Cardiovascular outcomes in patients with left atrial enlargement undergoing transcatheter aortic valve implantation

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Abstract

Background: Increased left ventricular afterload resulting from severe aortic stenosis (AS) leads to progressive cardiac remodeling. Left atrial enlargement (LAE) is an early manifestation in a series of maladaptive changes and may affect clinical outcomes after valvular replacement therapy. The aim of this study is to determine the impact of LAE on clinical outcomes in symptomatic patients with severe AS undergoing transcatheter aortic valve implantation (TAVI).

Methods: In a prospective single-center TAVI registry, we analyzed LA dimensions measured by echocardiography before intervention. Patients with atrial fibrillation or concomitant mitral valve disease were excluded. LAE was defined as indexed LA volume >34 ml/m². The primary endpoint was cardiovascular death (CVD) at 1 year.

Results: Among 1663 patients undergoing TAVI between August 2007 and December 2016, 768 (46.2%) were eligible for the present analysis and 486 patients had LAE. The prevalence of LAE was higher in males (68.3%) as compared to females (58.8%). Patients with LAE were older (82.3 ± 6.7 years vs. 80.0 ± 6.4 years) and had a higher STS-PROM score (6.1 ± 4.7% vs. 4.7 ± 2.9%). After adjustment, patients with LAE had an increased risk of CVD at 1-year compared to patients with normal LA dimensions (49 [10.4%] vs. 8 [2.9%]; HRadj. 3.52; 95% CI, 1.66–7.44]). In multivariable analysis, LAE was independently associated with an increased risk of CVD at 1-year (HRadj. 3.52; 95% CI, 1.66–7.44).

Conclusions: LAE secondary to AS was documented in a significant proportion of patients undergoing TAVI and was associated with a more than threefold increased risk of CVD at 1-year.

Abbreviations: AF, atrial fibrillation; AS, aortic valve stenosis; CI, confidence intervals; HR, hazard ratio; LAE, left atrial enlargement; LV, left ventricular; LAVi, indexed left atrial volume; MACCE, major adverse cardiac and cerebrovascular event; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation.

Masahiko Asami and Stephan Dobner contributed equally to this study.
1 | INTRODUCTION

Increased left ventricular (LV) afterload due to severe aortic stenosis (AS) leads to progressive, maladaptive cardiac remodeling. Structural and functional changes of cardiac chambers, the atrioventricular valve apparatus, and the pulmonary vasculature are signs of evolving cardiac damage related to AS, and have been integrated into a validated staging system delineating an incremental risk of death.1

Left atrial enlargement (LAE) is among the first secondary structural changes related to AS, and is followed by progressive downstream cardiac damage affecting the pulmonary vasculature, the tricuspid valve, and the right ventricle.2 LAE has previously been identified as a powerful predictor of cardiovascular events, including cardiovascular death, myocardial infarction, congestive heart failure, and ischemic stroke in patients with atherosclerotic or valvular heart disease.2-7 Even in patients without cardiovascular disease, LAE is associated with an increased risk of adverse cardiovascular events.8,9

The aim of the present analysis was to determine the impact of progressive LAE on clinical outcomes in symptomatic patients with severe AS undergoing transcatheter aortic valve implantation (TAVI).

2 | METHODS

2.1 | Study design and patient population

Consecutive patients with severe AS undergoing TAVI at Bern University Hospital (Bern, Switzerland) between August 2007 and December 2016 were enrolled into a prospective registry which is part of the Swiss TAVI Registry (ClinicalTrials.gov NCT01368250), and were considered eligible for the present analysis. Patients with a history of atrial fibrillation (AF), moderate or greater mitral stenosis, severe mitral regurgitation, or status postsurgical mitral valve replacement were excluded, as these conditions may independently lead to LA remodeling and enlargement. Furthermore, patients treated with a non-Confédération Européenne (CE)-marked device were excluded, as were those without a recent transthoracic echocardiogram, recorded <3 months before TAVI. The local heart team, consisting of cardiac surgeons, interventional cardiologists, imaging and heart failure subspecialists, determined eligibility for TAVI and treatment strategy. TAVI was performed according to standard techniques, as previously described.10 The local ethics committee approved the study protocol, and all procedures were conducted in accordance with the Declaration of Helsinki. All study participants provided written, informed consent for the intervention and prospective follow-up. All data were prospectively collected and entered into a dedicated online database managed at the Clinical Trials Unit at the University of Bern, Switzerland.

2.2 | Assessment of LAE

All patients underwent transthoracic and/or transesophageal echocardiography with a Philips iE33 machine (Philips Healthcare) <3 months before TAVI. At least three consecutive heartbeats were recorded and data averaged for the analysis of echocardiographic variables. Echocardiographic studies were performed by a board-certified cardiologist and evaluated at a workstation for offline analysis (Syngo Dynamics Workplace, version 9.5, Siemens Medical Solutions, Inc.) by an independent second reader, trained for echocardiographic analysis in the Core Lab. According to current guidelines for cardiac chamber quantification by the American Society of Echocardiography and European Association of Cardiovascular Imaging, indexed left atrial volume (LAVi) was used as a variable to evaluate LAE and calculated using the following formula: LAVi = LA volume/body surface area (ml/m²).11 LA volume was calculated using the area-length approximation, as previously described.11 LA volume was measured based on tracings of the blood–tissue interface on apical four- and two-chamber views and at the mitral valve level. The contour was closed by connecting the two opposite sections of the mitral annulus with a straight line. Left atrial appendage and pulmonary veins were excluded from the endocardial tracing. According to the latest European and American guidelines, upper normal LAVi was predefined as 34 ml/m².11 Patients with LAE were further divided into two groups: (1) nonsevere enlargement (34 ml/m² ≤ LAVi <60 ml/m²) and (2) severe enlargement (LAVi ≥ 60 ml/m²).4

2.3 | Clinical follow-up and endpoint assessment

After hospital discharge, clinical follow-up was performed 30 days and 1 year after TAVI by standardized interviews, documentation from referring physicians, and hospital discharge summaries. All suspected adverse events were independently adjudicated by the local clinical events committee according to the criteria by the Valve Academic Research Consortium-2.12 The primary endpoint of the study was cardiovascular death within 1 year after TAVI. Secondary endpoints included all-cause mortality, major adverse cardiac and cerebrovascular events (MACCE), disabling stroke, and myocardial infarction. MACCE was a composite of cardiovascular death, disabling stroke, and myocardial infarction.

2.4 | Statistical analysis

Binary and categorical variables are reported as frequencies (% of all nonmissing data). Patients with LAE versus patients with normal LA
dimensions are compared with Fisher's exact tests or χ² tests. Continuous variables are reported as mean values ± standard deviations and compared using Student's t tests. Time-to-event data are analyzed using the first event of each (subtype per patient only. Cumulative incidence curves are constructed using the Kaplan–Meier method. Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for these clinical outcomes are calculated using Cox's regressions with Wald test's p values. Multivariable adjustment was performed with variables including diabetes, age, history of stroke, post-TAVI aortic regurgitation moderate or severe, gender, renal insufficiency (estimated glomerular filtration rate <60 ml/min/1.73 m²), body mass index smaller or equal 20, coronary artery disease, New York Heart Association III or IV, peripheral vascular disease, LV ejection fraction, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score, femoral main access—again using Cox's regressions. The final Cox's model retained risk factors which obtained a p value of <0.2 in the multivariable model. Otherwise, a p value of <0.05 was considered significant. Statistical analyses were performed using Stata 16.1 (StataCorp).

3 | RESULTS

3.1 | Study population

The study flow diagram is presented in Figure 1. A total of 1643 patients underwent TAVI at our institution between August 2007 and December 2016. Echocardiographic data were available from 1252 patients. After the exclusion of 484 patients due to AF, concomitant mitral valve disease or incomplete echocardiography recordings, 768 individuals remained for the present analysis. Overall, LAE was documented in 486 patients, classified as moderate in 424 and severe in 68 patients.

Baseline characteristics of the study population are shown in Table 1. Patients with LAE were older (82.3 ± 6.7 years vs. 80.9 ± 6.4 years; p = 0.003), and the prevalence of LAE was higher in males (68.3%) as compared to females (58.8%, p = 0.01). Advanced disease with increased peri-interventional risk compared with controls was confirmed by higher STS-PROM score in patients with LAE as compared to those with normal LA dimensions (6.1 ± 4.7% vs. 4.7 ± 2.9%; p < 0.001). Chronic kidney disease was more common among patients with (72%) as compared to those without LAE (61%, p = 0.002). Antithrombotic treatment was comparable between patients with and without LAE (9.5% vs. 12.1%, p = 0.272).

Echocardiographic variables before TAVI are summarized in Table 2. Patients with LAE had markers of advanced stage of disease as evidenced by higher transvalvular mean gradients (44.5 ± 18.3 mmHg vs. 41.1 ± 16.7 mmHg, p = 0.04), lower LV ejection fraction (53.2 ± 15.2% vs. 59.3 ± 11.7%, p < 0.001), and more pronounced diastolic dysfunction (E/e': 21.5 ± 10.5 vs. 16.8 ± 7.9, p < 0.001) in comparison with patients with normal LA dimensions. Along the same line, brain natriuretic peptide levels were more than twofold higher in patients with LAE compared to patients with normal LA dimensions.

![Study Flow Diagram](image-url)
## Table 1  Baseline characteristics

|                        | Overall (N = 768) | Normal LA size (N = 282) | LA enlargement (N = 486) | p value |
|------------------------|-------------------|--------------------------|--------------------------|---------|
| Age, years             | 81.8 ± 6.6        | 80.9 ± 6.4               | 82.3 ± 6.7               | 0.003   |
| Female gender, n (%)   | 408 (53.1)        | 168 (59.6)               | 240 (49.4)               | 0.01    |
| Body mass index, kg/m² | 26.3 ± 5.1        | 26.7 ± 5.3               | 26.1 ± 5.0               | 0.14    |
| **Cardiac risk factors** |                   |                          |                          |         |
| Diabetes mellitus, n (%) | 194 (25.3)       | 79 (28.0)                | 115 (23.7)               | 0.20    |
| Hypercholesterolaemia, n (%) | 508 (66.1)    | 198 (70.2)               | 310 (63.8)               | 0.08    |
| Hypertension, n (%)    | 634 (82.6)        | 232 (82.3)               | 402 (82.7)               | 0.92    |
| **Past medical history** |                   |                          |                          |         |
| Previous myocardial infarction, n (%) | 119 (15.5)     | 38 (13.5)                | 81 (16.7)                | 0.26    |
| Previous PCI, n (%)    | 218 (28.4)        | 80 (28.4)                | 138 (28.4)               | 1.00    |
| Previous CABG, n (%)   | 86 (11.7)         | 23 (8.6)                 | 63 (13.5)                | 0.056   |
| Previous stroke or TIA, n (%) | 78 (10.2)      | 27 (9.6)                 | 51 (10.5)                | 0.71    |
| Peripheral vascular disease, n (%) | 106 (13.8)     | 30 (10.6)                | 76 (15.6)                | 0.07    |
| Chronic obstructive pulmonary disease, n (%) | 102 (13.3)    | 33 (11.7)                | 69 (14.3)                | 0.32    |
| Renal failure (eGFR < 60 ml/min/1.73 m²), n (%) | 522 (68.0)   | 172 (61.0)               | 350 (72.0)               | 0.002   |
| Pulmonary hypertension,* n (%) | 313 (41.7)    | 111 (34.9)               | 202 (41.6)               | 0.15    |
| **Baseline cardiac rhythm** |                   |                          |                          |         |
| Permanent pacemaker, n (%) | 54 (7.0)        | 17 (6.0)                 | 37 (7.6)                 | 0.47    |
| **Baseline hemodynamics** |                   |                          |                          |         |
| Systolic arterial pressure, mmHg | 140.4 ± 27.7    | 143.7 ± 26.7             | 138.7 ± 28.1             | 0.09    |
| Diastolic arterial pressure, mmHg | 64.6 ± 13.8     | 66.6 ± 13.3              | 63.6 ± 14.0              | 0.04    |
| LV systolic pressure, mmHg | 192.7 ± 35.1    | 196.0 ± 33.1             | 190.9 ± 36.2             | 0.18    |
| LV end-diastolic pressure, mmHg | 23.6 ± 7.9      | 23.4 ± 7.4               | 23.7 ± 8.3               | 0.72    |
| **Symptoms**            |                   |                          |                          |         |
| NYHA classification III or IV, n (%) | 502 (65.4)     | 178 (63.1)               | 324 (66.7)               | 0.35    |
| CCS III or IV, n (%)   | 68 (8.9)          | 20 (7.1)                 | 48 (9.9)                 | 0.24    |
| Syncope, n (%)          | 87 (11.3)         | 22 (7.8)                 | 65 (13.4)                | 0.02    |
| **Risk assessment**     |                   |                          |                          |         |
| Logistic EuroScore, %   | 18.7 ± 13.1       | 15.3 ± 11.9              | 20.7 ± 13.4              | <0.001  |
| TS score, %             | 5.6 ± 4.2         | 4.7 ± 2.9                | 6.1 ± 4.7                | <0.001  |
| **Laboratory values**   |                   |                          |                          |         |
| Brain natriuretic peptide, pg/ml | 215.5 (102.0–639.5) | 152.0 (86.0–311.5) | 322.0 (117.0–790.0) | <0.001 |

Note: Values are mean ± standard deviation (p value from unpaired t test), counts with percentages (p value from Fisher’s exact test or χ² test), or median (with 25%–75% interquartile range).

Abbreviations: CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; eGFR, estimated glomerular filtration rate; LV, left ventricular; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of thoracic surgeons; TIA, transient ischemic attack.

*Pulmonary hypertension: Mean pulmonary artery pressure ≥25mmHg by right heart catheterization in the SWISS TAVI registry.
Procedural characteristics are summarized in Table 3. Patients with LAE more commonly underwent TAVI by alternative access (13.2% vs. 7.4%; \( p = 0.02 \)) and more frequently had general anesthesia (26.7% vs. 20.2%, \( p = 0.05 \)) as compared to patients with normal LA dimensions.

### Clinical outcomes

Event rates with crude and adjusted HR for clinical outcomes within 1 year after TAVI are provided in Table 4. Patients with LAE had an increased risk of all-cause mortality (74 events [15.3%] vs. 15 events [5.4%]; HR\(_{adj} \), 3.01; 95% CI, 1.72–5.25), cardiovascular death (49 events [10.4%] vs. 8 events [2.9%]; HR\(_{adj} \), 3.52; 95% CI, 1.66–7.44), and composite outcomes of cardiovascular death and disabling stroke (15 events [5.4%] vs. 59 events [12.5%]; HR\(_{adj} \), 2.29; 95% CI, 1.30–4.04; \( p = 0.004 \)) compared to patients presenting with normal LA size (Figure 2). Numerically higher rates of disabling strokes in patients with LAE did not reach conventional levels of statistical significance.

#### 3.3 Severe LAE is associated with incremental risk

A subanalysis of the 68 (8.9%) patients with severe LAE (LAVi \( \geq 60 \text{ ml/m}^2 \)) indicated an incremental risk of mortality with progressive LAE (Table S1, Figure 2). Compared to patients with normal LA dimensions, patients with severe LAE had a particularly increased risk of all-cause mortality (14 events [22.6%] vs. 15 events [5.4%]; HR\(_{adj} \), 4.62; 95% CI, 2.23–9.58), cardiovascular death (9 events [14.9%] vs. 8 events [2.9%]; HR\(_{adj} \), 5.52; 95% CI, 2.13–14.3), and
composite outcomes of cardiovascular death and disabling stroke (15 events [5.4%] vs. 10 events (16.5%); HR adj, 3.08; 95% CI, 1.37–6.90; p = 0.01) at 1 year. The incremental risk emerged during the peri-procedural period and was maintained throughout the first year after the intervention. Numerically higher rates of disabling strokes with increasing LA diameters did not translate into statistically significant differences between groups.

3.4 | Predictor for cardiovascular death

Adjusting for confounding factors in multivariable analysis, LAE (HR adj, 3.52; 95% CI, 1.66–7.44; p = 0.001), renal failure (HR adj, 3.85; 95% CI, 1.65–8.98), and diabetes mellitus (HR adj, 1.95; 95% CI, 1.12–3.38) were identified as independent predictors of cardiovascular death 1 year after TAVI (Table 5).

4 | DISCUSSION

Maladaptive cardiac remodeling in the presence of severe AS is increasingly recognized as an important predictor of peri- and postoperative morbidity and mortality. In the present analysis based on a large prospective registry, LAE was documented in a significant proportion of patients undergoing TAVI. LAE was associated with a three-fold increased risk of death at 1 year, with a signal for an incremental risk of death with progressive LA dilatation. The difference manifested during the peri-procedural period and remained stable throughout the first year after the intervention. The risk of stroke paralleled the observed hazard of death without reaching conventional levels of statistical significance. Our findings confirm LAE as a prognostic marker for adverse clinical outcome in patients with AS and fuel calls for the integration of downstream cardiac damage to determine the optimal timing of valve replacement.

The findings of our study suggest that the majority of symptomatic patients with severe AS present for intervention at an advanced stage of the disease. Accordingly, LAE was associated with greater severity of stenosis, increased LV mass and more severe diastolic dysfunction. To accurately reflect downstream cardiac damage related to AS, we excluded patients with potential alternative causes of LA remodeling and enlargement, such as a history of AF or relevant mitral valve disease, from the present analysis.

We quantified the impact of LAE secondary to AS on clinical outcomes and identified LAE as an important predictor of death...
after TAVI. A gradual increase in major adverse clinical outcomes with progressive LAE increase even after adjustment for co-morbidities underscores LAE as an important marker of an advanced stage of the disease. The assessment of LA strain may further refine risk stratification in these patients.13 Compared to LAE, impaired LA strain shows a higher correlation with AS severity and may better predict clinical deterioration.14 Differences between groups of LA dimension emerged in the peri-procedural period and continued to diverge up to 1 year of follow-up. While not assessed as part of our routine follow-up, we hypothesize that new-onset AF associated with LAE may in part be responsible for the maintained increase in adverse events over time. Atrial remodeling is the structural substrate for the development of new-onset AF after TAVI with limited reversibility, despite targeted intervention.15 New-onset AF after TAVI has been documented in up to 12% of patients after TAVI in the randomized trials16–18 and has been associated with an increased risk of death and cerebrovascular events.19 In a meta-analysis of 65 studies including 43,506 patients after TAVI, the incidence of new-onset AF increased with extended follow-up from 11% at 1 month to 25% at 2 years and was associated with a 61% increased risk of death and a 79% increased risk of cerebrovascular events.19 Previously reported partial recovery of atrial mechanics after TAVI suggests that these adverse events may be amenable by timely intervention.20,21 Interestingly, we did not find an association of LAE with an increased incidence

| TABLE 4  | Short- and long-term clinical outcomes |
|-----------------|--------------------------------------|
| **Normal LA size** | **LA enlargement** | **Crude hazard ratio** | **Adjusted Hazard ratio** |
| **N = 282** | **N = 486** | **HR (95% CI)** | **p value** | **adj. HR (95% CI)** | **adj. p value** |
| 30 days follow-up | | | | | |
| All-cause mortality, n (%) | 5 (1.8) | 24 (4.9) | 2.81 (1.07–7.36) | 0.04 | 2.51 (0.96–6.60) | 0.06 |
| CV death, n (%) | 4 (1.4) | 21 (4.3) | 3.07 (1.05–8.94) | 0.04 | 2.70 (0.92–7.88) | 0.07 |
| Myocardial infarction, n (%) | 1 (0.4) | 7 (1.4) | 4.08 (0.50–33.2) | 0.19 | NA | NA |
| Cerebrovascular events | | | | | |
| Disabling stroke, n (%) | 5 (1.8) | 15 (3.1) | 1.76 (0.64–4.83) | 0.28 | 1.71 (0.62–4.72) | 0.30 |
| CV death & disabling stroke, n (%) | 7 (2.5) | 27 (5.6) | 2.26 (0.98–5.18) | 0.055 | 2.12 (0.92–4.89) | 0.08 |
| MACCE, n (%) | 7 (2.5) | 31 (6.4) | 2.60 (1.14–5.90) | 0.02 | 2.43 (1.07–5.53) | 0.03 |
| Bleeding | | | | | |
| Life-threatening, n (%) | 12 (4.3) | 39 (8.1) | 1.91 (1.00–3.65) | 0.05 | 1.91 (1.00–3.66) | 0.051 |
| Kidney injury | | | | | |
| Stage 3, n (%) | 3 (1.1) | 12 (2.5) | 2.36 (0.67–8.36) | 0.18 | 2.27 (0.64–8.11) | 0.21 |
| Access site complications | | | | | |
| Major, n (%) | 27 (9.6) | 45 (9.3) | 0.97 (0.60–1.56) | 0.89 | 0.95 (0.59–1.54) | 0.84 |
| VARC-2 early safety endpoints, n (%) | 48 (17.1) | 94 (19.3) | 1.15 (0.81–1.62) | 0.44 | 1.14 (0.80–1.62) | 0.46 |
| 1-year follow-up | | | | | |
| All-cause mortality, n (%) | 15 (5.4) | 74 (15.3) | 3.01 (1.73–5.24) | <0.001 | 3.01 (1.72–5.25) | <0.001 |
| CV death, n (%) | 8 (2.9) | 49 (10.4) | 3.72 (1.76–7.84) | 0.001 | 3.52 (1.66–7.44) | 0.001 |
| Myocardial infarction, n (%) | 4 (1.5) | 17 (3.7) | 2.29 (0.76–6.91) | 0.14 | 2.03 (0.67–6.14) | 0.21 |
| Cerebrovascular events | | | | | |
| Disabling stroke, n (%) | 9 (3.3) | 19 (4.0) | 1.26 (0.57–2.79) | 0.56 | 1.20 (0.54–2.67) | 0.65 |
| CV death and disabling stroke, n (%) | 15 (5.4) | 59 (12.5) | 2.39 (1.35–4.20) | 0.003 | 2.29 (1.30–4.04) | 0.004 |
| MACCE, n (%) | 18 (6.5) | 70 (14.8) | 2.31 (1.37–3.88) | 0.002 | 2.20 (1.30–3.70) | 0.003 |

Note: Values are given n (%). Hazard ratios (HR) (95% confidence intervals [CI]) from Cox regressions for time-to-event data. Adjusted hazard ratios (adj. HR) (95% CIs) from Cox regressions for time-to-event data if more than 10 events, adjustment for diabetes, and renal failure (<60 eGFR)

Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; NA, not analyzed; MACCE, major adverse cardiovascular and cerebrovascular events (composite of cardiovascular death, major stroke, and myocardial infarction); VARC, valvular academic research consortium.
of stroke. This may be owing to the fact that LAE represents an intermediate risk factor that mediates an increased risk of AF, and that patients with AF were excluded from the present analysis.

Our findings support the integration of downstream structural changes to refine the optimal timing of aortic valve replacement. LAE is one of the first objective manifestations of cardiac damage secondary to AS and can be readily quantified by the use of transthoracic echocardiography. More than one-third of patients in our cohort had comorbidities potentially leading to LAE irrespective of AS. Therefore, LAE needs to be interpreted in the entire context of patient comorbidities. While of limited significance in isolation, the presence of LAE warrants close clinical monitoring after TAVI, in particular for the incidence of AF.

### 4.1 Study limitations

The findings of the present analysis need to be interpreted in light of several limitations. First, two-dimensional echocardiography was performed to assess LA dimensions. Inter- and intraobserver variability are common using this technique. Three-dimensional echocardiography or computed tomography may allow a more accurate determination of LA size. Second, the data were collected at a single center with limited duration of follow-up. Therefore, larger studies with longer follow-up are warranted to corroborate our results. Conversely, our registry adheres to high standards of data quality with rigorous data collection, regular follow-up, and independent event adjudication. And finally, although we provide adjusted analyses of clinical endpoints, we cannot rule out residual confounding of effect estimates by variables not recorded in our database.
CONCLUSIONS

LAE secondary to AS is documented in a significant proportion of patients undergoing TAVI and associated with a more than three-fold increased risk of cardiovascular death at 1 year.

ACKNOWLEDGMENT

Open access funding provided by Universitat Bern.

CONFLICT OF INTERESTS

Dr. Windecker reports research and educational grants to the institution from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson&Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, Sinomed. He serves as unpaid advisory board member and/or unpaid member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, Astra Zeneca, BMS, Boston Scientific, Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Sanomed, V-Wave, and Xeltis, but has not received personal payments by pharmaceutical companies or device manufacturers. He is also a member of the steering/executive committee group of several investigated-initiated trials that receive funding by industry without impact on his personal remuneration. He is an unpaid member of the Pfizer Research Award selection committee in Switzerland. Dr. Stortecky reports having received research grants to the institution by Edwards Lifesciences, Medtronic, Abbott, and Boston Scientific, and speaker fees from Boston Scientific, Teleflex, and BTG. Dr. Praz has received speaker fees from Boston Scientific, Teleflex, and BTG. Dr. Praz has received research grants to the institution by Edwards Lifesciences, Medtronic, Abbott, and Boston Scientific, and speaker fees from Boston Scientific, Teleflex, and BTG. He is also a proctor for Boston Scientific and Medtronic. The remaining authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Asami M, Dobner S, Stortecky S, et al. Cardiovascular outcomes in patients with left atrial enlargement undergoing transcatheter aortic valve implantation. Catheter Cardiovasc Interv. 2022;99:1908-1917. doi:10.1002/ccd.30132