Atherosclerosis 246 (2016) 161–168

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Aorta calcification burden: Towards an integrative predictor of cardiac outcome after transcatheter aortic valve implantation

Brahim Harbaoui [a, b, *], Mathieu Montoy [a], Paul Charles [a], Loic Boussel [b, c], Hervé Liebgott [b], Nicolas Girerd [d], Pierre-Yves Courand [a, b], Pierre Lantelme [a, b]

[a] From the Cardiology Department, European Society of Hypertension Excellence Center, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, F-69004, Lyon, France
[b] Université de Lyon, CREATIS, CNRS UMR5220, INSERM U1044, INSA-Lyon, Université Claude Bernard Lyon 1, Hospices Civils de Lyon, France
[c] Radiology Department, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, F-69004, Lyon, France
[d] INSERM, Centre d'Investigations Cliniques-1433, and INSERM U1116 & CHU Nancy, Institut Lorrain du Cœur et des Vaisseaux, Vandoeuvre lès Nancy, France

A R T I C L E I N F O

Article history:
Received 21 November 2015
Received in revised form
24 December 2015
Accepted 8 January 2016
Available online 11 January 2016

Keywords:
Calcifications
Aorta
TAVI
Aortic stenosis
Stiffness
Outcomes

A B S T R A C T

Objective: The principal objective was to determine the effect of total aortic calcification (TAC) burden on outcomes (cardiac mortality, all-cause mortality, and heart failure (HF)) after transcatheter aortic valve implantation (TAVI). The secondary aim was to assess the contribution of each segment of the aorta to these outcomes.
Background: Indications for TAVI are increasing in number. Even after procedural success, however, some patients die soon afterwards, indicating the futility of TAVI in certain cases.
Methods: Aortic calcifications were measured on computed tomography in 164 patients treated by TAVI. TAC, ascending aortic calcification (AsAC), descending aorta calcifications, and abdominal aorta calcifications were expressed as tertiles and their prognostic values were assessed in a multivariable cox analysis adjusted for major confounders including EuroSCORE.
Results: Median duration of follow-up was 565 (interquartile range: 246 to 1000) days. TAC (tertile3 vs. tertile1) was significantly and strongly associated with cardiac mortality (hazard ratio [HR]: 16.74; 95% confidence interval [CI]: 2.21 to 127.05; $p = 0.006$) and all-cause mortality (HR: 2.39; 95% CI: 1.18 to 4.84; $p = 0.015$) but not with HF (HR: 1.84; 95% CI: 0.87 to 3.90; $p = 0.110$). Each segment was associated with cardiac mortality, while only AsAC (tertile 3 vs. tertile 1) appeared predictive of HF (hazard ratio: 2.29; 95% CI: 1.12 to 4.66; $p = 0.023$).
Conclusions: TAC is an integrative predictor of cardiac and all-cause mortality after TAVI. It should be included in the assessment of patients before TAVI in order to predict cardiac outcome after valve replacement and avoid futile interventions.

1. Introduction

Within the past few years, transcatheter aortic valve implantation (TAVI) has become a first-line therapy for inoperable patients with severe aortic stenosis or at high surgical risk [1–4]. More than 150,000 patients have undergone TAVI worldwide [5] since Cribier et al. performed the first implantation in 2002 [6]. Device and technical refinements have led to procedural success in most cases, yet TAVI seems futile for some patients who die rapidly after the procedure or experience only a very small improvement in quality of life [1,2,7–9].

Current risk scores based on heart surgery are not very discriminating in this high-risk population and are not therefore suitable for TAVI [10,11]. Furthermore, the question of long-term benefit is not addressed by any of the current risk models. Thus, optimization of patient selection is a major challenge today in the context of the growing indications for TAVI [12].

We recently reported that ascending aortic calcification (AsAC), a surrogate of aortic stiffness, is a powerful predictor of cardiac outcomes after TAVI [13,14]. In another setting, we found that

* Corresponding author. Cardiology Department, Hôpital de la Croix-Rousse, 103 Grande Rue de la Croix-Rousse, 69004, Lyon. France.
E-mail address: bharbaoui@gmail.com (B. Harbaoui).

http://dx.doi.org/10.1016/j.atherosclerosis.2016.01.013
0021-9150/

abdominal aortic remodeling was predictive of coronary events [15]. Thus, total aortic calcification (TAC) burden could represent an integrative marker of cardiac risk encompassing coronary events and heart failure (HF). While the role of aortic biomechanics is often overlooked in the field of cardiology, we present the hypothesis that such an extra-cardiac marker could be of great value and novelty for predicting cardiac outcome after TAVI. Thus, the major objective of this study was to evaluate the effect of TAC burden, measured over the whole aorta by computed tomography (CT), on cardiac mortality, all-cause mortality, and a composite of HF hospitalization or mortality after TAVI. The secondary aim was to assess the contribution of 3 aortic segments (ascending, thoracic descending, and abdominal) on each of these outcomes after TAVI.

2. Methods

2.1. Patient population

From April 2009 through January 2015, 189 patients were scheduled for TAVI in our group of hospitals (Croix-Rousse, Louis Pradel, and Saint-Luc Saint-Joseph, Lyon, France) as part of an ongoing prospective cohort [13]. The multidisciplinary team determined eligibility and vascular access for TAVI on the basis of systematic clinical evaluation, angiographic assessment, CT, and transthoracic echocardiography. An Edwards SAPIEN valve (Edwards Lifesciences LLC, Irvine, CA) was implanted in all eligible patients. Among patients who underwent TAVI, 164 with calcification measureable on at least 1 segment of the aorta on CT **prior to** TAVI were included. All patients provided written informed consent before undergoing the procedure, including consent for anonymous processing of their data. The study received ethical committee approval.

2.2. CT of the aorta

CT acquisition was performed on a Brilliance 64 CT scanner (Philips, Best, Netherlands) in the head-to-feet direction covering the whole thoracic and abdominal aorta, with the following parameters: number of detectors 64, individual detector width 0.625 mm, retrospective electrocardiogram gating, tube voltage/current 120 kV/600 mA s, pitch 0.2, and half rotation reconstruction. Contrast agent (80 ml) (Iomeron 400, Bracco, Italy) was injected at a rate of 3.5 ml/s followed by 50 ml of saline at the same rate. A bolus tracking method on the ascending aorta was used with a threshold of 200 UH. Reconstruction parameters for axial slices were 0.8 mm effective section thickness, 0.4 mm increment, and adapted field-of-view. Retrospective electrocardiogram-gated reconstruction was performed at 0%, 40%, and 75% of the R–R interval.

Analysis was performed with the IntelliSpace Portal (Philips, Best, Netherlands) on the 75% cardiac phase. All calcifications of the aorta were individually delineated from the aortic sinus to the aortic bifurcation with a semiautomatic segmentation tool available in the IntelliSpace Portal based on a level-set method constrained by the Hounsfield units of the delineated structures [16]. The total volume of the delineated aorta calcifications (TAC) and the total aortic volume were first calculated. Then, using 3-dimensional segmentation tools, the volume of aortic calcification was measured for 3 aortic segments: the ascending aorta (AsAC) from the aortic sinus to the left subclavian artery; the descending thoracic aorta (DAC), from the left subclavian artery to the aortic hiatus; and the abdominal aorta (AbAC), from the aortic hiatus to the aortic bifurcation. The same measures were performed for aortic volume. One trained operator blinded to clinical data and outcomes read all the CT scans. Inter-observer and intra-observer reproducibility of TAC were assessed in 2 samples of randomly selected patients. TAC, AsAC, DAC, and AbAC were used both as crude variables and corrected for volume of the corresponding aortic segment.

2.3. Follow-up and outcomes

Patient history and treatment were retrieved from medical files and from review of hospital records. Survival status was obtained by telephone contact with patients, their relatives or carers, or their physicians. The primary outcome was cardiac mortality including sudden death, fatal myocardial infraction, and death from HF. Secondary endpoints were all-cause mortality and a composite of hospitalization for HF or death from HF. Post-procedural aortic regurgitation (PAR) was assessed on the final aortogram or on transthoracic echocardiography when aortography was not available.

2.4. Statistical methods

Qualitative variables are summarized as means ± standard deviations, medians with interquartile ranges, or numbers and percentages, as appropriate. Interobserver and intraobserver reproducibility of TAC measurement was tested by the κ test and by a modified Bland–Altman plotting (mean of the 2 assessments on the x-axis and ratio of the 2 assessments on the y-axis).

Patients were classified according to TAC tertile. One-way analysis of variance, nonparametric analysis of variance (Mann–Whitney test), and the chi-square tests were used, as appropriate, to compare variables between tertiles. The correlations between TAC, AsAC, DAC, and AbAC were assessed with a linear regression analysis (Pearson's coefficient of correlation, r) after logarithmic transformation.

To assess the predictive value of TAC, AsAC, DAC, and AbAC, the different endpoints were first estimated by Kaplan–Meier survival curves (log-rank statistic) according to tertiles. Univariate Cox regressions were performed for putative predictors. A forward stepwise Cox multiple regression analysis was performed to assess the independent predictive value of TAC, AsAC, DAC, and AbAC after adjustment for EuroSCORE, atrial fibrillation, vascular access, estimated glomerular filtration rate, coronary artery disease, and PAR. A backward stepwise Cox multiple regression analysis was also performed for cardiac death. Additional models were used to take into account additional significant univariate predictors not included in the set of variables preselected for adjustment or significant differences in terms of baseline characteristics among tertiles.

To estimate the additional prognostic value of TAC, AsAC, DAC, and AbAC, the accuracy of different multivariable models of prediction was determined by using integrated discrimination improvement and net reclassification improvement (NRI) [17]. A receiver operating characteristic (ROC) curve approach was also used to allow for defining potential prognostic thresholds. The analyses were performed using SPSS software, release 20.0.0 (SPSS, Chicago, USA) and STATA 12 (Stata Corporation, College Station, USA). A p value < 0.05 was considered statistically significant.

3. Results

3.1. Patient baseline characteristics

Among the 164 patients with an available CT scan, TAC could be assessed in 155 patients, AsAC in 164, DAC in 158, and AbAC in 155. The transfemoral approach was by far the most frequently used (Table 1). Of note, no difference was observed between TAC tertiles for comorbidities or aortic stenosis severity (measured according to