in a significantly higher mortality at 30 days (19.6% vs. 5.1%, $p < 0.01$) and two years (54.2% vs. 22.5%, $p < 0.01$).

Conclusions: The updated echocardiographic PH probability model incorporating additional PH signs independently predicts early and late mortality after TAVI. Additional PH signs are of great value in assessing one's risks since its presence is strongly associated with early and late mortality.

1. Introduction

Transcatheter aortic valve implantation (TAVI) is currently being employed as an alternative to surgical aortic valve replacement for high-risk and inoperable patients suffering from severe symptomatic aortic stenosis [1–4]. However, pre-procedural risk assessment remains challenging since factors such as age, multiple comorbidities and frailty frequently interact, and because current surgical risk scores perform rather poorly in this population [5].

The prevalence of pulmonary hypertension (PH) in the TAVI population is high, ranging from 19% to 75%, depending on the studied population and definition of PH that is used [6–12]. PH in the TAVI population is most often caused by a chronic elevated left ventricular end-diastolic pressure, either in combination with diastolic dysfunction, the presence of mitral regurgitation or an impaired left ventricular function [13]. TAVI has been shown to decrease pulmonary artery (PA) pressure [8–11,14,15], a phenomenon associated with improved survival [16]. PH has been associated with short- and mid-term mortality after TAVI, but evidence is inconsistent [6,8,12,17,18].

As a PH screening tool, the systolic PA pressure can be estimated by measuring the peak tricuspid regurgitation velocity (TRV) on Doppler echocardiography [19]. However, systolic PA pressure estimation is often inaccurate and requires the presence of a sufficient tricuspid regurgitation, proper Doppler alignment, and optimal visualization of the regurgitant jet. Moreover, the absence of tricuspid regurgitation is not sufficient to exclude PH, and the TRV might be underestimated in patients with right ventricular enlargement and systolic dysfunction. These issues are frequently encountered in the TAVI population, and might explain the heterogeneity and conflicting results of studies investigating the prognosis of PH in patients undergoing TAVI.

Additional echocardiographic variables that might support suspicion of PH should always be evaluated. Therefore, the recently updated European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines on PH recommend using additional PH signs by

* Corresponding author at: Department of Cardiology, St. Antonius Hospital, Koekoekslaan 1 3435CM Nieuwegein, The Netherlands.
E-mail address: v.nijenhuis@antoniusziekenhuis.nl (V.J. Nijenhuis).
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assessing the ventricles, pulmonary artery, and inferior vena cava and right atrium in addition to the continuous wave Doppler measurement of the TRV [20]. Thereby, PH probability is classified as "low", "intermediate", or "high" [20].

Since TAVI facilitates treatment of patients in end-stage aortic stenosis, of whom many are suffering from severe PH, the impact of PH on prognosis in these patients has to be further elucidated. Furthermore, it remains undetermined whether the assessment of additional echocardiographic PH signs, as recently added to the PH probability classification [20], is beneficial in pre-procedural risk assessment. In the current study, we aimed to analyse the effects of PH probability on short- and mid-term clinical outcomes in patients undergoing TAVI.

2. Methods

2.1. Study design and data collection

All consecutive patients undergoing a TAVI from June 2007 to December 2015 in our centre were prospectively included. Depending on the referring hospitals' policy, some patients underwent a right heart catheterization (RHC) before TAVI. The local investigators had full access to the data and patients' medical records. The patients' vital status was ascertained from the national death registry. Follow-up was conducted on an outpatient basis or, when needed, by telephone. An ethics committee approved the study protocol (R&D/Z16.019).

2.2. Inclusion criteria and treatment

All patients were denied conventional aortic valve replacement and were selected for TAVI by a dedicated heart team consisting of at least one interventional cardiologist, cardiothoracic surgeon, and interventional cardiac imaging specialist. Patients undergoing TAVI for severe symptomatic aortic regurgitation were excluded from analysis.

2.3. Echocardiography

As part of the pre-procedural work-up, all patients underwent a transthoracic echocardiogram before TAVI. According to the recently updated ESC/ERS PH guidelines, we assessed peak TRV for assigning the echocardiographic PH probability [20]. Additional echocardiographic PH signs were classified as present if at least two of the following three categories (A-C) were present, as reported in the current guidelines [20]:

A. Ventricles: right ventricle/left ventricle basal diameter ratio >1.0, and/or flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole);
B. PA: a right ventricular outflow Doppler with either an acceleration time <105 ms or midsystolic notching, and/or early diastolic pulmonary regurgitation velocity > 2.2 m/s, and/or PA diameter >25 mm.
C. Inferior vena cava and right atrium: inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration), and/or right atrial area (end-systole) >18 cm^2.

As depicted in Fig. 1, patients were subsequently divided into one of three groups of PH probability: "low" (TRV ≤2.8 m/s or not measurable without additional PH signs), "intermediate" (TRV ≤2.8 m/s or not measurable with additional PH signs, or TRV 2.9 to 3.4 m/s without additional PH signs), or "high" (TRV 2.9 to 3.4 m/s with additional PH signs, or TRV >3.4 m/s).

Assessment of the right ventricular function was performed by measuring the tricuspid annular plane systolic excursion (TAPSE) and tricuspid peak systolic (S′) wave velocity according to the guidelines of the American Society of Echocardiography [21]. Left ventricular ejection fraction (LVEF) was measured using the biplane Simpson's method. Significant valvular disease was considered as moderate to severe according to the current recommendations [22,23].

2.4. Procedure

All procedures were performed under general anaesthesia by a multidisciplinary team of an interventional cardiologist, cardiac surgeon, interventional cardiac imaging specialist, anaesthesiologist, and trained Cathlab personnel in a specialized hybrid catheterization laboratory.

For transfemoral TAVI, the Edwards Sapien (XT), Medtronic CoreValve (Evolut) (Medtronic, Minneapolis, Minnesota), DirectFlow (Direct Flow Medical GmbH, Gießen), and Lotus (Boston Scientific, Marlborough, Massachusetts) were used. For transapical TAVI, the Edwards Sapien (XT) (Edwards Lifesciences, Irvine, California), JenaValve (JenaValve Technology GmbH, Munich), and Engager (Medtronic, Minneapolis, Minnesota) were used.

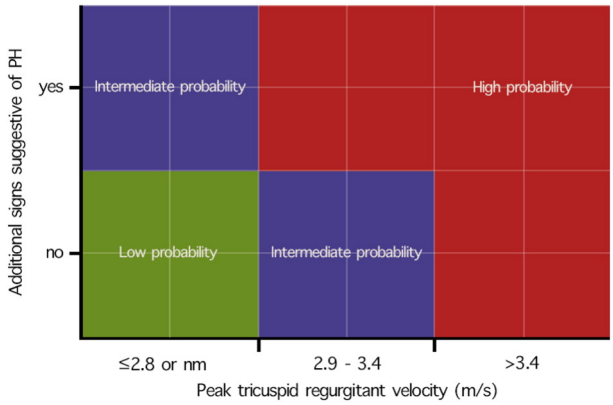

Fig. 1. Echocardiographic probability of pulmonary hypertension (PH) according to the updated ESC/ESR PH guidelines (2015). Classification according to the presence of additional PH signs is described in the Methods section. Nm: not measurable.

2.5. Endpoints and definitions

The primary endpoint was all-cause mortality after TAVI according to the PH probability and was analysed at 30 days and two years. All outcomes were analysed according to the criteria as proposed by the Valve Academic Research Consortium [5]. Definite diagnosis of PH was defined as an increase in mean PA pressure ≥25 mmHg at rest as assessed by RHC [24].

2.6. Data analysis

Continuous data are presented as mean ± standard deviation (SD) or median (25th–75th percentile range). Categorical variables are shown as frequencies and percentages. For continuous variables, a Student *t* test or Mann–Whitney *U* test was used for comparison between two groups. The analysis of variance (ANOVA) and Kruskall–Wallis test were used for more than two groups as appropriate. Post hoc analysis was performed using the Tukey HSD (honest significant difference) and Dunn's multiple comparison test, respectively. Categorical variables were compared using the χ^2 test with post hoc analysis using Bonferroni adjustment. Correlations were examined using the Pearson *r* correlation test. Logistic linear regression analysis was used for analysis of event data.

Kaplan–Meier estimates were used to construct survival curves for the time-to-event data and compared using the log-rank statistics. Time-to-event data analysis was performed using the Cox proportional hazards regression model. To take into account any imbalances between the groups regarding baseline prognostic variables, analyses were repeated using multivariable adjustment. Candidate variables for entering the model were chosen based on best subset selection performed on all available baseline parameters. We incorporated the following variables in the final model: PH probability, LVEF (<30% and 30%–50% compared to >50%), peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), and body mass index (BMI; >30 kg/m^2 and 25–30 kg/m^2 compared to <25 kg/m^2). Statistical significance was inferred at $p < 0.05$. All statistical analyses were performed using R (www.r-project.org, version 3.3.1).

3. Results

3.1. Baseline characteristics

Baseline characteristics are shown in Table 1. In total, 687 patients (mean age 80.9 ± 6.9 years, 56.3% female, mean logistic EuroSCORE 26.2 ± 16.3%) underwent a TAVI. After excluding patients with a primary indication of aortic regurgitation ($n = 35$) or insufficient quality of echocardiographic images in order to assess PH signs ($n = 61$), 591 patients remained for analysis and were subsequently divided into three groups according to PH probability: "low" ($n = 270$), "intermediate" ($n = 131$), and "high" ($n = 190$). Two-year follow-up was complete in 484 (81.9%) patients. Patients in the "high" group were at highest surgical risk, as captured by the logistic EuroSCORE and the Society of Thoracic Surgeons (STS) score. These patients had a lower BMI and the highest prevalence of atrial fibrillation (AF) and COPD. They were more symptomatic than those in the "low" or "intermediate" group, as