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ORIGINAL PAPER

Transcatheter valve-in-valve implantation (VinV-TAVR) for failed surgical aortic bioprosthetic valves

Bernhard Wernly[1] · Ann-Katrin Zappe[2] · Axel Unbehaun[3] · Jan-Malte Sinning[4] · Christian Jung[5] · Won-Keun Kim[6] · Stephan Fichtlscherer[7] · Michael Lichtenauer[1] · Uta C. Hoppe[1] · Brunilda Alushi[2] · Frederik Beckhoff[2] · Charlotte Wewetzer[2] · Marcus Franz[8] · Daniel Kretzschmar[8] · Eliano Navarese[9,10,11] · Ulf Landmesser[2] · Volkmar Falk[3,12,13] · Alexander Lauten[2,12]

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Abstract

Objective We sought to investigate the procedural and hemodynamic outcome after valve-in-valve transcatheter aortic valve replacement (VinV-TAVR) for different surgical (SBV) and transcatheter (TAVR) bioprosthetic valves.

Methods and results 223 patients (76 ± 11 years, STS-Score 8.3 ± 10.1) suffering from SBV failure treated with VinV-TAVR were enrolled at 6 centers across Germany. At time of the intervention, the majority of patients were in NYHA-class ≥ III (88%, $n = 180$). Failure mode of the SBVs was either stenosis, regurgitation (AR) or a combination of both in 85 (38%), 76 (34%) and 62 (28%) patients, respectively. 138 (62%) patients were treated with first generation TAVR valves (Edwards Sapien XT or CoreValve). Second generation valves were implanted in 85 (38%) patients (Sapien 3, Medtronic CoreValve Evolut, SJM-Portico, JenaValve). VinV-TAVR was associated with high procedural success rate, conversion to surgery was necessary in 3 (2%) patients. After VinV-TAVR procedure, 4 (2%) patients suffered from ≥ moderate AR. In 6 (3%) patients a second valve was implanted due to mispositioning of the first valve and subsequent severe paravalvular AR. Coronary obstruction was observed in 4 (2%) patients. Major bleeding and cerebrovascular complications (according to VARC) were reported in 3 (1%) and 4 (2%) patients at 30 days. Post-interventionally, 44/178 (25%) patients evidenced a mean pressure gradient (mPG) ≥ 20 mmHg. Residual stenosis was not associated with increased mortality (HR 0.39; 95% CI 0.13–1.22; $p = 0.11$).

Conclusion In VinV-TAVR for SBV-failure is a safe procedure resulting in hemodynamic improvement in the majority of patients. Residual stenosis is a common finding which can be observed in 1/4 of patients undergoing VinV-TAVR. However, this condition is not associated with increased 1-year-mortality.

Keywords TAVI · Valve-in-valve · Transcatheter aortiv valve implantation · TAVR · Residual stenosis

Introduction

The majority of surgical heart valves implanted today are bioprosthetic valves (SBV). With the advantage of avoiding anticoagulation and the preferred use in elderly patients a further increase in the use of SBV is projected in the future [1]. However, SBV have a limited durability of 10–20 years and valve deterioration is frequently observed [2–4]. Therefore, it is estimated that the number of patients requiring re-treatment for SBV failure is likely to rise within the next years [5–8]. As patients are frequently older and of higher surgical risk transcatheter valve-in-valve implantation (VinV) is considered as the treatment of choice [9, 10].

Transcatheter aortic valve-in-valve replacement is now an established, well-investigated treatment for native stenotic aortic valves and VinV transcatheter aortic valve-in-valve replacement (VinV-TAVR) has been demonstrated a safe and feasible procedure [11–33]. However, the hemodynamic outcome may not always be optimal as reported recently by Bleiziffer et al. and residual stenosis (defined as mean post-procedural gradient ≥ 20 mmHg) is a common finding after VinV-TAVR [34]. As hemodynamic outcome depends on characteristics and failure mode of the SBV and the selection of TAVR devices the postoperative mean gradient can be

Bernhard Wernly and Ann-Katrin Zappe contributed equally.

✉ Alexander Lauten
alexander.lauten@charite.de

Extended author information available on the last page of the article

difficult to predict [2, 5, 6, 35, 36]. Therefore, we sought to evaluate the procedural and hemodynamic outcome obtained after VinV-TAVR for different SBV- and TAVR devices to assist in procedural planning and patient monitoring during long-term follow-up.

Methods

Study design

The protocol for this study was approved by the local Ethics Committee of the contributing institutions. A total of 223 patients undergoing VinV-TAVR for SBV failure from 2010 to 2015 were enrolled at six cardiovascular centers across Germany. TAVR was performed via transfemoral and transapical access in 134 (60%) and 89 (40%) patients, respectively. Selection of TAVR device type and size was left up to the discretion of the operator. Balloon postdilatation was generally performed when a mean transvalvular gradient (mPG) of ≥ 10 mmHg was observed after valve deployment.

The pharmacological regimen after the procedure comprised either acetylsalicylic acid (100 mg) and clopidogrel (75 mg) for 3 months or oral anticoagulation based on guideline recommendation [37]. SBV failure mode, hemodynamic outcome and major clinical endpoints were defined according to the criteria of the American Society of Echocardiography and VARC II, respectively [38, 39]. The primary endpoint of the study was all-cause mortality at 30 days and 1 year. The secondary endpoint evaluated hemodynamic outcome and procedural characteristics (procedural success, device type and access route, device function) as well as the rate of adverse events (myocardial infarction, stroke, acute kidney injury, bleeding and vascular complications, permanent pacemaker requirement).

Statistical analysis

Statistical analysis was performed using SPSS (22.0, SPSS Inc., USA) and MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Data are given in mean ± standard deviation (SD) and compared by student`s t-test or ANOVA. Relevant candidate variables were analysed in a univariate logistic regression model after review of available literature. Data on 1-month mortality including date of death for logistic regression analysis were available for 206 patients. Data on 1-year mortality including date of death for logistic regression analysis were available for 155 patients which is a major limitation. Short-term, i.e., 30-day-mortality, and long-term, i.e., 1-year-mortality were analysed by logistic regression. For the multivariate regression model, cofounders with a p value < 0.10 in the univariate analysis were included, then a simultaneous regression analysis was performed. Elimination criterion was a p value of more than 0.10. A p value of < 0.05 was considered statistically significant.

Results

Baseline characteristics are shown in Table 1. Patients (age 76 ± 11 years) undergoing VinV TAVR presented a high surgical risk (EuroSCORE 27 ± 17, STS-Scores 8.3 ± 10.1). At the time of presentation, the majority of patients were in NYHA ≥ III (88%). The mean time from surgical valve implantation to VinV-TAVR was 110.2 ± 58.3 months.

VinV-TAVR resulted in a significant reduction of mean transvalvular aortic gradients (mPG 36 ± 27 vs 15 ± 9 mmHg; $p < 0.001$; peak pressure gradient (pPG) 59 ± 48 vs 26 ± 15 mmHg; $p < 0.001$). In six (3%) patients a second TAVR valve was required because of mispositioning of the first device and subsequent severe AR. Finally, after VinV-TAVR procedure, no patients suffered from severe aortic regurgitation (AR) after second valve, neither paravalvular nor valvular. Two patients (4%) suffered from moderate AR. Conversion to surgery was necessary in 3 (2%) patients.

Major bleeding was reported in three (2%) cases, coronary obstruction occurred in two (1%) cases. Four (2%) patients suffered from a periinterventional stroke, a new pacemaker was necessary in 6 patients (3%).

Post-interventional 44 of 178 (25%) patients evidenced a mPG ≥ 20 mmHg. At 30 days and 1 year, mortality was 11% (22 of 206) and 24% (37 of 155), respectively. Procedural Outcome is detailed further in Tables 2 and 3.

Impact of SBV failure mode on outcome

The failure mode of the SBV was stenosis and insufficiency in 85 and 76 patients, respectively. 62 patients presented a combination of both. Left ventricular ejection fraction (LVEF) did not differ between failure modes, whereas both peak (pPG) and mean pressure gradients (mPG) were higher in stenotic SBVs (Table 3). At 30 days after VinV-TAVR, mortality rate in stenotic (13%), insufficient (6%) and combined (13%) SBV failure was not statistically different ($p = 0.32$). After 12 months, mortality rates were at 29, 20 and 22% for stenotic, insufficient and combined failure modes, again at comparable levels ($p = 0.58$). In patients undergoing VinV-TAVR for SBV stenosis (33%) and combination of stenosis and insufficiency (28%), residual stenosis was observed more frequent compared to SBV insufficiency (14%; $p = 0.03$ vs stenosis and combined failure mode).

Table 1 Patient demographics

	Stenosis		Insufficiency		Combination		Overall		*p* value
	Mean	SD (±)	Mean	SD (±)	Mean	SD (±)	Mean	SD (±)	
Age (years)	74	12	76	8	77	12	76	11	0.26
BMI (kg/m^2)	43	60	33	43	31	34	36	48	0.46
EuroSCORE (points)	26	17	24	15	33	20	27	17	0.01
STS (points)	9	12	9	11	6	4	8	10	0.25
Creatinine (mmol/L)	48	57	57	79	48	49	52	64	0.61
EF (%)	50	14	50	13	52	14	51	14	0.65
Female	42%		36%		55%		42%		0.09
T2DM	39%		22%		17%		28%		0.01
aHT	88%		84%		81%		85%		0.53
CVD							61%		
1VD	49%		49%		28%		46%		0.1
2VD	39%		28%		19%		30%		0.04
3VD	35%		14%		28%		27%		0.01
History of MCI	13%		3%		7%		8%		0.053
MCI within 3 months	1%		1%		4%		2%		0.51
Pacemaker	29%		18%		22%		25%		0.29
Malignom	11%		16%		13%		14%		0.62
History of stroke	13%		10%		16%		12%		0.56
Stroke within 3 months	2%		0%		0%		1%		0.5
PAD	20%		21%		26%		21%		0.7
COPD	27%		30%		24%		27%		0.73
NYHA									
NYHA I	0%		1%		0%		0%		0.41
NYHA II	6%		14%		12%		11%		0.32
NYHA ≥ III	93%		85%		88%		88%		0.10

T2MD type 2 diabetes mellitus, *CVD* coronary artery disease, *MCI* myocardial infarction, *PAD* peripheral artery disease, *COPD* chronic obstructive pulmonary disease, *EF* left ventricular ejection fraction, *aHT* arterial hypertension, *BMI* body mass index

Table 2 Post-interventional outcomes at 30-days

	% (*n*)
AR	
No AR	77 (143)
AR I	21 (40)
AR ≥ II	2 (4)
Second valve	3 (6)
Major bleeding	2 (3)
TIA	2 (3)
Stroke	1 (1)
Residual stenosis	25 (44)
New permanent PM	3 (6)

AR aortic regurgitation, *TIA* transitory ischemic attack, *PM* pacemaker

Impact of surgical prosthesis type on outcome

Eight different SBV devices were specified: Mitroflow ($n=33$), Hancock ($n=63$), Carpentier Edwards ($n=36$), Labcor ($n=1$), Shelhigh ($n=9$), Edwards Perimount ($n=19$), homografts ($n=8$). 6 Patients underwent VinV-TAVR for a deteriorated CoreValve TAVR and 47 had other SBVs. Mortality rates after 30 days and 1 year did not differ between different SBV types. Figure 1 depicts pre- and post-interventional mPG based on distinct SBV devices and inner diameters for VinV-TAVR for SBV restenosis.

Impact of TAVR device selection on outcome

138 (62%) patients were treated with first generation TAVR valve [Edwards Sapien XT ($n=76$, 34%) or CoreValve ($n=62$, 28%)]. Second generation TAVR devices were implanted in 85 (38%) patients [Sapien 3 in 24 (11%) patients, Medtronic CoreValve Evolut in 35 (16%) patients, SJM Portico in 16 (7%) patients, Lotus in 2 (1%) patients, JenaValve in 3 (1%) patients, and others in 5 (2%)]. There was no significant difference between first- and second-generation valves or between CoreValve and Edwards Sapien groups with regard to the internal diameter (20 ± 2 vs 20 ± 3;

Table 3 Echo data pre-interventional

	Stenosis		Insufficiency		Combined		Overall		*p* value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
EF (%)	50	14	50	13	52	14	51	14	0.65
mPG (mmHg)	43	17	19	10	46	40	36	27	< 0.001
pPG (mmHg)	71	26	32	17	74	76	59	48	< 0.001
sPAP (mmHg)	52	13	52	14	55	18	53	15	0.72
AVA (qcm)	1	0	1	0	1	0	1	0	< 0.001
MINS > II	13%		18%		15%		15%		0.75
TRINS > II	40%		36%		38%		38%		0.91
30-day-mortality	13%		6%		13%		11%		0.32
12-month-mortality	29%		20%		22%		24%		0.58

EF ejection fraction, *mPG* mean pressure gradient, *pPG* peak pressure gradient, *sPAP* systolic pulmonary artery pressure, *AVA* aortic valve area, *MINS* mitral valve insufficiency, *TRINS* tricuspidal valve insufficiency

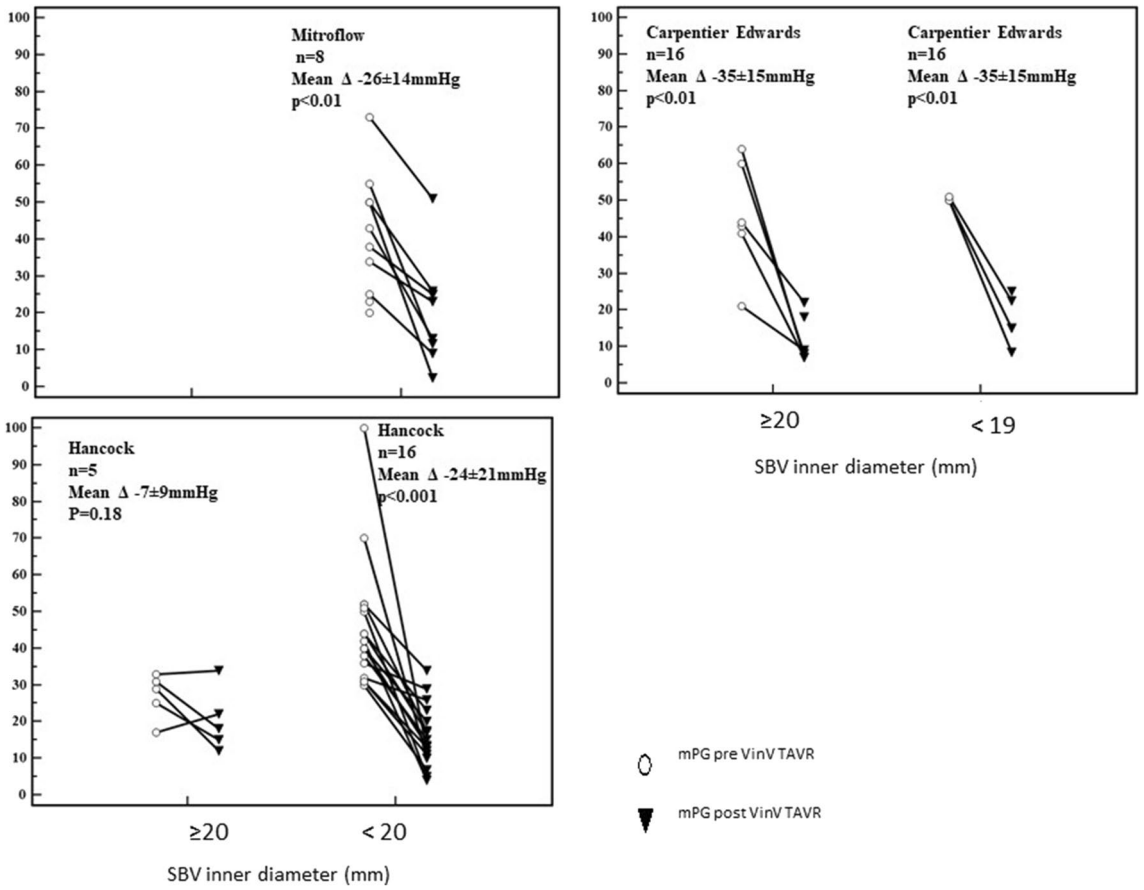

Fig. 1 mPG before and after VinV-TAVR for SBV restenosis for distinct BV inner diameters. *mPG* mean pressure gradient, SBV biopresthetic valve

$p = 0.79$) or the label size (24 ± 2 vs 24 ± 3; $p = 0.72$) of SBVs.

Treatment with a first vs second generation TAVR valve did not affect 30-day (HR 0.69 95% CI 0.28–1.68; $p = 0.41$), or 1-year-mortality (HR 0.73 95% CI 0.34–1.54; $p = 0.40$) in the overall population. Rates of residual stenosis did not differ between first- and second-generation TAVR devices (56 vs 66%; $p = 0.29$). Neither in first-generation nor in second-generation TAVR devices was

residual stenosis associated with increased mortality at 30 days or 1 year after VinV-TAVR, respectively.

Figure 2 depicts the relationship of mPG before and after VinV-TAVR for SBV restenosis in relation to SBV inner diameter for Edwards Sapien X, CoreValve, Sapien 3 and CoreValve Evolut.

Impact of SBV inner diameter on outcome

Median SBV inner diameter was 19 mm, ranging from 15.5 to 31 mm. An SBV inner diameter < 20 mm was considered to be small. SBV inner diameter did not correlate with post-interventional mPG ($r = -0.09$; $p = 0.35$). SBV inner diameter < 20 mm was not associated with increased 1-month-mortality (HR 0.59, 95% CI 0.22–1.60; $p = 0.30$) or 1-year-mortality (HR 0.52, 95% CI 0.22–1.22; $p = 0.13$). In patients with SBV inner diameter < 20 mm, residual stenosis was not significantly more frequent compared to larger SBVs (24 vs 35%; $p = 0.24$).

Impact of TAVR label size on outcome

Median TAVR label size was 23 mm, ranging from 22 to 31 mm. TAVR label size correlated with post-interventional mPG ($r = -0.31$; $p < 0.001$). A TAVR label size ≤ 23 mm was considered to be small. TAVR label size ≤ 23 mm was not associated with 1-month-mortality (HR 1.35, 95% CI 0.52–3.46; $p = 0.54$) but predictive for mortality 1 year after TAVI (HR, 2.76 95% CI 1.16–6.54; $p = 0.02$) in univariate regression. Figure 3 depicts the relationship of mPG before and after VinV-TAVR in relation to TAVR label size for distinct TAVR devices for VinV-TAVR for SBV restenosis. Patients treated with small TAVR label size evidenced residual stenosis at similar rates (18 vs 29%; $p = 0.11$).

Influence of left ventricular ejection fraction on outcome

A left ventricular EF < 35% was not associated with 1-month-mortality (HR 1.57, 95% CI 0.57–4.33; $p = 0.38$) nor with 1-year-mortality (HR 1.54, 95% CI 0.62–3.80; $p = 0.35$). EF correlated weakly with post-interventional mPG ($r = 0.17$; $p = 0.03$) but rates of residual stenosis did not differ between patients with EF below and above 35% (22 vs 27%; $p = 0.49$).

Predictors of 1-year-mortality

Residual stenosis (HR 0.39, 95% CI 0.13–1.22; $p = 0.11$) was not associated with 1-year-mortality. STS score was predictive for 1-year-mortality (HR 1.05, 95% CI 1.01–1.09; $p = 0.01$; AUC 0.63, 95% CI 0.54–0.71) and outperformed EuroSCORE (AUC 0.60, 95% CI 0.52–0.69; $p = 0.02$ vs STS). In univariate logistic regression, besides STS Score,

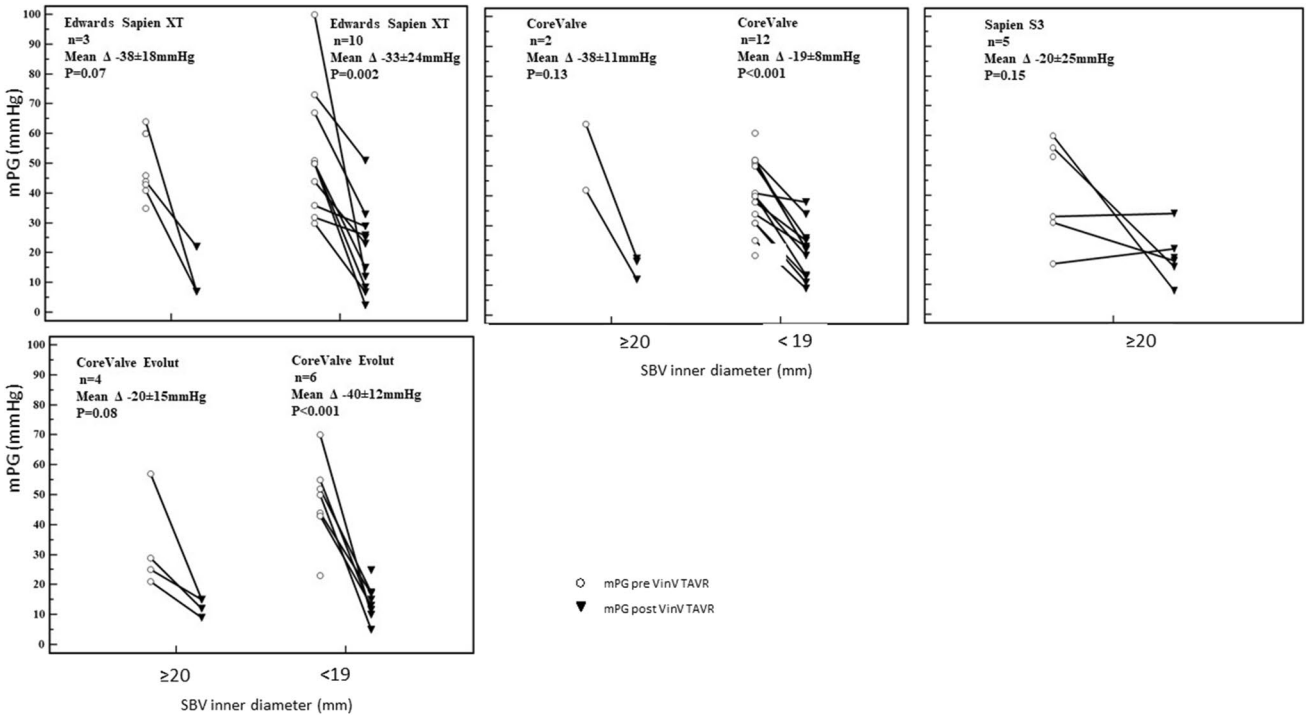

Fig. 2 mPG before and after VinV-TAVR for SBV restenosis for distinct SBV label sizes (mm) treated with distinct TAVR devices. *mPG* mean pressure gradient, SBV biopresthetic valve

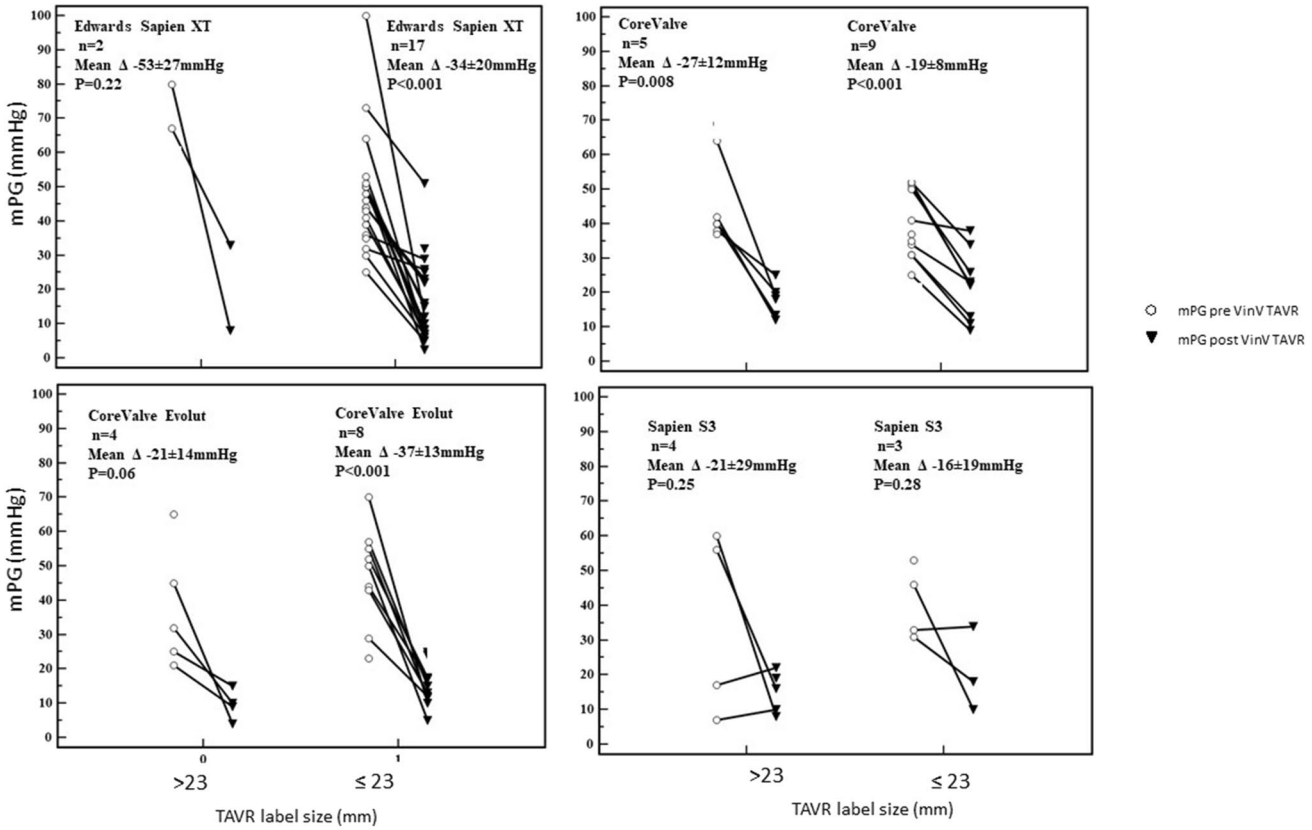

Fig. 3 mPG before and after VinV-TAVR for SBV restenosis for distinct TAVR label sizes (mm) treated with distinct TAVR devices. *mPG* mean pressure gradient, SBV biopresthetic valve

general anesthesia (HR 4.32, 95% CI 1.24–15.05; $p=0.02$), COPD (HR 3.71, 95% CI 1.67–8.22; $p=0.001$) and type 2 diabetes mellitus (T2DM) (HR 2.56, 95% CI 1.18–5.60; $p=0.02$) were predictive for 1-year-mortality after VinV-TAVR. Neither the use of early vs new generation valve systems, nor balloon valvuloplasty were associated with 1-year-mortality (Fig. 4). In a multivariate model consisting of COPD, T2DM, STS-score > 8%, intubation, and TAVR label size ≤ 23 mm only T2DM and COPD remained predictive for 1-year-mortality (Fig. 5).

Discussion

The main findings of this study are the following: (1) VinV-TAVR is a hemodynamically effective procedure, resulting in a significant reduction of the transvalvular gradient and/or the resolution of valvular AR. (2) A residual stenosis (mPG > 20 mmHg) is a frequent finding and occurs in ~25% of all patients undergoing VinV-TAVR. (3) A residual stenosis is more common in patients with a surgical SBV with an inner diameter of < 20 mm. (4) Residual stenosis is not associated with increased mortality.

The VinV-TAVR procedure was hemodynamically successful in the majority of patients and no patient evidenced severe aortic regurgitation after VinV-TAVR. The presence of mPG ≥ 20 mmHg, i.e. residual stenosis was not associated with adverse outcome. VinV-TAVR, therefore, seems to be reasonable in high risk patients for both restenosis and valve insufficiency even in patients with small SBV label size and TAVR label size thought to be at high risk for high residual gradients.

In our cohort of VinV-TAVR patients, mortality was relatively high with 11% after 30 days and 24% after 1 year, most probably due to the high-risk patient profile as evidenced by high STS scores and EuroSCORE. Whereas neither EuroSCORE nor STS Score was predictive for 1-month-mortality, STS Score had some value for prediction of 1-year-mortality after VinV-TAVR. Still, mortality rates were higher in our study cohort compared to other patient collectives evidencing similar baseline characteristics, regarding age, risk scores and concomitant diseases, undergoing VinV-TAVR [40–43]. Patients from Deeb et al. were included 3 years after the inclusion of our first patient, interventionalist's learning curves in our cohort might play a role. Compared to patients from the large valve-in-valve

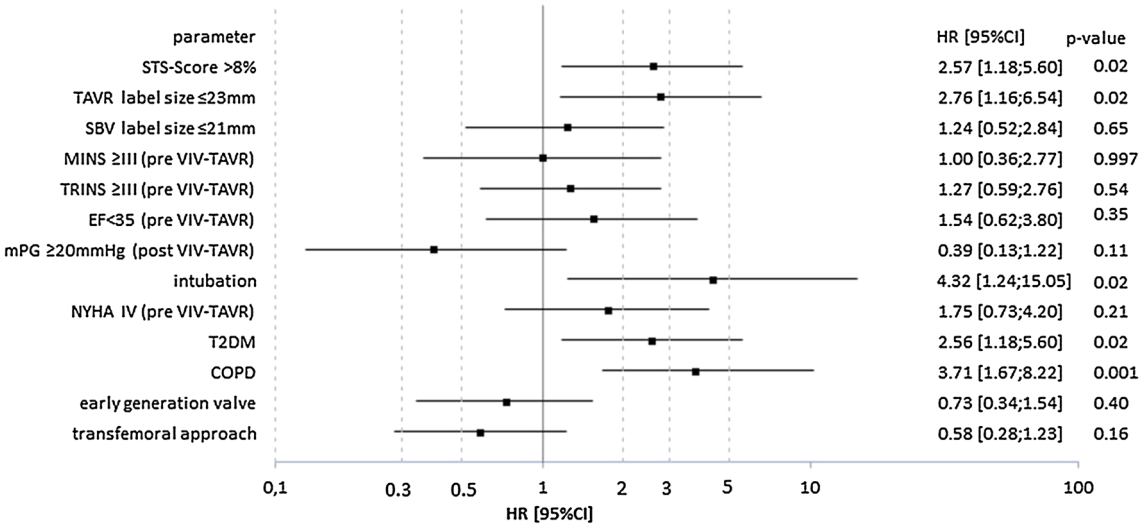

Fig. 4 Forrest plot of univariate logistic regression for 12 month-mortality. *STS* society of thoracic surgeons, *COPD* chronic obstructive pulmonary disease, *T2DM* type 2 diabetes, *MINS* mitral valve insufficiency, *TRINS* tricuspidal valve insufficiency, *EG* ejection fraction, *mPG* mean pressure gradient, *NYHA* New York Heart Association

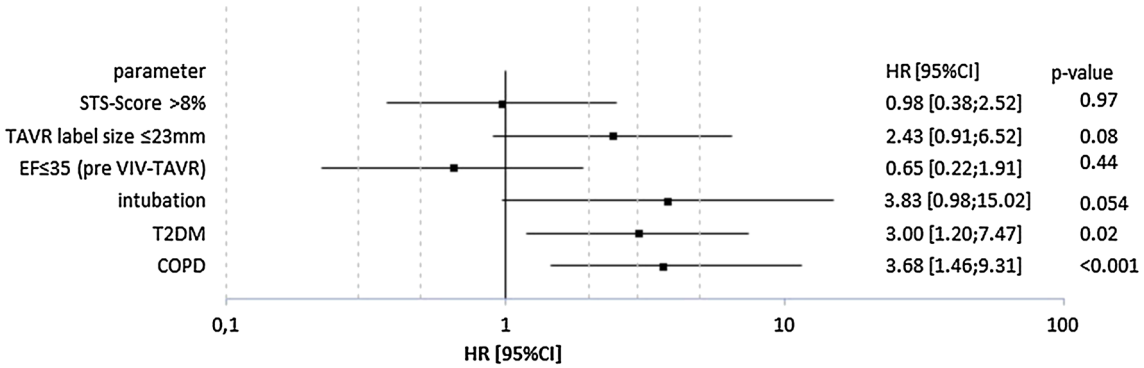

Fig. 5 Forrest plot of multivariate logistic regression for 12 month-mortality. *STS* society of thoracic surgeons, *COPD* chronic obstructive pulmonary disease, *T2DM* type 2 diabetes

international data (VIVID) closer medical follow-up at specialized centers might contribute to this finding. Still, the particular reasons for this trend towards higher mortality rates is beyond this analysis.

Neither residual stenosis nor small SBV inner diameter nor small TAVR label size were associated with adverse outcome within a 1-year follow-up period. These findings are in line with a recent report by Bleiziffer et al., confirming that residual stenosis is frequent after VinV-TAVR, however, not associated with adverse mortality. This notion is of particular importance for patients with small SBV size who are considered to have limited benefit from VinV-TAVR because of residual stenosis. Still, these findings are in contrast to earlier reports in patients undergoing SVR, in whom residual stenosis or a high mPG from patient-prothesis mismatch was shown to be associated with adverse outcome [44–48].

Several mechanisms were already discussed to contribute to this lack of association with residual aortic regurgitation, low stroke volume and concomitant diseases being the most likely factors to contribute to this puzzling finding. Still, in our cohort, no patient suffered from more than trace aortic regurgitation after VinV-TAVR. Further, excluding patients with an ejection fraction below 35%, a mPG above 20 mmHg again was not associated with adverse 1-year-mortality after VinV-TAVR. Certainly, in our cohort, due to its relative small size and the lack of mortality data in all patients, selection bias might contribute to this finding, but we think that first and foremost, concomitant diseases such as diabetes and COPD "overrule" sub-optimal hemodynamic situations in these high-risk patients. The relatively old and medically sick patient collective might also contribute to the finding that the use of second-generation TAVR devices was

not associated with better outcome, which might be anticipated by recent TAVR studies [49]. On the other, hand, this particular finding is in accord with Seiffert et al., who found no differences in safety and efficacy between a first generation vs a second generation TAVR device for VinV TAVR [50].

These notions are supported by our finding that concomitant diseases were highly predictive for mortality 1 year after VinV-TAVR even in a multivariate model. It seems, therefore, necessary to stratify patients with special regard to non-cardiac concomitant diseases to achieve optimal patient selection in future cohorts.

Limitations

The study has several limitations. The endpoint evaluates major adverse clinical events, however, no functional benefit endpoint is presented. For future studies on VinV-TAVR, endpoints beyond mortality are necessary to evaluate the effects of residual stenosis on functional outcome. Further, all echocardiographic values were reported by the centers and are not core-lab adjudicated.

Conclusion

We report important real-world values on valvular echo gradients before and after VinV-TAVR procedures for both distinct SBV and TAVR devices. High residual pressure gradients are relatively frequent, but the anticipation of high gradients should not be considered a contra-indication for VinV-TAVR as this condition is not associated with adverse outcome. STS score is of limited use for the prediction of mortality after VinV-TAVR, most likely due to a high-risk patient collective with severe concomitant diseases. Patient selection and risk stratification seems crucial for optimal outcomes.

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Affiliations

Bernhard Wernly[1] · Ann-Katrin Zappe[2] · Axel Unbehaun[3] · Jan-Malte Sinning[4] · Christian Jung[5] · Won-Keun Kim[6] · Stephan Fichtlscherer[7] · Michael Lichtenauer[1] · Uta C. Hoppe[1] · Brunilda Alushi[2] · Frederik Beckhoff[2] · Charlotte Wewetzer[2] · Marcus Franz[8] · Daniel Kretzschmar[8] · Eliano Navarese[9,10,11] · Ulf Landmesser[2] · Volkmar Falk[3,12,13] · Alexander Lauten[2,12]

1 Clinic of Internal Medicine II, Department of Cardiology, Paracelsus Medical University of Salzburg, Salzburg, Austria

2 Department of Cardiology, Charité-Universitaetsmedizin Berlin, Hindenburgdamm 30,, 12203 Berlin, Germany

3 German Heart Center Berlin, Berlin, Germany

4 Department of Medicine II, Heart Center Bonn, University Hospital Bonn, Bonn, Germany

5 Division of Cardiology, Pulmonology, and Vascular Medicine, Medical Faculty, University Duesseldorf, Düsseldorf, Germany

6 Department of Cardiology and Cardiac Surgery, Kerckhoff Heart and Lung Center, Bad Nauheim, Germany

7 Division of Cardiology, Department of Medicine III, Goethe University Hospital Frankfurt, Frankfurt am Main, Germany

8 Department of Cardiology, Universitätsherzzentrum Thüringen, Friedrich Schiller University Jena, Jena, Germany

9 Inova Center for Thrombosis Research and Drug Development, Inova Heart and Vascular Institute, Fairfax, VA, USA

10 SIRIO MEDICINE Network, Evidence-Based Section, Falls Church, VA, USA

11 Cardiovascular Institute, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

12 Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK), Berlin, Germany

13 Charité-Universitätsmedizin, Berlin, Germany