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1. Amsterdam EA et al. J Am Coll Cardiol 2014;64:2645-2687
2. Levine GN et al. J Am Coll Cardiol 2011;58:e44-e122

Original Studies

Angiographic Assessment of Aortic Regurgitation by Video-Densitometry in the Setting of TAVI: Echocardiographic and Clinical Correlates

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Objectives: We sought to investigate a new angiographic method for aortic regurgitation (AR) severity assessment in the setting of transcatheter aortic valve implantation (TAVI). Background: AR after TAVI is common but challenging to quantitate, especially in the cath-lab. Methods: In 228 patients, AR was quantitated before and after TAVI by echocardiography and by video-densitometric analysis of aortograms. Contrast time–density curves for the aortic root (the reference region) and the left ventricular outflow tract, LVOT were generated. LVOT-AR was calculated as the area under the curve of the LVOT as a fraction of the area under the curve of the reference region. Results: LVOT-AR was 0.10 ± 0.08, 0.13 ± 0.10 and 0.28 ± 0.14 in none-trace, mild and moderate-severe post-TAVI AR as defined by echocardiography ($P < 0.001$) and a cut-point of >0.17 corresponded to moderate-severe AR on echocardiography (area under the curve = 0.84). At follow-up (median, 496 days), patients with LVOT-AR $\leq$ 0.17 showed a significant reduction of LV mass index (LVMi; 121 [95–148] vs. 140 [112–169] g/m^2, $P = 0.009$) and the prevalence of LV hypertrophy (LVH; 64 vs. 88%, $P = 0.001$) compared to baseline. In patients with LVOT-AR > 0.17, LVMi (149 [121–178] vs. 166 [144–188] g/m^2, $P = 0.14$) and the prevalence of LVH (74 vs. 87%, $P = 0.23$) did not show a significant change. Compared to patients with LVOT-AR $\leq$ 0.17, those with LVOT-AR > 0.17 had an increased 30-day (16.4% vs. 7.1%, $P = 0.035$) and one year mortality (32.9 vs. 14.2%, log rank P value = 0.001; HR: 2.690 [1.461–4.953], $P = 0.001$). Conclusions: LVOT-AR > 0.17 corresponds to greater than mild AR as defined by

Additional Supporting Information may be found in the online version of this article.

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echocardiography and predicts impaired LV reverse remodeling and increased early and midterm mortality after TAVI.

Key words: aortic stenosis; transcatheter aortic valve implantation; paravalvular regurgitation; angiography; echocardiography

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is increasingly accepted as an alternative to surgery for treating aortic stenosis [1]. Although initially designated for prohibitive and high surgical risk patients, TAVI is gradually being accepted as an option in younger and lower risk patients [2].

The severity of aortic regurgitation (AR) after TAVI is an important determinant of procedural success and clinical outcomes [3–5]. Transthoracic echocardiography (TTE), typically integrating multiple parameters, is the imaging modality of choice for serial evaluation of AR [6] and is recommended by the valve academic research consortium (VARC) as the mainstay diagnostic tool of post-TAVI AR [7].

However, aortic root angiography is the initial screening tool for postimplantation AR in most laboratories. It is readily available, can give quick data and guide timely provision of corrective measures and is a friendly tool to interventional cardiologists. Furthermore, it does not need anesthesia that is necessary for transesophageal echocardiography (TEE). The most commonly used method to asses AR by angiography is the visual Sellers' grading method [8].

Quantification of contrast time–density changes in the left ventricle (LV) compared to the aortic root—as a reference—by digital subtraction videodensitometry (VD) is known to improve reproducibility of angiographic AR assessment [9,10]. Additionally, VD indices provide a continuous quantitative scale for AR severity unlike the categorical qualitative Sellers' grading. In the post-TAVI setting, VD method has been shown to be feasible, and reproducible [11,12]. However, clinicians remain adherent to the classical mild–moderate–severe scale and tend to get confused when they are offered a continuous numerical scale, potentially hindering the implementation of VD indices in the clinical domain.

In the present study, we aimed to determine the cut-point of VD angiographic method that best defines significant post-TAVI AR and correlates with outcomes after TAVI.

METHODS

Patient Population

The study included 399 patients representing all cases with complete angiographic data from the Brazilian multicenter TAVI registry. List of participating centers, details of inclusion and exclusion criteria, TAVI-procedure technical aspects, and adjudication of adverse events have been previously described [13]. The study protocol has been approved by the ethical committee at each of the participating centers and all patients provided informed written consent. All patients had postimplantation aortic root angiography and were scheduled for TTE during the same admission for the index procedure (predischarge TTE) and for planned follow-up at 6 and 12 months and annually thereafter.

Angiography

Aortic root angiography was performed before and, at least 10 min, after valve implantation in the same projection as the preprocedural aortogram. Aortography was performed using a nonionic contrast injected through a pigtail catheter positioned above the prosthetic valve (in case of a balloon-expandable device) or within the distal third of the prosthetic valve (in case of a self-expanding device). Out of 399 aortograms, 61 aortograms were unreliable for determination of AR severity due to disturbance of the valve competence by a guide wire/catheter during acquisition.

Videodensitometric Analysis of Aortographic Data

VD analysis was performed using a dedicated software (CAAS A-Valve 2.0.2: Pie Medical Imaging, Maastricht, The Netherlands) where a contour is drawn to include the contrast-filled aortic root (which serves as the reference region) and the left ventricular outflow tract (LVOT) which serves as the region of interest (ROI) (Fig. 1). Contrast time–density curves (TDCs) are generated for the reference region and for the ROI through weighing the summated pixel density against time. The relative area under the curve (RAUC) is calculated as the area under the TDC of the ROI as a fraction of the area under the TDC of the reference region. RAUC is averaged over the first three cardiac cycles after the start of contrast arrival at the aortic root after subtracting the static background radiodensities. RAUC has a theoretical range of zero (indicating no contrast leaking to the ROI) to one (indicating that the density of contrast in the ROI is exactly the same as that in the reference area). Further technical

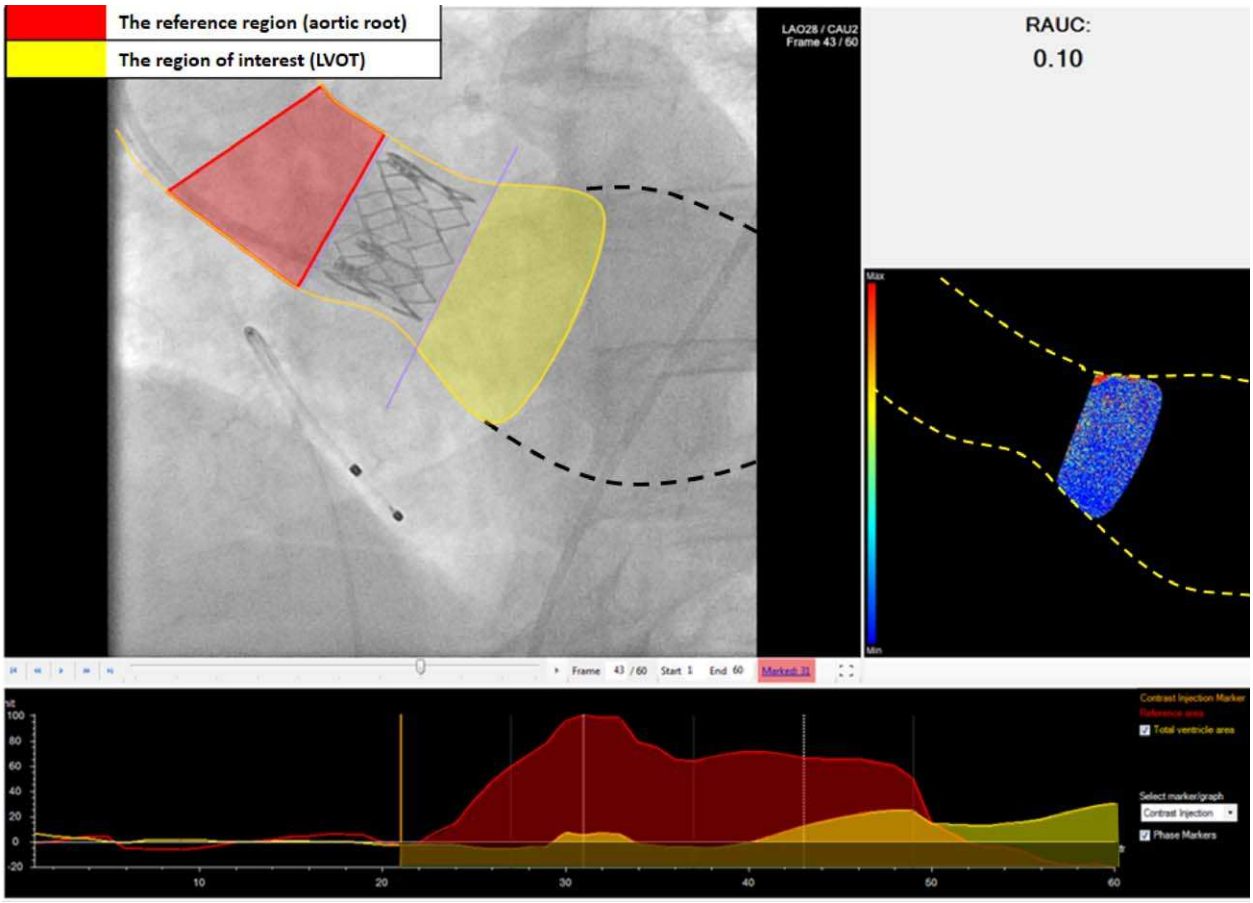


Fig. 1. The subaortic segment of the ventricle (LVOT) is interrogated as a region of interest (yellow), while the aortic root serves as the reference region (red). Time–density curves (lower) and color-weighted contrast time–density map (right) are generated. The relative area under the time–density curve (RAUC) of the region of interest as a fraction of that of the reference region is computed (0.10 in this case). [Color figure can be viewed at wileyonlinelibrary.com]

details of VD analysis have been previously described [11,12].

Echocardiography

Echocardiographic data were analyzed in accordance with the recommendations of the American Society of Echocardiography/European Association of Cardiovascular Imaging [6,14–16]. Color Doppler evaluation was performed at the level of the valve stent inflow (for paravalvular AR), and at the leaflets coaptation point (for transvalvular AR). All available windows were utilized for color Doppler assessment with the parasternal short axis view being the principal view for assessing the number, the location and the severity of paravalvular AR. The regurgitant volume and fraction (using the right and left ventricular outflow tract method), the effective regurgitant orifice area and the reversal of aortic diastolic flow were assessed and combined (whenever available) with color Doppler parameters in a multiparametric scheme that was finally used to grade AR as recommended by the VARC [7]. Post-TAVI assessment of AR was completely blinded to the results of VD analysis.

Left ventricular (LV) mass was calculated using the cube formula as follows [17]: LV mass $= 0.8 \times 1.04 \times [(\text{IVS} + \text{LVID} + \text{PWT})^3 - \text{LVID}[3]] + 0.6$ g, where IVS is interventricular septum thickness; LVID is LV internal diastolic diameter, and PWT is posterior (inferolateral) wall thickness. LV mass was indexed to body surface area (BSA) as follows: LVMi = LVM/BSA g/m^2. LV hypertrophy (LVH) was defined as LVMi $>$ 95 g/m^2 in females, or $>$115 g/m^2 in males [17]. The relative wall thickness (RWT) was calculated from the formula $(2 \times \text{PWT})/\text{LVID}$. RWT $>$ 0.42 was considered as a cutpoint to indicate concentric pattern of LV hypertrophy/remodeling [17].

Statistical Methods

Continuous variables are expressed as mean± standard deviation (SD) or as median and interquartile range (IQR), as appropriate.

Categorical variables are presented as frequencies and percentages. Between-group differences were computed using the Student *t* test or the one-way ANOVA (if normally distributed numerical variables are studied) while categorical variables were compared using chi-squared test. For non-normally distributed numerical variables, between-group differences were computed using Mann–Whitney *U* test or Kruskal–Wallis *H* test. Receiver-operating characteristics (ROC) curves were generated for the diagnosis of moderate-severe AR by LVOT-AR. The cutpoints were defined using ROC curves on the basis of the highest sum of sensitivity and specificity for the definition of moderate-severe AR.

Time-to-event analysis was performed with the use of Kaplan–Meier estimation, while comparison between the groups was done using log-rank test. To test the association of LVOT-AR with mortality, cox proportional-hazards regression analysis was performed. The assumption of proportionality of hazard was tested using a time-dependent Cox model with the time treated as a continuous variable.

Statistical analysis was performed with SPSS 23 (IBM, Armonk, NY, USA). All probability values were two-tailed, and a P value < 0.05 was considered significant.

RESULTS

LVOT-AR was analyzable in 228 patients who constituted the population of the present study. The reasons for nonanalyzability of LVOT-AR are shown in Supporting Information Table SI. Baseline and procedural characteristics of the study population are summarized in Table I. Patients (age, 81.4 ± 7.3 years) were predominantly males (55%) with severe heart failure symptoms (NYHA III or IV in 81%) and were deemed at high surgical risk (STS score, 12.7 ± 10.4). The majority of procedures was performed under general anesthesia (96%) and the implanted transcatheter valves were CoreValve (n = 155, 67%), Sapien-XT (n = 71, 31%), and Inovare (n = 4, 2%).

AR Severity on Echocardiography and Videodensitometry Angiography

On predischarge echocardiographic assessment, AR was mild in 69% and moderate-severe in 8% of patients. Complete echocardiographic data at baseline, before discharge and at follow-up (median [range], 391 [116–666] days) were available in 136 patients. In

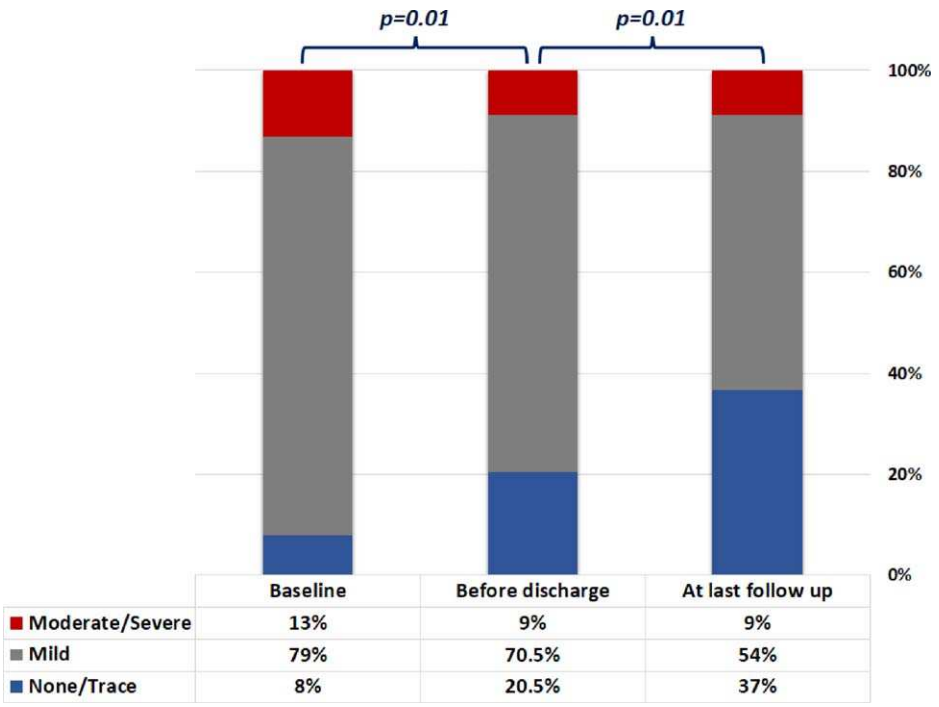
TABLE I. Baseline and Procedural Characteristics in patients with LVOT-AR Available After TAVI, (n = 228)

	Mean ± SD/frequency (%)
Age (years)	81.4 ± 7.3
Male gender	126 (55)
Body surface area (m^2)	1.76 ± 0.20
Body mass index (kg/m^2)	25.7 ± 4.0
NYHA functional class	
I	10 (4)
II	35 (15)
III	117 (51)
IV	66 (30)
EuroSCORE	18.1 ± 12.6
STS-PROM	12.7 ± 10.4
Coronary artery disease	130 (57)
Prior myocardial infarction	25 (11)
Pulmonary hypertension	39 (17)
Prior permanent pacemaker	24 (11)
Atrial fibrillation/flutter	31 (14)
Prior CABG	38 (17)
Prior PCI	73 (32)
Prior BAV	21 (9)
Diabetes mellitus	57 (25)
Hypertension	160 (70)
Chronic obstructive pulmonary disease	51 (22)
Chronic kidney disease[a]	170 (75)
Prior stroke	18 (8)
Carotid artery disease	28 (12)
Peripheral arterial disease	30 (13)
Porcelain aorta	16 (7)
Aortic aneurysm	17 (8)
Aortic valve area (cm^2)	0.65 ± 0.18
Aortic annulus diameter (mm)	23.6 ± 2.9
Cover index (%)[b]	9.2 ± 14.0
TAVI performed under GA	218 (96)
TAVI guided by TEE	198 (87)
Transfemoral access	215 (94)
Transcatheter valve type	
CoreValve	155 (67)
Sapien-XT	71 (31)
Inovare	4 (2)
Transcatheter valve size (mm)	
23	29 (13)
26	85 (38)
29	81 (36)
31	32 (14)
28	1 (0.04)
Predilatation	104 (46)
Postdilatation	102 (45)
Preprocedural aortic PG	63.7 ± 25.4
Postprocedural aortic PG	5.5 ± 9.2
Device success	203 (89)

CABG = coronary artery bypass grafting, EuroSCORE = European System for Cardiac Operative Risk Evaluation, GA = general anesthesia, NYHA = New York Heart Association, PCI = percutaneous coronary intervention, PG = pressure gradient, BAV = balloon aortic valvuloplasty, STS-PROM = The Society of Thoracic Surgeons-predicted risk of 30-day mortality, TAVI = transcatheter aortic valve implantation, TEE = transesophageal echocardiography.

[a]Defined as glomerular filtration rate <60 mL/min.

[b]Calculated as: 100 × ([prosthesis diameter – annular diameter]/prosthesis diameter.



	Baseline	Before discharge	At last follow up
Moderate/Severe	13%	9%	9%
Mild	79%	70.5%	54%
None/Trace	8%	20.5%	37%

Fig. 2. Changes in the severity of aortic regurgitation in paired echocardiographic studies at three time points; baseline, before discharge after TAVI and at follow-up (median; 391 days). [Color figure can be viewed at wileyonlinelibrary.com]

those patients with paired echocardiographic studies, AR severity decreased significantly from baseline (none = 11 [8%], mild = 107 [79%], and moderate-severe = 18 [13%]) to before discharge (none-trace = 28 [20.5%], mild = 96 [70.5%], and moderate-severe = 12 [9%]; $P = 0.01$). A further significant reduction was seen at latest echocardiographic follow-up compared to predischarge assessment (none-trace = 50 [37%], mild = 74 [54%], and moderate-severe = 12 [9%]; $P = 0.01$) (Fig. 2). Overall, 26% of patients ($n = 35$, 20 received CoreValve and 15 received Sapien XT) had an improvement of AR from predischarge to latest follow-up (from moderate-severe to mild in four patients and from mild to none-trace in the remainder).

Overall, LVOT-AR averaged (median [IQR]) 0.12 [0.06–0.19] and was significantly higher in patients who received a CoreValve (0.13 [0.07–0.22]) than in those who received a Sapien-XT (0.10 [0.05–0.14], $P = 0.002$).

Before TAVI, LVOT-AR was 0.03 [0.0–0.06], 0.08 [0.01–0.16], and 0.20 [0.06–0.35] in none-trace, mild and moderate-severe AR as defined by echocardiography ($P = 0.015$). After TAVI, LVOT-AR was 0.10 [0.04–0.16], 0.12 [0.06–0.19], and 0.25 [0.16–0.34] in none-trace, mild and moderate-severe AR as defined by echocardiography ($P < 0.001$). As shown in Fig. 3A, there was a significant overlap of LVOT-AR between the "none-trace" and the "mild" grades.

ROC curves were used to define LVOT-AR cutpoint that corresponds to a moderate-severe AR on echocardiography. LVOT-AR > 0.17 corresponded to a moderate-severe AR in both pre-TAVI (AUC = 0.71) and post-TAVI (AUC = 0.84) settings (Fig. 3B).

Impact of AR Severity as Defined by Videodensitometry Angiography on LV Remodeling

In 111 patients with echocardiographic data of LVMi available at baseline and at a post-TAVI interval of at least 6 months (median, 496 [IQR, 296–696] days), LV reverse remodeling was studied. LVMi was significantly lower at follow-up (123 [89–157] g/m^2) than at baseline (153 [119–187] g/m^2, $P = 0.002$). Reverse remodeling was however incomplete and LVH persisted in 67% of patients at follow-up (vs. 88% at baseline, $P = 0.001$). RWT tended to be lower at follow-up than at baseline (0.44 [0.40–0.49] vs. 0.47 [0.43–0.52], $P = 0.053$) and fewer patients had a concentric pattern of LV hypertrophy/remodeling at follow-up (56%) than at baseline (70%, $P = 0.043$). This pattern of LV reverse remodeling was driven by a

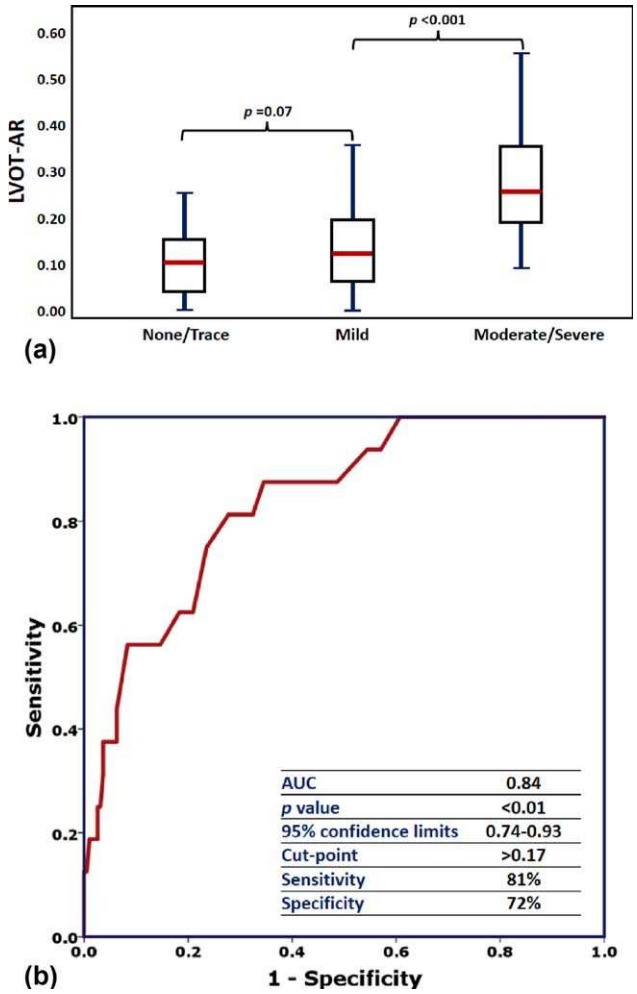


Fig. 3. (A) The distribution of LVOT-AR across the echocardiographic grades of aortic regurgitation after TAVI. The box (interquartile range) and whiskers (95% confidence interval) plot shows a significant overlap of LVOT-AR between the none-trace and the mild grades of aortic regurgitation on echocardiography. (B) Receiver operating characteristics curve of LVOT-AR corresponding to greater than mild AR as defined by echocardiography after TAVI. AUC = area under the curve. [Color figure can be viewed at wileyonlinelibrary.com]

significant reduction of SWT and PWT and a trend towards LVID reduction (Table II).

Those patients were divided into two groups, the first had post-TAVI LVOT-AR ≤ 0.17 ($n = 71$) and the second had a post-TAVI LVOT-AR > 0.17 ($n = 40$). Baseline, procedural and follow-up characteristics of both groups are summarized in Supporting Information Table SII. In patients with LVOT-AR ≤ 0.17, LVMi was significantly lower (121 [95–148] vs. 140 [112–169] g/m^2, $P = 0.009$) and the prevalence of LVH was significantly less (64% vs. 88%, $P = 0.001$) at follow-up than at baseline. In patients with LVOT-AR > 0.17, LVMi (149 [121–178] vs. 166 [144–188] g/m^2, $P = 0.14$) and the prevalence of LVH (74% vs. 87%, $P = 0.23$) did not show a significant improvement at follow-up compared to baseline (Fig. 4).

Impact of AR Severity as Defined by Videodensitometry Angiography on Mortality After TAVI

Thirty-day all-cause mortality rate was higher in patients with LVOT-AR >0.17 than in those with LVOT-AR $\leq$ 0.17 (16.4 vs. 7.1%, $P = 0.035$; odds ratio: 2.575 [95% CI: 1.078–6.154], $P = 0.033$). One year all-cause mortality was significantly higher in patients with LVOT-AR > 0.17 (32.9%) than in patients with LVOT-AR ≤ 0.17 (14.2%, log rank P value $= 0.001$). After adjustment for chronic obstructive pulmonary disease, chronic kidney disease, STS score, LVEF, and MR severity at baseline, an LVOT-AR > 0.17 was independently associated with increased mortality (hazard ratio: 2.690 [1.461–4.953], $P = 0.001$) (Fig. 5).

DISCUSSION

In this study, LVOT-AR was defined by videodensitometric analysis of aortography, and increased stepwise with increasing severity of post-TAVI AR on echocardiography. LVOT-AR > 0.17, identified a subgroup of patients that shows a less effective LV reverse remodeling and a higher mortality at midterm after TAVI.

It is now established that significant AR, typically and most commonly paravalvular, after TAVI portends poor outcome [3]. It is also recognized that adequate quantitation of AR is a crucial determinant of procedural success and patients' functional recovery and long-term mortality [5]. Although long-term surveillance is important, immediate postimplantation detection and accurate quantification remain most critical in tackling post-TAVI AR. Postdilation, retrieval, and reposition, and valve-in-valve implantation are options to mitigate AR before the patient leaves the cath-lab. Proper provision of those corrective measures needs AR to be timely detected and accurately quantitated. For intraprocedural surveillance, a point-of-care hemostatic test (closure time with adenosine diphosphate [CT-ADP]) was recently shown to predict the presence of paravalvular AR after TAVI [18]. Notwithstanding, procedural guidance typically uses a combination of angiography and TEE.

Aortography as the Main Tool to Adjudicate AR in the Cath-Lab

The "minimalist" approach (implying performing TAVI through a transfemoral approach under sedative rather

TABLE II. Changes in the Left Ventricular Geometry and Function and in the Aortic and Mitral Valve Function in Patients with Echocardiographic Data Complete at Baseline and at ≥6 Months Post-TAVI (*n* = 111)

		Baseline	Follow-up	*P*
Mean aortic pressure gradient (mm Hg)		49.0 [38.8–59.2]	9.0 [6.5–11.5]	<0.001
Aortic regurgitation				
	None/trace	16 (7)	52 (37)	**<0.01**
	Mild	178 (80)	78 (55)	
	Moderate/Severe	29 (13)	12 (9)	
Mitral regurgitation				
	None/trace	14 (13)	20 (19)	0.453
	Mild	68 (61)	64 (61)	
	Moderate/Severe	20 (26)	21 (20)	
Left ventricular mass index (g/m^2)		153.2 [119.6–186.8]	123.0 [89.1–156.9]	**0.002**
Left ventricular hypertrophy[a]		93 (88)	65 (67)	**0.001**
Relative wall thickness		0.47 ± 0.09)	0.44 ± 0.09	0.053
Concentric left ventricular hypertrophy/remodeling[b]		74 (70)	55 (56)	**0.043**
Ejection fraction (%)		61.50 [51.8–71.3]	63.0 [55.3–70.1]	0.130
Ejection fraction <50%		30 (27.3)	21 (19.8)	0.205
Ejection fraction <30%		8 (7.3)	2 (1.9)	0.102
Left ventricular diastolic dimension (cm)		5.2 ± 0.8	5.1 ± 0.8	0.406
Septal wall thickness (cm)		1.20 [1.14–1.27]	1.20 [1.15–1.35]	**<0.001**
Posterior wall thickness (cm)		1.20 [1.10–1.30]	1.10 [1.0–1.20]	**<0.001**

Data presented as mean ± SD, median [IQR] or frequency (%).
[a]Defined as left ventricular mass index >95 g/m^2 ♀,>115 g/m^2 ♂.[17]
[b]Defined as a relative wall thickness >0.42.[17]

than general anesthesia in a cath-lab) is increasingly adopted by TAVI centers [2,19,20]. This "minimalist" approach has been shown to be associated with minimal morbidity and mortality and equivalent effectiveness [19,21], shorter length of hospitalization [20,21], and less resource use [21] compared with the conventional approach. TEE is therefore progressively less utilized and whether transthoracic [22,23] or intracardiac [23,24] echocardiography can effectively replace it, is to-date unclear. On the other hand, angiography remained irreplaceable in procedural guidance. Exclusive angiographic guidance has been shown to be feasible and safe and to afford equivalent efficacy to TEE guidance [25]. Angiography has some advantages over echocardiography for quantification of AR after TAVI, as it is not influenced by the calcium/metal artifacts and it weighs the total amount of contrast leaking to the LV representing the sum of all regurgitant jets irrespective of their number, location and direction [12]. However, the classic Sellers' visual method of angiographic assessment has important shortcomings including subjectivity, low reproducibility, qualitative nature, and lack of adequate validation in the post-TAVI setting [26].

Video-Densitometric Analysis Can Improve the Diagnostic Value of Aortography

VD has been shown to overcome some of those limitations especially inter- and intra-observer variability [12]. VD provides multiple continuous indices of AR severity including peak contrast density, mean contrast density, quantitative regurgitation analysis (qRA) index and absolute and relative area under the curve (RAUC). RAUC is an index that includes most of the data obtained from the contrast time–density curves [12]. RAUC of the contrast leaking to the subaortic segment of the LV (LVOT-AR) has been shown to be less influenced by background radiodensities, patient/table motion and variability of the LV size and function [10–12] than the entire-LV interrogation method.

The Clinical Utility of LVOT-AR to Guide Decision-Making

In the present study, LVOT-AR > 0.17 was shown to correspond to greater-than-mild AR on echocardiography, consistently for pre-TAVI trans-valvular AR and for post-TAVI (often paravalvular) AR. The same cut-point could characterize the subgroup of patients with impaired LV recovery denoting a significant volume overload partially precluding the benefit from relieving LV outflow obstruction. Moreover, the group of patients with LVOT-AR > 0.17 demonstrated a higher incidence of mortality after TAVI. We can now, with reasonable confidence, propose this cutpoint to risk-stratify TAVI patients immediately after implantation and to guide the decision to provide—and the judgment of the efficacy of—corrective measures.

Although the clinical importance of AR after TAVI and the importance of efficient antileak corrective interventions are well-acknowledged, few data are

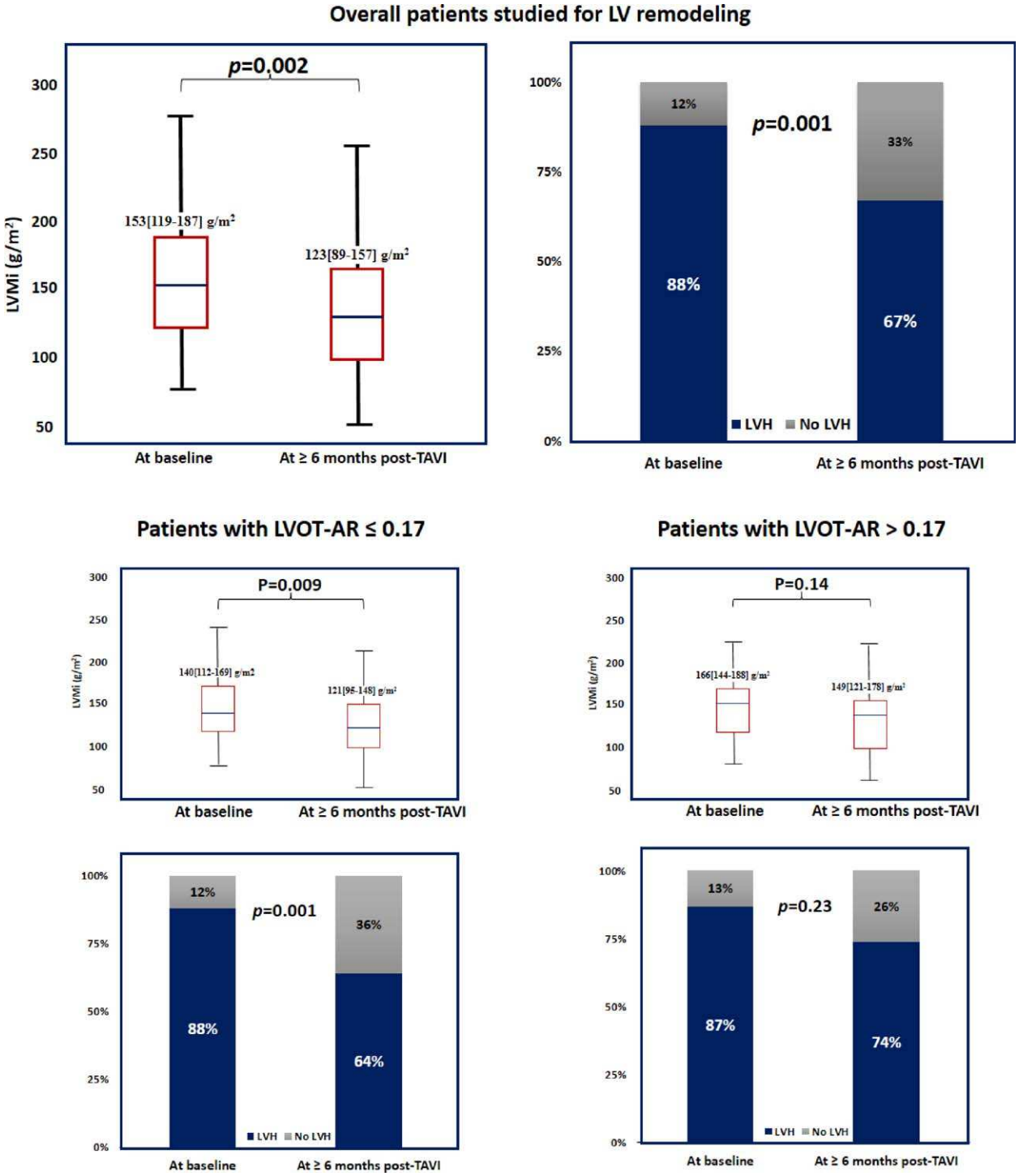


Fig. 4. Left ventricular reverse remodeling studied in all patients with complete echocardiographic follow-up at ≥6 months (upper panel), in patients with LVOT-AR ≤ 0.17 (left lower panel), and in patients with LVOT-AR > 0.17 (right lower panel). LV = left ventricle, LVH = left ventricular hypertrophy, LVM_i = left ventricular mass index. [Color figure can be viewed at wileyonlinelibrary.com]

available to support the use of certain cutpoints to guide these interventions. Among few examples, AR index <25 was used for stratifying AR developing immediately post-TAVI in terms of relevance to worse clinical outcomes [27]. However, the frequency of a low AR index among TAVI patients is very high,

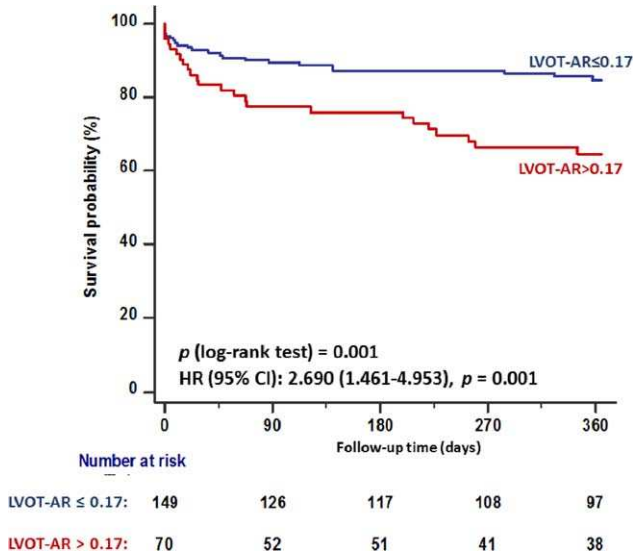


Fig. 5. Kaplan–Meier estimates of cumulative survival up to 1 year after TAVI, stratified according to the degree of LVOT-AR. CI = confidence interval, HR = hazard ratio. [Color figure can be viewed at wileyonlinelibrary.com]

ranging from 34 to 57% [27–29] and often coexists with no/trivial AR, particularly in the presence of relative bradycardia [29]. A nonspecific elevation of the LV end-diastolic pressure might lead to a low transvalvular end-diastolic gradient and thus to a false positive AR index. This underscores the complementary value of the AR index, which should not be used as a stand-alone index but rather in combination with other imaging methods. Another example, is vena contracta area $\geq$10 mm^2 by TEE [30]. Although association with worse outcomes has been shown, this criterion is usable only in TEE-guided procedures. The good alignment with echocardiography (optimizing intertechnique reproducibility) and the association of LVOT-AR $>$ 0.17 with impaired LV recovery and increased risk of death all support the use of this index for "online" prognostication in the cath-lab.

Limitations

Analyzability of VD indices is generally suboptimal in retrospectively-acquired aortograms especially when the entire LV is interrogated [12]. Our group has previously [11] proposed limiting the ROI to the sub-aortic segment (LVOT-AR) aiming at improving analyzability by avoiding many confounding radio-dense objects (e.g., the contrast-filled descending aorta, and diaphragmatic shadow). In the present study, adequate analysis of LVOT-AR was feasible in 68% of angiograms, further emphasizing the main limitation of VD methods-the limited feasibility of adequate analysis if acquisition is not standardized. In a study by Schultz et al. [12], analyzability could be significantly improved by simple standardization of acquisition in a small prospective series. A straightforward rule to define a patient-specific overlap-free fluoroscopic projection has been developed and can effectively improve the feasibility of the technology (Dr. Carl Schultz, MD, PhD, and Dr. Hiroki Tateishi, MD, PhD, Unpublished data, 2016).

Post-implantation angiography and pre-discharge echocardiography were not performed simultaneously and this might have introduced some variability between the results of both techniques. In fact, using echocardiography as a reference standard is a limitation of the study. Although the echocardiographic criteria used as a reference are recommended by the VARC-II report, those criteria lack adequate validation in the post-TAVI setting [7]. Notwithstanding, echocardiography remains the main tool for the non-invasive evaluation of AR after TAVI, and maintaining good agreement between angiographic and echocardiographic criteria is important for follow-up.

Finally, volume and rate of contrast used for aortography were not standardized nor was the position of the tip of pig tail catheter in relation to the aortic valve. These limitations are more relevant to visual assessment of AR where the absolute extent of LV opacification is the mainstay of assessment. Using VD analysis, these limitations are less relevant as the "relative" opacification of the ROI in comparison to that in aortic root is used to judge AR severity.

CONCLUSION

Angiographic LVOT-AR $>$ 0.17 corresponds to greater than mild AR as defined by echocardiography and patients with LVOT-AR $>$ 0.17 after TAVI are characterized by impaired LV reverse remodeling and worse clinical outcomes. This index can be used in the cath-lab to judge procedural success and to guide provision of corrective measures against AR.

DISCLOSURE

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REFERENCES

1. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–2198.
2. Wenaweser P, Stortecky S, Schwander S, et al. Clinical outcomes of patients with estimated low or intermediate surgical risk undergoing transcatheter aortic valve implantation. Eur Heart J 2013;34:1894–1905.
3. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–1695.
4. Athappan G, Patvardhan E, Tuzcu EM, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: Meta-analysis and systematic review of literature. J Am Coll Cardiol 2013;61:1585–1595.
5. Kodali S, Pibarot P, Douglas PS, et al. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: Characterizing patients and impact on outcomes. Eur Heart J 2015;36:449–456.
6. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.
7. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document (VARC-2). Eur J Cardiothorac Surg 2012;42:S45–S60.
8. Sellers RD, Levy MJ, Amplatz K, et al. Left retrograde cardioangiography in acquired cardiac disease: Technic, indications and interpretations in 700 cases. Am J Cardiol 1964;14:437–447.
9. Booth DC, Nissen S, De Maria AN. Assessment of the severity of valvular regurgitation by digital subtraction angiography compared to cineangiography. Am Heart J 1985;110:409–416.
10. Klein LW, Agarwal JB, Stets G, et al. Videodensitometric quantitation of aortic regurgitation by digital subtraction aortography using a computer-based method analyzing time–density curves. Am J Cardiol 1986;58:753–756.
11. Tateishi H, Campos CM, Abdelghani M, et al. Video densitometric assessment of aortic regurgitation after transcatheter aortic valve implantation: Results from the Brazilian TAVI registry. EuroIntervention 2016;11:1409–1418.
12. Schultz CJ, Slots TL, Yong G, et al. An objective and reproducible method for quantification of aortic regurgitation after TAVI. EuroIntervention 2014;10:355–363.
13. de Brito FS, Jr., Carvalho LA, Sarmento-Leite R, et al. Outcomes and predictors of mortality after transcatheter aortic valve implantation: Results of the Brazilian registry. Catheter Cardiovasc Interv 2015;85:E153–E162.
14. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: An executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611–644.
15. Zamorano JL, Badano LP, Bruce C, et al. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. Eur Heart J 2011;32:2189–2214.
16. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound: A report From the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. J Am Soc Echocardiogr 2009;22:975–1014 (quiz 1082-1084).
17. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39 e14.
18. Van Belle E, Rauch A, Vincent F, et al. Von Willebrand factor multimers during transcatheter aortic-valve replacement. New Engl J Med 2016;375:335–344.
19. Oguri A, Yamamoto M, Mouillet G, et al. Clinical outcomes and safety of transfemoral aortic valve implantation under general versus local anesthesia: Subanalysis of the French Aortic National CoreValve and Edwards 2 registry. Circ Cardiovasc Interv 2014;7:602–610.
20. Durand E, Eltchaninoff H, Canville A, et al. Feasibility and safety of early discharge after transfemoral transcatheter aortic valve implantation with the Edwards SAPIEN-XT prosthesis. Am J Cardiol 2015;115:1116–1122.
21. Babaliaros V, Devireddy C, Lerakis S, et al. Comparison of transfemoral transcatheter aortic valve replacement performed in the catheterization laboratory (minimalist approach) versus hybrid operating room (standard approach): Outcomes and cost analysis. JACC Cardiovasc Interv 2014;7:898–904.
22. Sengupta PP, Wiley BM, Basnet S, et al. Transthoracic echocardiography guidance for TAVR under monitored anesthesia care. JACC Cardiovasc Imaging 2015;8:379–380.
23. Bartel T, Edris A, Velik-Salchner C, et al. Intracardiac echocardiography for guidance of transcatheter aortic valve implantation under monitored sedation: A solution to a dilemma? Eur Heart J Cardiovasc Imaging 2016;17:1–8.
24. Dhoble A, Nakamura M, Makar M, et al. 3D intracardiac echocardiography during TAVR without endotracheal intubation. JACC Cardiovascular Imaging 2016;9:1014–1015.
25. Attizzani GF, Ohno Y, Latib A, et al. Transcatheter aortic valve implantation under angiographic guidance with and without adjunctive transesophageal echocardiography. Am J Cardiol 2015;116:604–611.
26. Abdelghani M, Soliman OI, Schultz C, et al. Adjudicating paravalvular leaks of transcatheter aortic valves: A critical appraisal. Eur Heart J 2016;37:2627–2644.
27. Sinning JM, Hammerstingl C, Vasa-Nicotera M, et al. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. J Am Coll Cardiol 2012;59:1134–1141.
28. Vasa-Nicotera M, Sinning JM, Chin D, et al. Impact of paravalvular leakage on outcome in patients after transcatheter aortic valve implantation. JACC Cardiovasc Interv 2012;5:858–865.
29. Jilaihawi H, Chakravarty T, Shiota T, et al. Heart-rate adjustment of transcatheter haemodynamics improves the prognostic evaluation of paravalvular regurgitation after transcatheter aortic valve implantation. EuroIntervention 2015;11:456–464.
30. Mihara H, Shibayama K, Jilaihawi H, et al. Assessment of post-procedural aortic regurgitation after TAVR: An Intraprocedural TEE study. JACC Cardiovasc Imaging 2015;8:993–1003.