

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

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17 **Tweet:** “LVOT calcification matters: increased risk of annular rupture, PVL & second
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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.

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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

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Introduction

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

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Methods

Study population

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

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

109 *Transcatheter aortic valve replacement*

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

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

127 *Grading of left ventricular outflow tract calcification*

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

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

144 *Data collection and clinical follow-up*

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

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

153 *Statistical analysis*

154 Categorical data are represented as frequencies and percentages and the
155 differences between groups are evaluated with the Chi-square test or Fisher's exact test.

156 Continuous variables are expressed as mean values \pm standard deviation or median values
157 (interquartile range) and compared between groups using Student's t test or Wilcoxon

158 rank-sum test. Event-free survival curves were constructed using the Kaplan-Meier
159 method. Univariate Cox proportional hazards model was used to calculate crude hazard
160 ratios (HRs) and 95% confidence intervals (95% CI) for the clinical outcomes.

161 Multivariable Cox regression was performed to calculate adjusted HR for 1-year mortality.

162 All the clinical variables with a p-value <0.10 (body mass index, diabetes mellitus, and
163 mitral stenosis) at baseline as well as age, sex, and Society of Thoracic Surgeons (STS)

164 predicted risk of mortality were used for the adjustment. Throughout the present study, a
165 p-value of <0.05 was considered significant. Statistical analyses were performed using

166 Stata 15.1 (StataCorp, College Station, TX, USA).

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Results

169 *Patient population*

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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) mm³ for mild, 13.0 (95%CI: 7.9-18.7) mm³ for moderate, and 61.4 (95%CI: 33.8-105.0) mm³ for severe.

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Baseline and procedural characteristics

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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

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

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

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

228 We performed subgroup analyses to investigate the impact of moderate/severe
229 LVOT calcification on clinical outcomes according to the valve design (balloon-
230 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

263 generation THVs [Sapien 3, Evolut R/PRO, Portico, Symetis ACURATE/ACURATE
264 neo, Lotus/Lotus Edge] are summarized in [Supplemental Table 3](#). Consistent with the
265 results of the overall cohort, mechanically-expandable valves were more commonly
266 used in patients with moderate/severe LVOT calcification (20.6% vs. 9.3%, $P<0.001$).
267 The risk of procedural complications, including annular rupture (0.9% vs. 0.3%,
268 $P=0.210$), bail-out valve-in-valve implantation (2.2% vs. 0.8%, $P=0.070$), and residual
269 moderate or severe aortic regurgitation (4.0% vs. 3.3%, $P=0.539$) were comparable
270 between patients with moderate/severe LVOT calcification and those with none/mild
271 LVOT calcification. Subgroup analyses to investigate the impact of moderate/severe
272 LVOT calcification on clinical outcomes for each newer generation THV individually
273 are shown in [Supplemental Table 4](#). As with the overall cohort, there was no
274 significant interaction between the THV design and LVOT calcification with regard to
275 the need for the implantation of a second valve and relevant aortic regurgitation at
276 discharge (p for interaction [balloon-expandable, self-expanding, mechanically-
277 expandable] 0.442 and 0.791, respectively). Annular rupture was only observed in
278 patients treated with balloon-expandable valves.

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Discussion

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The principal findings of the present analysis can be summarized as follows:

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Moderate or severe LVOT calcification was encountered in one quarter of patients

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undergoing TAVR and was associated with increased risks of annular rupture, need for a

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second valve, and moderate or severe residual aortic regurgitation. The effect was

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largely consistent across the valve designs and the generations. In patients with

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moderate/severe LVOT calcification, balloon-expandable valves were however

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associated with higher rates of annular rupture as compared to self-expanding and

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mechanically-expandable valves. Moreover, we observed a trend towards an increased

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risk of death at one year in patients with moderate/severe LVOT calcification.

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We documented a lower prevalence of diabetes and a lower BMI in patients with

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moderate/severe LVOT calcification as compared to those with none/mild LVOT

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calcification. While this observation contrasts with the current understanding that

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cardiac valvular calcification shares similar risk factors and atherosclerotic

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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

327 of multimodality imaging assessment.

328 *LVOT calcification and residual aortic regurgitation*

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

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

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

351 *LVOT calcification and mortality*

352 LVOT calcification has been associated with an increased risk of mortality
353 following TAVR in previous reports (7,11,12). Studies by Watanabe and colleagues and
354 Jochheim and colleagues both documented an association of calcification of the aortic
355 valve and the LVOT with an increased risk of mortality at 30 days in a modest number
356 of patients(12). In contrast, there was no increased risk of mortality at 30 days in the
357 study by Maeno and colleagues, including 107 patients with moderate/severe LVOT
358 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.

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

391 **Conclusions and clinical perspectives**

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

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Perspectives

398 **What Is Known?**

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

403 **What Is New?**

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

409 **What Is Next?**

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

413

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Figure Legends

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

498 A, B) 1 nodule of calcification extending <5mm in any dimension and covering
499 <10% of the perimeter of the LVOT. C) 1 nodule of calcification extending >5mm in
500 any direction. D) 2 nodules of calcification. E) 1 nodule of calcification covering
501 >10% of the perimeter of the LVOT. F) Multiple nodules of calcification of single
502 focus extending >10 mm. G) Multiple nodules of calcification covering >20% of the
503 perimeter of the LVOT. Yellow arrows indicate nodules of calcification.

504 **Figure 2. Residual AR at discharge according to none/mild or moderate/severe**

505 **LVOT calcification**

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

510 **Figure 3. Kaplan-Meier curve of mortality according to none/mild or**

511 **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.

521

523 **Table 1.** Baseline characteristics according to none/mild or moderate/severe LVOT
524 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/cm ²) | 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 (cm ²) | 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 (mm ²) | 452.01±84.92 | 450.06±83.86 | 457.88±87.89 | 0.108 |
| AVC calcium (mm ³) | 336.95±360.04 | 268.76±264.32 | 542.01±503.79 | <0.001 |
| LVOT calcium (mm ³) | 0.0 (0.0; 9.3) | 0.0 (0.0; 0.0) | 37.0 (16.5; 78.4) | <0.001 |
| <p>Depicted are means with standard deviations (±SD), counts with percentages (%) or median with interquartile ranges (25%; 75%).</p> <p>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.</p> | | | | |

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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 | | | | |

531

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). | | | | |
| <ul style="list-style-type: none"> • 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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