Title: Hemodynamic structural valve deterioration following transcatheter aortic valve implantation with latest-generation balloon-expandable valves.

Authors: Tobias Rheude, M.D; Costanza Pellegrini, M.D; Salvatore Cassese, M.D, PhD; Jens Wiebe, M.D; Sophia Wagner, M.D; Teresa Trenkwalder, M.D; Hector Alvarez, M.D; N. Patrick Mayr, M.D; Christian Hengstenberg, M.D; Heribert Schunkert, M.D; Adnan Kastrati, M.D; Oliver Husser, M.D, PhD; Michael Joner, M.D

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Hemodynamic structural valve deterioration following transcatheter aortic valve implantation with latest-generation balloon-expandable valves

Running title: Hemodynamic SVD after TAVI

Tobias Rheude¹, MD, Costanza Pellegrini¹, MD, Salvatore Cassese¹, MD, PhD, Jens Wiebe¹, MD, Sophia Wagner¹, MD, Teresa Trenkwalder¹, MD, Hector Alvarez¹,², MD, N. Patrick Mayr⁴, MD, Christian Hengstenberg⁵, MD, Heribert Schenkert¹,⁶, MD, Adnan Kastrati¹,⁶, MD, Oliver Husser¹,³, MD, PhD, Michael Joner¹,⁶, MD

¹Klinik für Herz- und Kreislaufferkrankungen, Deutsches Herzzentrum München, Technische Universität München, Munich, Germany
²Klinische Abteilung für Kardiologie, Universitätsklinik für Innere Medizin II, Medizinische Universität Wien, Vienna, Austria
³Klinik für Innere Medizin I, St.-Johannes-Hospital, Dortmund, Germany
⁴Institut für Anästhesiologie, Deutsches Herzzentrum München, Technische Universität München, Munich, Germany
⁵Hospital de Cardiología, Centro Médico Nacional Siglo XXI (Instituto Mexicano del Seguro Social, IMSS), Ciudad de México, México
⁶DZHK (German Center for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany

Corresponding author:
Michael Joner, MD
Klinik für Herz- und Kreislaufferkrankungen,
Deutsches Herzzentrum München,
Technische Universität München, Munich, Germany
Telephone number: +49-1218-4587
E-mail address: joner@dhm.mhn.de

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Abstract

Aims:
Elevated gradients have been proposed to be associated with hemodynamic structural valve deterioration (SVD) after transcatheter aortic valve implantation (TAVI) and data regarding their characterization remain scarce.

Methods and results:

691 patients undergoing transfemoral TAVI were enrolled. The primary endpoint was moderate or severe hemodynamic SVD during 12-month follow-up after TAVI, defined as (I) mean transvalvular gradient ≥20 mmHg or (II) mean transvalvular gradient change ≥10 mmHg. The primary endpoint was observed in 10.3% after TAVI. Use of 20mm valve, valve-in-valve procedure and oral anticoagulation (OAC) were independently associated with hemodynamic SVD, whereas valve-in-valve procedure and OAC were the only significant variables after accounting for death as a competing event. OAC was significantly associated with both, hemodynamic SVD (RR 8.65; p=0.004) and death (RR 3.57; p=0.06), whereas valve-in-valve procedure was only associated with hemodynamic SVD (RR 52.76; p<0.001). Valve thrombosis was present in 0.87% (6/691) of all patients.

Conclusions:
The prevalence of moderate or greater hemodynamic SVD during the first 12 months after TAVI is 10.3%. Procedural factors and pharmacotherapy seem to play a key role during manifestation. Future studies should focus on the underlying mechanisms.
Classifications
Aortic stenosis, TAVI, Non-invasive imaging

Condensed abstract
Long-term valve function has become a major issue after TAVI with rising numbers of procedures. Elevated gradients have been proposed to be associated with hemodynamic SVD. This study sought to investigate the prevalence and predictors of moderate or greater hemodynamic SVD after TAVI and further assess the incidence of valve thrombosis. The prevalence of hemodynamic SVD during the first 12 months after TAVI is 10.3% and valve thrombosis was present in 0.87% of all patients. Procedural factors and pharmacotherapy seem to play a key role during manifestation of hemodynamic SVD.

Abbreviations
CIF: Cumulative Incidence Function
CRR: Competing Risk Regression
LVEF: Left Ventricular Ejection Fraction
NYHA: New York Heart Association
OAC: Oral Anticoagulation
SVD: Structural valve deterioration
TAVI: Transcatheter Aortic Valve Implantation
THV: Transcatheter Heart Valves
VARC: Valve Academic Research Consortium
Introduction

Transcatheter aortic valve implantation (TAVI) has been increasingly performed over the last decade and is currently recommended for patients with severe aortic stenosis who are considered at high- or intermediate risk for conventional aortic valve replacement[1]. Results from contemporary randomized trials in low-risk TAVI patients will likely broaden the indication of use with this disruptive technology[2,3].

Although the efficacy and safety of TAVI has been demonstrated in large, randomized trials[4,5], data regarding long-term valve function are limited[6–8]. Standardized definitions of bioprosthetic structural valve deterioration (SVD) after TAVI have been published recently to enable objective evaluation of transcatheter heart valves (THV) and elevated gradients have been proposed to be associated with hemodynamic SVD[9].

The objective of this study was to investigate the prevalence and predictors of moderate or greater hemodynamic SVD during follow-up in the first 12 months after TAVI with balloon-expandable valves in a large contemporary patient cohort and further assess the prevalence of valve thrombosis.

Methods

Study population and procedures

Between January 2014 and April 2018, 872 consecutive patients with severe aortic stenosis or degenerated bioprosthetic aortic valves underwent transfemoral TAVI with balloon-expandable valves, SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA), at the Department of Cardiovascular Diseases, German Heart Centre Munich, Germany. Patients with device failure according to the updated Valve Academic Research Consortium (VARC)-2 criteria were excluded from final analyses (n=78)[10]. Patients with missing echocardiographic data during follow-up were further excluded from final analyses (n=103). Finally, a total of 691 patients
satisfied these criteria and were included in the final analysis. All patients were discussed by a multidisciplinary heart team and found eligible for transfemoral TAVI. All patients provided written informed consent. Postprocedural pharmacotherapy consists of dual antiplatelet treatment with aspirin and clopidogrel for at least three months in patients without indication for oral anticoagulation (OAC) or prior coronary intervention; when patients had an indication for OAC, single-therapy OAC was prescribed unless the patient also had indication for anti-platelet treatment. Triple therapy was only prescribed in case of recent coronary intervention entailing reduced dose OAC.

**Definition of endpoints and follow-up**

The primary endpoint of this study was moderate or greater hemodynamic SVD during follow-up in the first 12 months after TAVI, defined as (I) mean transvalvular gradient $\geq$ 20 mmHg or (II) mean transvalvular gradient change $\geq$ 10 mmHg compared with previous measurements after TAVI. Moreover, crude rates of both, moderate and severe hemodynamic SVD as well as bioprosthetic valve failure (BVF) were reported individually. Additionally, elevated transvalvular gradients were further investigated by transesophageal echocardiography and/or multislice computed tomography (CT) at the discretion of the treating physician to rule out valve thrombosis.

Data collection involved demographic information, procedural data, as well as clinical and echocardiographic assessment. Adverse events were recorded throughout the follow-up period. All clinical endpoints, procedural data and in-hospital complications were categorized according to the updated VARC-2 criteria. Transthoracic echocardiography was performed at baseline, at discharge, at least once during 12-month follow-up after TAVI and yearly thereafter (up to four years).

**Statistical analysis**
Categorical variables are expressed as frequencies and proportions and were compared using the chi-square or Fisher’s exact test, as appropriate. Continuous variables are presented as mean with standard deviation (SD) or median with interquartile range (IQR) and compared using Student t-test or Mann-Whitney U-test, respectively.

For dichotomous analysis, patients were divided into strata with and without hemodynamic SVD. Cox proportional hazard analysis was performed to determine factors associated with the primary endpoint. Possible covariables were selected by clinical relevance and were as follows: female gender, New York Heart Association (NYHA) class III/IV, previous myocardial infarction, previous stroke, previous malignancy, previous pacemaker implantation, peripheral artery disease, anemia, left ventricular ejection fraction <35%, mitral regurgitation grade III/IV, valve-in-valve procedure, use of 20mm valve, predilatation, postdilatation and OAC at discharge. Corresponding hazard ratios (HR) were computed.

Additionally, multivariable competing risk regression (CRR) was performed using the R package “cmprsk”. Similar to conventional multivariable regression analysis, this method is aimed to find predictors of the primary endpoint while adjusting for statistically relevant cofactors and accounting for death as competing event. Due to the limited number of events (hemodynamic SVD and/or death), risk regression models were constraint to the following predictor variables to avoid model overfitting: age, use of 20mm valve, previous malignancy, valve-in-valve procedure and OAC. Additionally, cumulative incidence function (CIF) estimates from competing risk data were calculated for valve-in-valve procedures and OAC.

A 2-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using JMP (Version 13, SAS Institute Inc., Cary, NC), R (Version 3.3.2, R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics (Version 24.0 for Macintosh, IBM Corp., Armonk, NY).
Results

Baseline characteristics of the entire population are shown in Table 1. A total of 691 patients were included in this analysis (mean age: 80.0 ± 6.2 years, 42% female). The population was a contemporary and unselected cohort of patients with a median logistic European System for Cardiac Operative Risk Evaluation (Euro)-SCORE I of 13.0% [7.9-21.4]. Procedural data and in-hospital outcome are provided in Table 2.

Hemodynamic SVD after TAVI

The prevalence of moderate or greater hemodynamic SVD during the first 12 months after TAVI was 10.3% (71/691). There was incremental prevalence observed over time during the first 12 months after TAVI: 1.9% (13/691) at 30-day and 10.3% (71/691) at 12-month follow-up. Moderate hemodynamic SVD was observed in 9.4% (65/691), whereas severe hemodynamic SVD was observed in only 0.9% (6/691). Moreover, BVF was observed in 1.88% (13/691).

Baseline characteristics according to the primary endpoint are shown in Table 1. Patients with hemodynamic SVD (n=71) had a lower rate of atrial fibrillation (p=0.003) and previous strokes (p=0.03), and were less likely treated with oral anticoagulants (p=0.007). Regarding procedural data, valve-in-valve procedures (p<0.001) were more frequently performed, whereas predilatation (p=0.023) was less frequently performed in patients with elevated gradients (Table 2).

Cox proportional hazard analysis revealed the following independent predictors of hemodynamic SVD during follow-up after TAVI: use of 20mm valve (Hazard Ratio (HR) 9.43; p<0.001), valve-in-valve procedure (HR 9.92; p<0.001) and oral anticoagulation (HR 0.46; p=0.003). Based on these observations, crude rates of hemodynamic SVD were further analyzed in patients with and without OAC (Figure 1).
The crude mortality rate 12 months after TAVI was 4.3% (30/691). After competing risk regression accounting for death as competing event, valve-in-valve procedure (relative risk (RR) 13.01; p<0.001) and oral anticoagulation (RR 0.39; p<0.001) were the only significant predictors of hemodynamic SVD. According to CIF estimates, OAC was significantly associated with both, hemodynamic SVD (RR 8.65; p=0.004) and death (RR 3.57; p=0.06), whereas valve-in-valve procedure was only significantly associated with hemodynamic SVD (RR 52.76; p<0.001), but not with death (RR 0.89; p=0.35) (Figure 2).

Long-term echocardiographic follow-up was available in a subgroup of patients, namely 107 patients at 2-year follow-up and 48 and 31 patients at 3 and 4 year follow-up, respectively. Hemodynamic SVD was observed in 9.3% (10/107) at 2 years, 10.4% (5/48) at 3 years and 6.5% (2/31) at 4 year follow-up.

**Bioprosthetic valve thrombosis**

Bioprosthetic valve thrombosis was present in 0.87% (6/691) of the entire cohort and 8.5% (6/71) of patients with hemodynamic SVD during follow-up after TAVI (Figure 3 and Supplemental Video 1/2). Clinical characteristics of patients with valve thrombosis are shown in detail in Supplementary Table 1. At detection time, median transvalvular gradient was 28 mmHg [IQR 25-47]. All patients were on single or dual antiplatelet therapy. OAC with either Phenprocoumon (International Normalized Ratio (INR) target range 2.0-3.0) or Apixaban (5 mg twice daily) was initiated in all cases after valve thrombosis was diagnosed and valve thrombosis was successfully resolved in all cases (Figure 4).
Discussion

The present study investigates the prevalence of moderate or greater hemodynamic SVD during follow-up after TAVI and further assesses the prevalence of valve thrombosis. To our knowledge, this is the first study using competing risk regression to account for the probability of death as a competing event. The results can be summarized as follows: The prevalence of hemodynamic SVD was 10.3% during 12-month follow-up after TAVI. Cox proportional hazard analysis revealed that hemodynamic SVD after TAVI was more frequent using a 20mm valve or in case of valve-in-valve procedures and less frequent in case of OAC. After accounting for death as a competing event, valve-in-valve procedure and OAC remained independently associated with hemodynamic SVD, whereas only OAC was also predictive for death. Valve thrombosis was present in 0.87% of the entire cohort during follow-up after TAVI.

Bioprosthetic structural valve deterioration

Bioprostheses are prone to structural valve deterioration. Experiences from surgically implanted bioprostheses indicate onset of SVD six to eight years after implantation [11]. Heterogeneous definitions have been a major limitation in the past[12]. In most of these studies, diagnosis of SVD often involved the need for re-operation or clinically apparent symptoms, hence the prevalence of SVD likely has been underestimated.

Despite the widespread use of TAVI since its inception in 2007, long-term data beyond five years are still limited[6–8]. As we proceed into the time span, in which SVD was observed with surgical bioprostheses, standardized definitions have been proposed recently[9]. Hemodynamic SVD, which can be assessed by means of echocardiography, require special attention. According to updated VARC-2 and European Association of Percutaneous Cardiovascular Intervention (EAPCI) criteria, we further investigated moderate or greater hemodynamic SVD during the first 12 months after TAVI[9,10].

Prevalence and predictors of hemodynamic SVD
In this study, hemodynamic SVD were present in 10.3% of all patients treated with balloon-expandable valves. To date, available studies regarding hemodynamic SVD after TAVI are scarce with conflicting results. Early randomized TAVI studies and large registries report unchanged valve function up to five years after TAVI, although these data are generally limited by high mortality rates in this cohort of inoperable/high-risk patients[6,7,13]. In contrast, other authors have reported low rates of hemodynamic SVD in up to 5% as well as a mild, but significant increase of gradients over time after TAVI[14,15].

The clinical relevance of hemodynamic SVD after TAVI is unknown. So far, an association with an increased risk for adverse cardiovascular events has not been reported[16]. Nevertheless, given the current trend to treat younger, lower-risk patients, identifying predictors associated with an increased risk for hemodynamic SVD is of utmost relevance and further research is needed to assess the clinical impact of hemodynamic SVD. Apparently, short-term follow-up after TAVI seems to be crucial, as patients with ascertained hemodynamic SVD failed to display further valve deterioration beyond one year[14].

In the present Cox proportional hazard analysis, hemodynamic SVD was less frequently observed in case of treatment with oral anticoagulants after TAVI and more frequent using a 20mm valve or in case of valve-in-valve TAVI procedures. The observed association of OAC and hemodynamic valve function is in line with previous studies that have already reported on significant increments in transvalvular gradients and a greater risk of hemodynamic SVD in case of absence of anticoagulation therapy after TAVI[14,15]. This particular finding is of tremendous interest given the current uncertainty and low evidence level with regard to the optimal pharmacotherapy after TAVI.

Just recently, the authors of the France TAVI registry have shown for the first time that OAC at discharge is a significant and independent predictor of increased long-term mortality after TAVI[17]. As a higher operative risk might partly account for this observation, competing
risk regression with death as a competing event seems appropriate in these patients. Our analysis revealed that OAC is significantly associated with both, hemodynamic SVD after TAVI and death.

The observational character of our and other available studies and the given collinearity of several variables further support the urgent need for data from ongoing randomized trials evaluating at the optimal pharmacotherapy after TAVI. For the time being, pharmacotherapy after TAVI should be applied according to current guidelines [1].

**Mechanisms of structural valve deterioration**

Currently, mechanisms leading to (hemodynamic) SVD are incompletely understood and various reasons might account for elevated transvalvular gradients after an initially successful procedure. In the present analysis, patients with device failure according to VARC-2 criteria were excluded from further analyses to focus on actual valve deterioration during follow-up.

Recently, bioprosthesis thrombosis after TAVI has become a major concern [18]. The incidence of valve thrombosis after TAVI ranges from 0.6-2.8% in the literature [19–21], whereas subclinical leaflet thrombosis has been observed in 6-40% [18,22]. In our current analysis, valve thrombosis was present in 0.87% of the entire cohort and 8.5% of patients with hemodynamic SVD. Interestingly, it was observed in both, patients with moderate (≥20 mmHg and <40 mmHg) and severe (≥40 mmHg) hemodynamic SVD.

So far, the clinical relevance of bioprostheses thrombosis is not fully understood [18]. Mostly, data regarding subclinical leaflet thrombosis derive from routine CT scans after TAVI and mid-term follow-up excluded an impact on mortality or stroke rates in these patients [22]. Yet, thorough validation of elevated transvalvular gradients to predict (subclinical) leaflet thrombosis remains an important unmet need.

In contrast to the uncertainty regarding to the optimal pharmacotherapy after TAVI until ongoing randomized trials will bridge the gap of low-level evidence, OAC seems effective.
in treating actual bioprosthesis thrombosis after TAVI[15,20,21]. In our cohort, all cases of valve thrombosis were on antiplatelet therapy at detection and thrombosis had resolved after initiation of OAC with either Phenprocoumon or Apixaban with a reduction of mean transvalvular gradients <20 mmHg. The duration of required OAC has yet to be established.

Trials comparing different valve designs, will also provide further information on a potential role of valve designs on transvalvular gradients. Presumably, there will be a predominance of elevated gradients in balloon-expandable valves, which is most likely due to their deployment in an intra-annular position introducing bias towards higher transvalvular gradients, when compared to self-expanding valves placed in supra-annular position.

Future research should focus on the underlying mechanisms to enable differentiation of isolated elevated gradients, subclinical leaflet thrombosis and symptomatic valve thrombosis and their clinical impact.

Limitations

This is a single-center observational study. Only patients with device success and available echocardiographic examinations during follow-up were included. Consequently, major findings of the current analysis cannot be extrapolated to patients surviving in the absence of echocardiographic follow-up.

Conclusions

10.3% of the entire cohort had moderate or greater hemodynamic SVD during the first 12 months after TAVI and valve thrombosis was observed in 0.87% of all patients. Pharmacotherapy and procedural factors seem to play a key role during manifestation. Future histopathological and imaging studies should focus on dissecting mechanisms of early hemodynamic SVD, subclinical leaflet thrombosis and manifest transcatheter heart valve
thrombosis, while prospective randomized trials are required to investigate optimal pharmacotherapy after TAVI.

**Impact on daily practice**

So far, data regarding the prevalence and predictors of hemodynamic SVD remain scarce. This study provides evidence that 10.3% of all patients treated with latest-generation balloon-expandable valves developed moderate or greater hemodynamic SVD during the first 12 months after TAVI. Valve thrombosis was present in 0.87% of the entire cohort. Procedural factors and pharmacotherapy seem to play a key role during manifestation. After accounting for death as a competing event, oral anticoagulation and valve-in-valve procedures were significantly associated with hemodynamic SVD.

**Funding**

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**Conflict of interest:**

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.
References


Figure Legends

**Figure 1.** Crude rates of hemodynamic structural valve deterioration during follow-up after TAVI in patients with and without oral anticoagulation.

**Figure 2.** Cumulative incidence function estimates from competing risk data for oral anticoagulation and valve-in-valve procedures.

**Figure 3:** Computed tomography images showing a case of heart valve thrombosis after valve-in-valve TAVI.

**Figure 4:** Mean transvalvular gradients of patients with valve thrombosis at baseline, after TAVI and during follow-up after TAVI.
Table 1 – Baseline characteristics

<table>
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<tr>
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<th>All patients (n=691)</th>
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<th>Yes (n=71)</th>
<th>p-value</th>
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<td>Age (years)</td>
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<td>80.0±6.1</td>
<td>79.9±6.4</td>
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<td>Female gender</td>
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<td>258 (41.6%)</td>
<td>33 (46.5%)</td>
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<td>BMI (kg/m²)</td>
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<td>27.0±4.7</td>
<td>26.9±4.5</td>
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<td>NYHA class III/IV</td>
<td>451 (65.3%)</td>
<td>409 (66.0%)</td>
<td>42 (59.2%)</td>
<td>0.253</td>
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<td>Arterial hypertension</td>
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<td>561 (90.5%)</td>
<td>62 (87.3%)</td>
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<td>471 (76.0%)</td>
<td>48 (67.6%)</td>
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<td>Diabetes mellitus</td>
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<td>Coronary artery disease</td>
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<td>452 (72.9%)</td>
<td>49 (69.0%)</td>
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<td>Previous myocardial infarction</td>
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<td>Previous PCI</td>
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<td>266 (42.9%)</td>
<td>26 (36.6%)</td>
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<td>Previous CABG</td>
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<td>52 (8.4%)</td>
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<td>Previous stroke</td>
<td>73 (10.6%)</td>
<td>71 (11.5%)</td>
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<td>Previous malignancy</td>
<td>137 (19.8%)</td>
<td>124 (20.0%)</td>
<td>13 (18.3%)</td>
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<td>Previous pacemaker</td>
<td>82 (11.9%)</td>
<td>78 (12.6%)</td>
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<td>Peripheral artery disease</td>
<td>96 (13.9%)</td>
<td>88 (14.2%)</td>
<td>8 (11.3%)</td>
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<tr>
<td>COPD</td>
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<td>87 (14.0%)</td>
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<td>Atrial fibrillation</td>
<td>291 (42.1%)</td>
<td>273 (44.0%)</td>
<td>18 (25.4%)</td>
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<td>Anemia</td>
<td>304 (44.0%)</td>
<td>278 (44.8%)</td>
<td>26 (36.6%)</td>
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<td>LVEF ≤ 35%</td>
<td>80 (11.6%)</td>
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<td>7 (9.9%)</td>
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<td>Mitral regurgitation grade III/IV</td>
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<td>27 (4.4%)</td>
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<td>PAP &gt;60 mmHg</td>
<td>76 (11.3%)</td>
<td>69 (11.4%)</td>
<td>7 (10.3%)</td>
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<td>Mean gradient (mmHg)</td>
<td>43 [34-51]</td>
<td>42 [34-50]</td>
<td>46 [37-53]</td>
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<td>Aortic valve area (cm²)</td>
<td>0.72 [0.59-0.88]</td>
<td>0.72 [0.59-0.88]</td>
<td>0.73 [0.59-0.84]</td>
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<td>Creatinine clearance (ml/min)</td>
<td>56±21</td>
<td>56±21</td>
<td>54±18</td>
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<td>Medication at discharge</td>
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<td>Dual antiplatelet therapy</td>
<td>379 (54.8%)</td>
<td>330 (53.2%)</td>
<td>49 (69.0%)</td>
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<td>Oral anticoagulation</td>
<td>308 (44.6%)</td>
<td>287 (46.3%)</td>
<td>21 (29.6%)</td>
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Abbreviations:

BMI: Body Mass Index, CABG: Coronary Artery Bypass Grafting, COPD: Chronic Obstructive Pulmonary Disease, EuroSCORE: European System for Cardiac Operative Risk Evaluation-SCORE, LVEF: Left ventricular ejection fraction, NYHA: New York Heart Association, PAP: Pulmonary artery pressure, PCI: Percutaneous Coronary Intervention

Definitions:

Dual antiplatelet therapy: Aspirin plus second antithrombotic agent
Table 2 – Procedural data and in-hospital outcome

<table>
<thead>
<tr>
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<tr>
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<tr>
<td>Valve-in-valve procedure</td>
<td>16 (2.3%)</td>
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<td>Predilatation</td>
<td>640 (92.6%)</td>
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<td>Postdilatation</td>
<td>201 (29.1%)</td>
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<tr>
<td>Procedural time (min)</td>
<td>49.0 [41.0-60.0]</td>
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<td>Fluoroscopy time (min)</td>
<td>11.1 [8.3-14.5]</td>
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<tr>
<td>Contrast (ml)</td>
<td>100 [85-130]</td>
</tr>
<tr>
<td>Major vascular complication</td>
<td>46 (6.7%)</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>18 (2.6%)</td>
</tr>
<tr>
<td>Major stroke</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>Renal failure (incl. dialysis)</td>
<td>8 (1.2%)</td>
</tr>
<tr>
<td>New pacemaker implantation</td>
<td>51 (7.4%)</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>5.0 [4.0-6.0]</td>
</tr>
<tr>
<td>Days on intensive care unit</td>
<td>1.0 [1.0-1.0]</td>
</tr>
</tbody>
</table>
Figure 1. Crude rates of hemodynamic SVD during follow-up after TAVI in patients with and without oral anticoagulation.
Figure 2. Cumulative incidence function estimates from competing risk data for oral anticoagulation and valve-in-valve procedures.
Figure 3: Computed tomography images showing a case of heart valve thrombosis after valve-in-valve TAVI
Figure 4: Mean transvalvular gradients of patients with valve thrombosis at baseline, after TAVI and during follow-up after TAVI.
Supplementary Table 1 – Characteristics of patients with diagnosed valve thrombosis during follow-up after TAVI (n=6)

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Gender</th>
<th>Valve size</th>
<th>Time to valve thrombosis (days)</th>
<th>NYHA</th>
<th>Pharmacotherapy</th>
<th>Therapy of valve thrombosis*</th>
<th>Mean gradient at detection</th>
<th>Mean gradient after initiation of OAC</th>
<th>Resolution of valve thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At discharge after TAVI</td>
<td>At detection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>73</td>
<td>male</td>
<td>29mm</td>
<td>370</td>
<td>NYHA I-II</td>
<td>ASS+Clopidogrel</td>
<td>ASS</td>
<td>Phenprocoumon</td>
<td>45mmHg</td>
<td>10mmHg</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>female</td>
<td>23mm</td>
<td>54</td>
<td>NYHA II-III</td>
<td>ASS+Clopidogrel</td>
<td>ASS+Clopidogrel</td>
<td>Phenprocoumon</td>
<td>29mmHg</td>
<td>12mmHg</td>
</tr>
<tr>
<td>3</td>
<td>81</td>
<td>male</td>
<td>23mm</td>
<td>74</td>
<td>NYHA II</td>
<td>ASS+Clopidogrel</td>
<td>ASS+Clopidogrel</td>
<td>Apixaban</td>
<td>27mmHg</td>
<td>14mmHg</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>female</td>
<td>23mm</td>
<td>48</td>
<td>asymptomatic</td>
<td>ASS+Clopidogrel</td>
<td>ASS+Clopidogrel</td>
<td>Phenprocoumon</td>
<td>52mmHg</td>
<td>15mmHg</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>male</td>
<td>29mm</td>
<td>320</td>
<td>asymptomatic</td>
<td>ASS+Clopidogrel</td>
<td>ASS</td>
<td>Apixaban</td>
<td>24mmHg</td>
<td>11mmHg</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>male</td>
<td>26mm</td>
<td>40</td>
<td>NYHA I-II</td>
<td>ASS+Clopidogrel</td>
<td>ASS+Clopidogrel</td>
<td>Phenprocoumon</td>
<td>25mmHg</td>
<td>15mmHg</td>
</tr>
</tbody>
</table>

**Abbreviations:** ASS: Aspirin, NYHA: New York Heart Association, OAC: Oral anticoagulation,
*either Apixaban 5 mg twice daily or Phenprocoumon (INR target range 2.0-3.0)