Impact of left ventricular outflow tract calcification on procedural outcomes after transcatheter aortic valve replacement

Taishi Okuno, MD[a]; Masahiko Asami, MD[a]; Dik Heg, PhD[b]; Jonas Lanz, MD, MSc[a]; Fabien Praz, MD[a]; Daniel Hagemeyer, MD[a]; Nicolas Brugger, MD[a]; Christoph Gräni, MD[a]; Adrian Huber, MD[c]; Alessandro Spirito, MD[a]; Lorenz Räber, MD, PhD[a]; Stefan Stortecky, MD[a]; Stephan Windecker, MD[a]; Thomas Pilgrim, MD[a]

[a]Department of Cardiology, Inselspital, University of Bern, Bern, Switzerland
[b]Clinical Trials Unit, University of Bern, Bern, Switzerland
[c]Department of Diagnostic, Interventional and Pediatric Radiology, Inselspital, University of Bern, Bern, Switzerland

Twitter handle: Thomas Pilgrim (@ThomPilgrim), Taishi Okuno (@taishiokuno)
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Corresponding Author:
Thomas Pilgrim, MD
Department of Cardiology
Inselspital, Bern University Hospital
University of Bern
CH-3010 Bern
Phone: 0041 31 632 21 11
Fax: 0041 31 632 47 70
Mail: thomas.pilgrim@insel.ch

ABSTRACT

Objectives: We aimed to systematically assess the importance of left ventricular outflow tract (LVOT) calcification on procedural outcomes and device performances with contemporary transcatheter heart valve (THV) systems.

Background: LVOT calcification has been associated with adverse clinical outcomes following transcatheter aortic valve replacement (TAVR). The available evidence is however limited to observational data with modest numbers and incomplete assessment of the effect of the different THV systems.

Methods: In a retrospective analysis of a prospective single-center registry, LVOT calcification was assessed in a semiquantitative fashion. Moderate/severe LVOT calcification was documented in the presence of 2 nodules of calcification, or 1 extending >5 mm in any direction, or covering >10 % of the perimeter of the LVOT.

Results: Among 1635 patients undergoing TAVR between 2007 and 2018, moderate/severe LVOT calcification was found in 407 patients (24.9%). Patients with moderate/severe LVOT calcification had significantly higher incidences of annular rupture (2.3% vs. 0.2%, P<0.001), bailout valve-in-valve implantation (2.9% vs. 0.8%, P=0.004), and residual aortic regurgitation (11.1% vs. 6.3%, P=0.002). Balloon-expandable valves conferred a higher risk of annular rupture in the presence of moderate/severe LVOT calcification (4.0% vs. 0.4%, P=0.002) as compared to the other valve designs. There was no significant interaction of valve design/generation and LVOT calcification with regards to the occurrence of bail-out valve-in-valve implantation and residual aortic regurgitation.

Conclusion: Moderate/severe LVOT calcification confers increased risks of annular rupture, residual aortic regurgitation, and implantation of a second valve. The risk of residual aortic regurgitation is consistent across valve designs and generations.

Clinical Trial Registration: https://www.clinicaltrials.gov. NCT01368250.

Keywords: transcatheter aortic valve replacement; left-ventricular outflow tract calcium; balloon-expandable valve; self-expanding valve; mechanically-expandable valve.

CONDENSED ABSTRACT

We systematically assessed the impact of LVOT calcification on procedural outcomes after TAVI in a retrospective analysis. Moderate/severe LVOT calcification was found in 407 patients (24.9%) and was associated with significantly higher incidences of annular rupture (2.3% vs. 0.2%, P<0.001), bailout valve-in-valve implantation (2.9% vs. 0.8%, P=0.004), and residual aortic regurgitation (11.1% vs. 6.3%, P=0.002). Balloon-expandable valves conferred a higher risk of annular rupture in the presence of moderate/severe LVOT calcification (4.0% vs. 0.4%, P=0.002). There was no significant interaction of valve design/generation and LVOT calcification with regards to the occurrence of bail-out valve-in-valve implantation and residual aortic regurgitation.

Abbreviations:

LVOT = Left ventricular outflow tract
SAVR = Surgical aortic valve replacement
STS PROM= Society of Thoracic Surgery-Predicted Risk Of Mortality
TAVR = Transcatheter aortic valve replacement
THV = Transcatheter heart valve
VARC = Valve Academic Research Consortium

Introduction

Left ventricular outflow tract (LVOT) calcification has previously been singled out as one of the anatomical features representing a particular challenge in patients undergoing transcatheter aortic valve replacement (TAVR). LVOT calcification has been associated with increased risks of annular rupture(1-3) and residual aortic regurgitation(4-7) following TAVR. The available evidence is however limited to observational data with modest patient numbers and incomplete assessment of the effect of different transcatheter heart valve (THV) designs on procedural outcomes. The impact of the severity and distribution of LVOT calcification on clinical outcomes remains poorly understood. We therefore aimed to systematically assess the importance of LVOT calcification on procedural outcomes and device performances with contemporary THV systems.

Methods

Study population

All patients undergoing TAVR at Bern University Hospital, Bern, Switzerland, are consecutively recorded in a prospective institutional database which is a part of the Swiss

TAVI registry (NCT01368250)(8). The registry was approved by the Bern cantonal ethics committee, and patients provided written informed consent for participation. The present analysis included patients that underwent TAVR for native aortic valve stenosis with CE marked devices between August 2007 and June 2018. All patients entering the analysis were required to have adequate pre-procedural multi-detector computed tomography (MDCT) data for systematic evaluation of the aortic valvular complex.

Transcatheter aortic valve replacement

Patients scheduled for TAVR were evaluated and discussed in the institutional heart team meeting. The THV type and size as well as access route were determined by the team based on preprocedural MDCT measurements and clinical considerations. During the study period, balloon-expandable (SAPIEN THV/XT, SAPIEN 3 [Edwards Lifesciences, Irvine, CA, USA]), self-expanding (CoreValve, Evolut R/PRO [Medtronic, Minneapolis, MN, USA]), Portico [Abbott, Chicago, IL, USA], Symetis ACURATE/ACURATE neo [Boston Scientific, Marlborough, MA, USA]), and mechanically-expandable devices (Lotus/Lotus Edge [Boston Scientific, Marlborough, MA, USA]) were used. The decision to perform pre- and/or post-dilation was left to the

discretion of the operator and was device-dependent. TAVR was performed via transfemoral route under conscious sedation by default; an alternative access approach was explored in the case of poor femoral access. Treatment strategy for procedural complications was discussed with cardiac surgeons. Standardized transthoracic echocardiography was performed before discharge by a board-certified cardiologist. The severity of residual aortic regurgitation was assessed using a multi-parametric approach and classified in accordance with the definition recommended by the Valve Academic Research Consortium (VARC-2)(9).

Grading of left ventricular outflow tract calcification

All MDCT examinations were performed as previously described(10) and independently re-evaluated by two investigators blinded to clinical outcomes, by using dedicated TAVR planning software (3mensio Structural Heart, 3mensio Medical Imaging BV, Bilthoven, the Netherlands). The images were reconstructed to achieve a double-oblique transverse reconstruction at the level of the basal aortic annulus ring using the build-in module. The LVOT calcification was assessed and classified in a semiquantitative fashion as previously described(1,11-14): mild calcification was

recorded in the presence of one nodule of calcification extending <5 mm in any dimension and covering <10% of the perimeter of the LVOT; moderate calcification was documented in the presence of two nodules of calcification or one extending >5 mm in any direction or covering >10 % of the perimeter of the LVOT; severe calcification was considered in case of multiple nodules of calcification of single focus extending >10 mm in length or covering >20% of the perimeter of the LVOT (**Figure 1**). LVOT calcification was also quantified in the contrast images by using a Hounsfield unit threshold of 850 HU as previously described(6). The region of interest was defined from the basal annular plane to a perpendicular plane 5 mm below the basal plane.

Data collection and clinical follow-up

Baseline clinical data, procedural characteristics, and follow-up data were prospectively recorded in a dedicated database, which is independently held and maintained at the Clinical Trials Unit of the University of Bern, Switzerland. Clinical follow-up was obtained at 30 days and 1 year by standardized interviews, documentation from referring physicians, and hospital discharge summaries. All adverse events of interest were systematically collected and adjudicated by a dedicated clinical event

committee, involving cardiologists and cardiac surgeons, according to the VARC-2 criteria(9).

Statistical analysis

Categorical data are represented as frequencies and percentages and the differences between groups are evaluated with the Chi-square test or Fisher's exact test. Continuous variables are expressed as mean values ± standard deviation or median values (interquartile range) and compared between groups using Student's t test or Wilcoxon rank-sum test. Event-free survival curves were constructed using the Kaplan-Meier method. Univariate Cox proportional hazards model was used to calculate crude hazard ratios (HRs) and 95% confidence intervals (95% CI) for the clinical outcomes. Multivariable Cox regression was performed to calculate adjusted HR for 1-year mortality. All the clinical variables with a p-value <0.10 (body mass index, diabetes mellitus, and mitral stenosis) at baseline as well as age, sex, and Society of Thoracic Surgeons (STS) predicted risk of mortality were used for the adjustment. Throughout the present study, a p-value of <0.05 was considered significant. Statistical analyses were performed using Stata 15.1 (StataCorp, College Station, TX, USA).

Results

Patient population

A total of 1635 patients were eligible for the present study. LVOT calcification was found in 650 patients (39.8%) and semi-quantitatively categorized as mild in 243 (14.9%), moderate in 153 (9.4%), and severe in 254 patients (15.5%). The median volume of calcium per group was 3.0 (95%CI: 1.0-6.3) mm^3 for mild, 13.0 (95%CI: 7.9-18.7) mm^3 for moderate, and 61.4 (95%CI: 33.8-105.0) mm^3 for severe.

Baseline and procedural characteristics

Clinical, echocardiographic, and MDCT characteristics are summarized in **Table 1**. Patients with none/mild versus moderate/severe LVOT calcification were comparable in terms of age, sex, and STS risk scores. Patients with moderate/severe LVOT calcification had less frequent diabetes (20.4% vs. 26.9%, P=0.010) and lower body mass index (BMI) (25.60±5.20 vs. 26.93±5.27, P<0.001) as compared to patients with none/mild LVOT calcification. On echocardiography, patients with moderate/severe LVOT calcification had more frequently mitral stenosis as compared to patients with

183 none/mild calcification (30.3% vs. 12.6%, P<0.001). Procedural characteristics are
184 summarized in **Table 2**. TAVR was performed by transfemoral route in 89% of patients
185 without differences between the groups. Balloon-expandable valves and self-expandable
186 valves were evenly distributed between the groups, while mechanically-expandable
187 valves were more commonly used in patients with moderate/severe calcification (11.3%
188 vs. 6.0%, P=0.001). The rate of pre-dilation was significantly higher in patients with
189 moderate/severe LVOT calcification (79.6% vs. 71.9%, P=0.002), whereas the rate of
190 post-dilation was comparable between the groups (30.7% vs. 27.1%, P=0.162).

191 *Clinical outcomes*

192 Procedural outcomes according to the presence or absence of moderate/severe
193 LVOT calcification are displayed in **Table 3**. Annular rupture occurred more frequently
194 in patients with moderate/severe as compared to those with none/mild LVOT calcification
195 (2.3% vs. 0.2%, P<0.001). Among the ten patients with annular rupture, surgical
196 treatment including repair of the ruptured lesion and surgical aortic valve replacement
197 (SAVR)/composite valve graft implantation was performed in three patients. Bail-out
198 interventional treatment using the Amplatzer vascular plug was performed in one patient,

199 which resulted in incomplete coverage of the leak. The other six patients were treated
200 with conservative strategies such as resuscitation with or without mechanical support,
201 optimization of the coagulation status, and pericardial drainage. Seven out of the ten
202 patients died in-hospital as a consequence of the complication (**Supplemental Table 1**).
203 Extent and localization of calcification in the patients are shown in **Supplemental Figure**.
204 LVOT calcification was located in the region of the free myocardial wall of the left
205 ventricle in all cases, in the region below the noncoronary sinus of Valsalva in 6 cases,
206 and in the interventricular septum in 3 cases.

207 Bail-out valve-in-valve procedures were more frequently performed in patients
208 with moderate/severe as compared to those with none/mild LVOT calcification (2.9% vs.
209 0.8%, P=0.004). At discharge, residual moderate or severe aortic regurgitation was more
210 frequently documented in patients with moderate/severe LVOT calcification as compared
211 to patients with none/mild LVOT calcification (11.1% vs. 6.3%, P=0.002) (**Figure 2**).
212 Procedural outcomes according to a more detailed stratification into none, mild, moderate,
213 and severe LVOT calcification are summarized in **Supplemental Table 2**. There was no
214 significant difference between the two groups with regard to the VARC-2 early composite

safety endpoint at 30 days (moderate/severe LVOT calcification: 20.4% versus none/mild LVOT calcification: 18.4%, P=0.432). Along the same line, there were no differences in the occurrence of 30-day mortality, disabling stroke, or permanent pacemaker implantation as a function of the presence or absence of moderate/severe LVOT calcification (**Table 4**).

Patients with moderate/severe LVOT calcification had a numerically higher incidence of all-cause mortality at 1 year as compared to patients with none/mild LVOT calcification, that was borderline statistically significant (15.4% vs. 11.6%, crude HR=1.35, 95%CI 1.00 to 1.82, P=0.048)(**Figure 3**). In a multivariate analysis, moderate/severe LVOT calcification did not emerge as an independent predictor of all-cause mortality at 1-year (adjusted HR=1.16, 95%CI 0.77 to 1.74, P=0.472).

Impact of LVOT calcification on clinical outcomes according to the design and generation of THV

We performed subgroup analyses to investigate the impact of moderate/severe LVOT calcification on clinical outcomes according to the valve design (balloon-expandable, self-expanding, mechanically-expandable) and the valve generation (earlier-

231 generation [Sapien THV/XT and CoreValve], newer-generation [Sapien 3, Evolut
232 R/PRO]). Relevant residual aortic regurgitation was more common in patients with
233 moderate/severe LVOT calcification as compared to those with none/mild LVOT
234 calcification irrespective of balloon-expandable (7.4% vs. 3.7%, P=0.047) or self-
235 expanding valve design (12.5% vs. 7.3%, P=0.038) (p for interaction 0.491). Along the
236 same line, the risk of need for a second valve was higher in patients with moderate/severe
237 LVOT calcification as compared to those with none/mild LVOT calcification without
238 significant interaction as a function of balloon-expandable (1.7% vs. 0.4%, P=0.084) or
239 self-expanding (4.9% vs. 1.4%, P=0.008) valve design (p for interaction 0.774). In
240 patients treated with mechanically-expandable valves, the incidences of relevant residual
241 aortic regurgitation and need for a second valve implantation were comparable between
242 patients with moderate/severe and those with none/mild LVOT calcification (2.1% vs.
243 2.7%, P=0.841; 0% vs. 0%, p-values not available; respectively) (p for interaction
244 [balloon-expandable, self-expanding, mechanically-expandable] 0.676 and 0.773,
245 respectively). Balloon-expandable valves conferred a higher risk of annular rupture in the
246 presence of moderate/severe LVOT calcification (4.0% vs. 0.4%, P=0.002), while annular

247 rupture rarely occurred regardless of the presence of moderate/severe LVOT calcification
248 among patients treated with self-expanding (0.5% vs. 0%, P=not available) and
249 mechanically-expandable (0% vs. 0%, P=not available) valves (p-values for interaction
250 not available) (**Central Illustration**). Furthermore, the annular rupture in the patient
251 treated with a self-expanding valve was attributed to aggressive post-dilation performed
252 to mitigate residual paravalvular leak.

253 The incidence of annular rupture was significantly higher (3.3% vs. 0%,
254 P=0.039) in the presence of moderate/severe LVOT calcification among patients treated
255 with earlier-generation THVs, while the difference was not statistically significant
256 (1.3% vs. 0.4%, P=0.198) among patients treated with newer generation THVs (p-value
257 for interaction not available). There was no significant interaction of the valve
258 generation and LVOT calcification with regard to the occurrences of need for the
259 implantation of a second valve (p for interaction 0.693) and relevant aortic regurgitation
260 at discharge (p for interaction 0.836) (**Central Illustration**).

261 *Outcomes in current THVs*

262 Procedural characteristics and clinical outcomes of patients treated with newer

generation THVs [Sapien 3, Evolut R/PRO, Portico, Symetis ACURATE/ACURATE neo, Lotus/Lotus Edge] are summarized in **Supplemental Table 3**. Consistent with the results of the overall cohort, mechanically-expandable valves were more commonly used in patients with moderate/severe LVOT calcification (20.6% vs. 9.3%, P<0.001). The risk of procedural complications, including annular rupture (0.9% vs. 0.3%, P=0.210), bail-out valve-in-valve implantation (2.2% vs. 0.8%, P=0.070), and residual moderate or severe aortic regurgitation (4.0% vs. 3.3%, P=0.539) were comparable between patients with moderate/severe LVOT calcification and those with none/mild LVOT calcification. Subgroup analyses to investigate the impact of moderate/severe LVOT calcification on clinical outcomes for each newer generation THV individually are shown in **Supplemental Table 4**. As with the overall cohort, there was no significant interaction between the THV design and LVOT calcification with regard to the need for the implantation of a second valve and relevant aortic regurgitation at discharge (p for interaction [balloon-expandable, self-expanding, mechanically-expandable] 0.442 and 0.791, respectively). Annular rupture was only observed in patients treated with balloon-expandable valves.

Discussion

The principal findings of the present analysis can be summarized as follows: Moderate or severe LVOT calcification was encountered in one quarter of patients undergoing TAVR and was associated with increased risks of annular rupture, need for a second valve, and moderate or severe residual aortic regurgitation. The effect was largely consistent across the valve designs and the generations. In patients with moderate/severe LVOT calcification, balloon-expandable valves were however associated with higher rates of annular rupture as compared to self-expanding and mechanically-expandable valves. Moreover, we observed a trend towards an increased risk of death at one year in patients with moderate/severe LVOT calcification.

We documented a lower prevalence of diabetes and a lower BMI in patients with moderate/severe LVOT calcification as compared to those with none/mild LVOT calcification. While this observation contrasts with the current understanding that cardiac valvular calcification shares similar risk factors and atherosclerotic pathophysiological pathways as vascular calcification(15,16), it is consistent with

295 previous reports(7,11). We can only speculate on the underlying cause for this
296 observation. One possible explanation may be that patients known to have diabetes or
297 metabolic syndrome had more severe coronary artery disease; in combination with
298 significant LVOT calcification, this may have led to a preference for SAVR in
299 combination with coronary artery bypass graft surgery rather than TAVR in combination
300 with percutaneous coronary intervention.
301 *LVOT calcification and annular rupture*
302 Annular rupture is a rare (0.5 to 1.0%) but life-threatening complication
303 following TAVR, associated with an in-hospital mortality of up to 50%(1,17-19). In a
304 multicenter analysis of 31 patients from 16 centers, patients with LVOT calcification
305 treated with balloon-expandable devices had a more than 10-fold increased risk of
306 annular rupture as compared to matched controls(1,3). Consistently, in a retrospective
307 analysis of 537 consecutive patients treated with balloon-expandable valves in 90% of
308 the patients, the incidence of aortic annulus injury was significantly higher in patients
309 with moderate/severe LVOT calcification as compared with patients with none/mild
310 LVOT calcification (3.7% vs. 0.2%, P=0.006)(11). In the present study, we corroborate

311 these findings in a considerably larger patient population from a prospective registry
312 with comprehensive imaging data and independent event adjudication. In contrast to the
313 above mentioned studies, more than half of all patients with moderate/severe LVOT
314 calcification were treated with self-expanding or mechanically-expandable valves in our
315 study. While annular rupture was exceedingly rare in patients with self-expanding or
316 mechanically-expandable valves, we found no significant interaction of the occurrence
317 of annular rupture as a function of treatment with early or newer generation valves.
318 While valve designs have substantially been refined over recent years, sizing
319 recommendations have largely remained unchanged. In eight out of the ten patients with
320 annular rupture, oversizing rate was >10%, in two of which oversizing rate was >20%.
321 Implantation of smaller sized THV may have prevented annular rupture in these cases.
322 Calcification in the LVOT in direct extension of the left coronary sinus of Valsalva is
323 considered to entail the greatest risk due to its proximity to the epicardial fat and
324 pericardial cavity(4,19). In the present study, although all ruptured cases had
325 calcification adjacent to the free myocardial wall, a correlation between the distribution
326 of the calcification and the location of rupture could not be assessed due to the absence

of multimodality imaging assessment.

LVOT calcification and residual aortic regurgitation

We found a higher risk of residual moderate or severe aortic regurgitation in patients with significant LVOT calcification, thus corroborating the findings of previous studies reporting an increased risk of residual aortic regurgitation due to LVOT calcification in patients treated with balloon-expandable(4,6) and self-expanding valves(5). In our study, there was no significant interaction of the effect of LVOT calcification on aortic regurgitation as a function of balloon-expandable or self-expanding valve design. Of note, among patients treated with mechanically-expandable valves, the rate of moderate/severe aortic regurgitation were comparable in patients with none/mild (2.7%) versus moderate/severe (2.1%) LVOT calcification (P=0.841). This observation confirms our clinical experiences and accounts for the disproportionately higher use of mechanically-expandable valves in patients with moderate/severe LVOT calcification in our registry.

In a study by Nomura and colleagues including 433 patients with mild or more LVOT calcification, newer-generation THVs (SAPIEN 3 and Evolut R) were found to

have a numerically lower rate of moderate or severe paravalvular leak as compared with earlier-generation THVs (SAPIEN THV/XT and CoreValve)(13). In contrast, we found a consistent risk of residual aortic regurgitation across different valve generations. The implantation of a second-valve during the index procedure closely correlated with residual aortic regurgitation. The majority of second valves were implanted due to excessive aortic regurgitation after the first valve in patients with moderate/severe LVOT calcification (**Supplemental Table 5**). The risk of bail-out implantation of a second valve was comparable across the valve designs and generations.

LVOT calcification and mortality

LVOT calcification has been associated with an increased risk of mortality following TAVR in previous reports (7,11,12). Studies by Watanabe and colleagues and Jochheim and colleagues both documented an association of calcification of the aortic valve and the LVOT with an increased risk of mortality at 30 days in a modest number of patients(12). In contrast, there was no increased risk of mortality at 30 days in the study by Maeno and colleagues, including 107 patients with moderate/severe LVOT calcification(11). In the latter analysis, LVOT calcification however emerged as an

359 independent predictor of death at 2 years in a multivariable analysis. In the present
360 study including a considerably larger number of patients compared with the previous
361 reports, we observed a 35% increased risk of death at 1 year in patients with
362 moderate/severe LVOT calcification as compared to those with none/mild LVOT
363 calcification. Consistent with a previous report(10), LVOT calcification was associated
364 with mitral stenosis in approximately one third of patients in our cohort. Calcification of
365 the aortic valve complex often coexists with mitral annular calcification due to the
366 shared pathophysiological mechanism of atherosclerosis(15). The observed effect of
367 LVOT calcification may therefore be confounded by concomitant mitral stenosis. Along
368 this line, in a multivariable analysis including mitral stenosis, LVOT calcification did
369 not independently effect mortality at 1 year in the present study. In addition, a higher
370 rate of residual aortic regurgitation in patients with moderate/severe LVOT calcification
371 may have contributed to the increased risk of death at one year. The adverse effect of
372 residual aortic regurgitation after TAVR has been reported previously(20).

373 *Study Limitations*

374 The findings of our study need to be interpreted in light of several limitations.

First, even though the current study provides the largest dataset on systematically assessed CT data of patients undergoing TAVR, the low event rate of rare but devastating complications such as annular rupture warrants cautious interpretation of the statistical analysis. Second, the selection of valve type was based on a heart team decision and was performed in a non-randomized fashion; the impact of LVOT calcification as a function of valve type may therefore be confounded and needs to be interpreted with caution. Furthermore, although we excluded patients with inadequate pre-procedural MDCT images from the present analysis, some of the included patients still had MDCT images of borderline quality, which may have led to inaccurate valve sizing. Third, the risk of residual aortic regurgitation and need for a second valve implantation is multifactorial and not solely determined by the severity of LVOT calcification. Finally, while previous reports investigating the effect of LVOT calcium had a focus on balloon-expandable valves, we studied the impact of LVOT calcification on the entire spectrum of valve types; however, the number of patients treated with mechanically-expandable valves was modest limiting the robustness of the reported findings.

Conclusions and clinical perspectives

Presence of LVOT calcification in TAVR candidates carries an increased risk of annular rupture, residual aortic regurgitation and need for implantation of a second valve, and should be considered in the heart team decision on the optimal treatment strategy for patients with aortic stenosis.

Perspectives

What Is Known?

LVOT calcification has been suggested to confer increased risks of annular rupture, residual aortic regurgitation, and mortality following TAVR. However, there is limited evidence on the effect of different THV designs or generations on the procedural outcomes in the presence of significant LVOT calcification.

What Is New?

Patients with moderate/severe LVOT calcification had significantly higher incidences of annular rupture, bailout valve-in-valve implantation, and residual aortic regurgitation. While balloon-expandable valves had the greatest risk of annular rupture, the risk of residual regurgitation or implantation of a second valve was comparable across valve types.

What Is Next?

LVOT calcification requires special consideration in peri-procedural planning. Refinemens of valve designs are needed to overcome the limitations of current devices in this patient population.

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Figure Legends

Figure 1. Categorization of LVOT calcification and prevalence per group.

A, B) 1 nodule of calcification extending <5mm in any dimension and covering <10% of the perimeter of the LVOT. C) 1 nodule of calcification extending >5mm in any direction. D) 2 nodules of calcification. E) 1 nodule of calcification covering >10% of the perimeter of the LVOT. F) Multiple nodules of calcification of single focus extending >10 mm. G) Multiple nodules of calcification covering >20% of the perimeter of the LVOT. Yellow arrows indicate nodules of calcification.

Figure 2. Residual AR at discharge according to none/mild or moderate/severe LVOT calcification

Bar graph illustrating the prevalence of aortic regurgitation in patients with moderate/severe LVOT calcification and none/mild LVOT calcification. Light blue = no aortic regurgitation; grey = mild aortic regurgitation; dark blue = moderate aortic regurgitation; red = severe aortic regurgitation.

Figure 3. Kaplan-Meier curve of mortality according to none/mild or moderate/severe LVOT calcification

512 Blue line indicates none/mild LVOT calcification; Red line indicates moderate/severe

513 LVOT calcification.

514 **Central Illustration. The impact of LVOT calcification stratified by THV designs**

515 **and THV generation.**

516 Depicted are numbers of events/patients with percentages (%), rate ratios (robustified

517 standard errors) with 95% confidence interval and p-values, and interaction p-values.

518 Balloon-expandable valves include SAPIEN THV/XT, SAPIEN 3. Self-expandable

519 valves include CoreValve, Evolut R/PRO, Portico, Symetis ACURATE/ACURATE

520 neo. Mechanical-expandable valves include Lotus/Lotus Edge.

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Tables

Table 1. Baseline characteristics according to none/mild or moderate/severe LVOT calcification

Table 1. Baseline characteristics according to none/mild or moderate/severe LVOT calcification				
	All patients (n=1635)	**LVOT calcification**		**P-value**
		None/ Mild (n=1228)	**Moderate/Severe** (n=407)	
Clinical characteristics				
Age (years)	82.22±5.94	82.13±5.82	82.50±6.30	0.270
Female gender (n, %)	865 (52.9%)	654 (53.3%)	211 (51.8%)	0.647
Body mass index (kg/cm²)	26.60±5.28	26.93±5.27	25.60±5.20	<0.001
Logistic Euro Score	17.60±13.27	17.56±13.44	17.73±12.77	0.818
STS PROM	5.34±3.53	5.30±3.55	5.46±3.49	0.420
NYHA III or IV (n, %)	1140 (69.9%)	866 (70.6%)	274 (67.5%)	0.236
Hypertension (n, %)	1387 (84.8%)	1049 (85.4%)	338 (83.0%)	0.264
Diabetes mellitus (n, %)	413 (25.3%)	330 (26.9%)	83 (20.4%)	0.010
CKD (GFR<60) (n, %)	1090 (66.8%)	819 (66.8%)	271 (66.7%)	1.000
COPD (n, %)	209 (12.8%)	162 (13.2%)	47 (11.5%)	0.441
Atrial fibrillation (n, %)	549 (33.6%)	419 (34.1%)	130 (31.9%)	0.432
Coronary artery disease (n, %)	1021 (62.4%)	763 (62.1%)	258 (63.4%)	0.679
Cerebrovascular accident (n, %)	187 (11.4%)	140 (11.4%)	47 (11.5%)	0.929
Peripheral artery disease (n, %)	223 (13.6%)	162 (13.2%)	61 (15.0%)	0.360
Previous pacemaker (n, %)	141 (8.6%)	104 (8.5%)	37 (9.1%)	0.685
Echocardiographic data				
Aortic Valve Area (cm²)	0.66±0.24	0.67±0.25	0.60±0.22	<0.001
LVEF (%)	55.10±14.28	54.87±14.18	55.78±14.58	0.272
Moderate/severe AR (n, %)	11 (0.9%)	7 (0.7%)	4 (1.2%)	0.495
Moderate/severe MR (n, %)	234 (18.0%)	168 (17.6%)	66 (18.9%)	0.625
Moderate/severe TR (n, %)	181 (14.0%)	123 (13.0%)	58 (16.7%)	0.104
Mitral stenosis (n, %)				<0.001
Normal	814 (82.7%)	632 (87.4%)	182 (69.7%)	<0.001
Mild	128 (13.0%)	76 (10.5%)	52 (19.9%)	<0.001

Moderate	39 (4.0%)	13 (1.8%)	26 (10.0%)	<0.001
Severe	3 (0.3%)	2 (0.3%)	1 (0.4%)	1.000
Multidetector computed tomography data				
Annulus area (mm2)	452.01±84.92	450.06±83.86	457.88±87.89	0.108
AVC calcium (mm³)	336.95±360.04	268.76±264.32	542.01±503.79	<0.001
LVOT calcium (mm³)	0.0 (0.0; 9.3)	0.0 (0.0; 0.0)	37.0 (16.5; 78.4)	<0.001

Depicted are means with standard deviations (±SD), counts with percentages (%) or median with interquartile ranges (25%; 75%).
STS PROM = Society of Thoracic Surgeons Predicted Risk Of Mortality; NYHA = New York Heart Association; CKD = Chronic kidney disease; GFR = Glomerular filtration rate; COPD = Chronic obstructive pulmonary disease; LVEF = Left ventricular ejection fraction; AR = Aortic regurgitation; MR = Mitral regurgitation; TR = Tricuspid regurgitation; AVC = Aortic valvular complex; LVOT = Left ventricular outflow tract.

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529 **Table 2.** Procedural characteristics according to none/mild or moderate/severe LVOT

530 calcification

Table 2. Procedural characteristics according to none/mild or moderate/severe LVOT calcification				
	All patients (n=1635)	**LVOT calcification**		**P-value**
		None/ Mild (n=1228)	**Moderate/Severe** (n=407)	
Fluoroscopy time (min)	18.07 ± 15.66	17.61 ± 12.10	19.45 ± 23.27	0.054
General anesthesia (n, %)	355 (21.7%)	254 (20.7%)	101 (24.8%)	0.083
Femoral main access site (n, %)	1460 (89.3%)	1100 (89.6%)	360 (88.5%)	0.518
Type of valve (n, %)				0.002
Balloon-expandable* (n, %)	742 (45.4%)	566 (46.1%)	176 (43.3%)	0.358
Self-expanding** (n, %)	771 (47.2%)	587 (47.8%)	184 (45.3%)	0.39
Mechanically-expandable***: (n, %)	120 (7.3%)	74 (6.0%)	46 (11.3%)	0.001
Pre-dilation (n, %)	1206 (73.8%)	883 (71.9%)	323 (79.6%)	0.002
Post-dilation (n, %)	458 (28.0%)	333 (27.1%)	125 (30.7%)	0.162
Depicted are means with standard deviations (±SD), counts with percentages (%). * SAPIEN THV/XT, SAPIEN3 ** CoreValve, Evolut R/ PRO, Portico, Symetis ACURATE/ACURATE neo *** Lotus/ Lotus Edge				

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532 **Table 3.** Procedural outcomes according to none/mild or moderate/severe LVOT

533 calcification

Table 3. Procedural complications according to none/mild or moderate/severe LVOT calcification				
	All patients (n=1635)	**LVOT calcification**		**P-value**
		None/ Mild (n=1228)	**Moderate/Severe** (n=407)	
Bail-out valve-in-valve (n, %)	22 (1.3%)	10 (0.8%)	12 (2.9%)	0.004
Valve dislocation/embolization (n, %)	27 (1.9%)	19 (1.8%)	8 (2.3%)	0.509
Annular rupture (n, %)	10 (0.7%)	2 (0.2%)	8 (2.3%)	<0.001
Cardiac tamponade/rupture (n, %)	14 (0.9%)	9 (0.7%)	5 (1.2%)	0.356
Coronary artery occlusion (n, %)	6 (0.4%)	4 (0.4%)	2 (0.6%)	0.642
Moderate/severe residual AR at discharge (n, %)	122 (7.5%)	77 (6.3%)	45 (11.1%)	0.002
Depicted are counts with percentages (%).				

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536 **Table 4.** Clinical outcomes at 30 days according to none/mild or moderate/severe LVOT

537 calcification

Table 4. Clinical outcomes at 30 days according to none/mild or moderate/severe LVOT calcification				
	LVOT calcification severity		**Crude Rate ratio**	
	None/Mild	Moderate/Severe	Moderate/Severe vs. None/Mild	
	(n=1228)	(n=407)	RR (95% CI)	p-value
All-cause mortality (n, %)	34 (2.8%)	14 (3.4%)	1.24 (0.67-2.31)	0.496
Myocardial infarction (n, %)	7 (0.6%)	4 (1.0%)	1.73 (0.51-5.91)	0.382
Disabling stroke (n, %)	24 (2.0%)	11 (2.7%)	1.39 (0.68-2.84)	0.365
Major or life-threatening bleeding (n, %)	232 (18.9%)	79 (19.4%)	1.02 (0.79-1.32)	0.867
Major vascular complication (n, %)	126 (10.3%)	46 (11.3%)	1.10 (0.78-1.54)	0.581
Kidney injury stage 3 (n, %)	20 (1.6%)	9 (2.2%)	1.37 (0.62-3.00)	0.436
Permanent pacemaker implantation (n, %)	224 (20.1%)	81 (20.1%)	1.00 (0.78-1.29)	0.984
All-cause mortality or any Stroke (n, %)	64 (5.2%)	27 (6.6%)	1.28 (0.82-2.01)	0.277
VARC-2 early composite safety endpoint*	226 (18.4%)	83 (20.4%)	1.11 (0.86-1.42)	0.432

Number of first events are presented (% from life table estimate for 30 days).

- VAR-2 early composite safety includes all-cause mortality, stroke, life-threatening bleeding, acute kidney injury (stage 2 or 3), coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure.

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