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ORIGINAL PAPER

Transcatheter aortic valve replacement for pure aortic valve regurgitation: "on-label" versus "off-label" use of TAVR devices

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Abstract

Introduction Transcatheter aortic valve replacement (TAVR) has become the mainstay of treatment for aortic stenosis in patients with high surgical risk. Pure aortic regurgitation (PAR) is considered a relative contraindication for TAVR; however, TAVR is increasingly performed in PAR patients with unfavorable risk profile. Herein, we aim to summarize available data on TAVR for PAR with special emphasis on "on-label" versus "off-label" TAVR devices.

Methods and results Pubmed was searched for studies of patients undergoing TAVR for PAR. Primary outcome was 30 day-mortality. Pooled estimated event rates were calculated. Twelve studies including a total of 640 patients were identified until December 2017. Among these, 208 (33%) patients were treated with devices with CE-mark approval for PAR ("on-label"; JenaValve and *J* valve). Overall, the procedural success rate was 89.9% (95% CI 81.1–96.1%; I^2 80%). Major bleeding was reported in 6.4% (95% CI 2.9–10.8%; I^2 48%). All-cause mortality at 30 days was 10.4% (95% CI 7.1–14.2%; I^2 20%). Stroke occurred in 2.2% (95% CI 0.9–3.9%; I^2 0%). A permanent pacemaker was required in 10.7% (95% CI 7.3–14.6%; I^2 23%). At 30 days after TAVR, ≥ moderate AR post-interventional was observed in 11.5% (95% CI 2.9–23.6%; I^2 90%). In the "on-label"-group, success rate was 93.0% (95% CI 85.9–98.1%; I^2 52%). 30-day-mortality was 9.1% (95% CI 3.7–16.0%; I^2 36%). More than trace AR was present in 2.8% (95% CI 0.1–7.6%; I^2 0%). Compared to first-generation devices, second-generation devices were associated with significantly lower 30-day-mortality ($r = -0.10$; $p = 0.02$), and significantly higher procedural success rates ($r = 0.28$; $p < 0.001$). Compared to other second-generation devices, the use of *J* valve or JenaValve was not associated with altered mortality ($r = 0.04$; $p = 0.50$), rates of > trace residual AR ($r = -0.05$; $p = 0.65$) but with a significantly higher procedural success ($r = 0.15$; $p = 0.042$).

Conclusion Based on this summary of available observational data TAVR for PAR is feasible and safe in patients deemed inoperable. First-generation TAVR devices are associated with inferior outcome and should be avoided. The "on-label" use of PAR-certified TAVR devices is associated with a significantly higher procedural success rate and might be favorable compared to other second-generation devices.

Keywords TAVR · TAVI · Aortic insufficiency · Aortic regurgitation · Transcatheter aortic valve replacement · Transcatheter aortic valve implantation

Introduction

Transcatheter aortic valve replacement (TAVR) is now a well-established treatment option for both high and intermediate risk patients suffering from symptomatic severe aortic stenosis (AS) [1, 2]. Since the first introduction of TAVR into clinical practice, devices have substantially evolved, including the reduce of delivery profile, features to decrease the rate of paravalvular leaks and the ability for

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repositioning, and resulted in a constant improvement of clinical outcomes in patients with AS [3–14].

Patients with severe pure aortic regurgitation (PAR) presenting with clinical symptoms, left ventricular dilatation or impaired left ventricular ejection fraction should undergo surgical aortic valve replacement (SAVR) and TAVR was considered to be relatively contraindicated in those patients [15, 16]. Still, there is a growing number of elderly patients with a high surgical risk profile suffering from PAR. Leaving these patients to medical management is associated with unfavorable outcomes and high morbidity [17]. Although originally developed for heavily calcified, tricuspid and stenotic valves, TAVR is increasingly considered for treatment of PAR [18]. Multiple reports and patient series have demonstrated feasibility of this treatment approach, however, first-generation valves have shown an increased risk for residual AR, rupture of the aortic annulus, valve dislocation and low device success rates in PAR [19, 20]. With the second-generation valves, the technique advanced and the JenaValve has even been CE certified in the indication PAR. Another valve, the *J* valve has been certified for PAR by China Food and Drug Administration.

We therefore conducted a literature review and a meta-analysis of reports evaluating TAVR for PAR. Special focus was put on the comparison of "on label" (JenaValve and *J* valve) versus "off-label" devices and the comparison of first- versus second-generation valves.

Methods

This study was performed according to established methods [21] and in adherence to preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement for reporting systematic reviews and meta-analyses in health care interventions [22].

Literature search

The PRISMA flow chart illustrating publication screening and reasons for exclusion is shown in Appendix Fig. 1. We performed our search in PubMed Central in English language. Keywords used were "TAVI insufficiency", "TAVI regurgitation"; "TAVR insufficiency", "TAVR regurgitation"; transcatheter AND "aortic regurgitation"; transcatheter AND "aortic insufficiency"; transfemoral AND "aortic insufficiency"; transfemoral AND "aortic regurgitation"; transfemoral AND "aortic valve insufficiency"; transfemoral AND "aortic valve regurgitation"; transcatheter AND "aortic valve insufficiency"; transcatheter AND "aortic valve regurgitation". Databases were searched on December 16th, 2017. The most updated or inclusive data for each study were used for abstraction. References of original and review articles were cross-checked.

Selection criteria and internal validity

Citations were screened at title/abstract level and retrieved as full reports if they fulfilled the inclusion criteria: (1) human studies; (2) studies reporting outcomes of more than five patients (3) English language. Two independent reviewers (BW and SE) selected the studies included, extracted studies and patients' characteristics of interest and relevant outcomes; divergences were resolved by consensus after discussion with a third reviewer (AL).

Study end points (reported according to VARC definition)

Primary endpoint was mortality at 30 days. Secondary endpoints were stroke, major bleeding, need for new permanent pacemaker, more than moderate postinterventional aortic regurgitation, need for second valve implantation, major vascular complication, acute kidney injury (AKI) above stadium 2 (AKI), myocardial infarction (MI) at 30 days. Bleeding, definition of severe AR as well as procedural success definitions of reported studies were applied (Table 2).

Data synthesis and analysis

Study-level data were analyzed. Heterogeneity was assessed using the I^2 statistic. Pooled proportions, i.e., event rates were calculated using a random-effects model (DerSimonian and Laird) incorporating Freeman–Tukey Double Arcsine transformation of proportions [23]. Pooled event rates were obtained for each subset of studies and combined in a random effect meta-analysis. The effect of study-level covariates (use of first-generation versus second-generation devices, use of on-label versus off-label devices) on the rate of all-cause death at 30 days was explored with a meta-regression analysis. Open meta-analyst was used for statistical computations and graphical work-up based on the *metafor* package for R [24, 25].

Results

Patient cohort

The search terms yielded 3480 studies, with 1572 remaining after exclusion of duplicates. We included 12 studies reporting data from 640 patients in this analysis (Table 1) [26–37]. All studies reported 30-day outcomes. Mean age ranged from 73 ± 9 to 80 ± 6 years, logistic EuroScore from 17.7 ± 14.8 to 34 ± 8, STS score from 4.9 ± 3.5 to 13.1 ± 2.

Table 1 Baseline characteristics, devices and access route of studies included in this analysis

Study	Device	Number	Female	Age (years)		STS (%)		EUROScore (%)		Access
	Type (*n*)	*n*	*n*	Mean	SD	Mean	SD	Mean	SD	*n*
Roy [28]	CoreValve	43	23	75	9	10	5	27	18	Transfemoral
Schlingloff [33]	JenaValve	10	4	79	9	7	1	28	17	Transapical
Seiffert [34]	JenaValve	31	11	73	9	5	4	24	15	Transapical
Testa [27]	CoreValve	26	10	73	10	13	2	24	8	Transfemoral (21) Subclavia (4) Direct (1)
Wendt [32]	Acurate TA	8	3	73	8	7	3	34	8	Transapical
Frerker [33]	CoreValve (21) Sapien XT (1)	22	10	80	6	n/a		25	18	n/a
Schofer [31]	DirectFlow Valve	11	7	75	13	9	9	20	7	Transfemoral (10)
Wei [37]	*J* valve	6	2	75	8	n/a		29	8	Transapical
Zhu [40]	*J* valve	44	13	74	6	9	4	25	5	Transapical
Sawaya [30]	CoreValve (33), Evolut R (5), JenaValve (23) DirectFlow (6), Lotus (6), Sapien XT (4) Sapien 3 (1)	78	32	74	10	7	5	20	12	Transfemoral (51) Subclavia (2) Direct (2) Transapical (23)
Silaschi [35]	JenaValve	30	18	74	9	5	4	18	15	Transapical (30)
Yoon [29]	SapienXT (9), Sapien 3 (41), CoreValve (110) Evolut R (50), JenaValve (64), Direct Flow (35) *J* valve (1), Engager (7), Portico (3) Acurate (5), Lotus (6)	331	159	74	12	7	7	n/a		Transfemoral (233) Subclavia (10) Direct (6) Carotis (2) Transapical (80)

Table 2 Success rates, echocardiographic parameters, bleeding and AR definitions of studies included in this analysis

Study	Success (%)	Annulus size (mm)		LVEDD		Bleeding definition	AR definition
		Mean	SD	Mean	SD		
Roy [28]	98%	24	2	59	14	VARC-1	n/a
Schlingloff [33]	100%	n/a	n/a	62	2	VARC-2	n/a
Seiffert [34]	97%	24	2	n/a	n/a	VARC-1	EAE (49)
Testa [27]	77%	23	3	n/a	n/a	VARC-2	EAE (49)
Wendt [32]	n/a	24	3	n/a	n/a	VARC-2	n/a
Frerker [33]	n/a	n/a	n/a	n/a	n/a	VARC-2	n/a
Schofer [31]	91%	25	2	59	8	VARC-2	ESC (50)
Wei [37]	100%	23	2	52	3	VARC-2	n/a
Zhu [40]	98%	23	2	n/a	n/a	n/a	n/a
Sawaya [30]	71%	n/a	n/a	59	10	VARC-2	n/a
Silaschi [35]	97%	24	2	n/a	n/a	VARC-1	n/a
Yoon [29]	74%	25	n/a	n/a	n/a	VARC-2	n/a

247 (39%) patients received a first-generation valve (CoreValve or Sapien XT) and 393 (61%) patients a second-generation valve (*J* valve, JenaValve, Acurate TA, DirectFlow, Evolut R, Lotus, Engager, Portico, Sapien 3). 208 (33% of overall cohort, 53% of second-generation valves) patients were treated with either *J* valve or JenaValve.

Access route was reported for 617 (96%) patients. 350 (56.7%) underwent transfemoral, 20 (3.2%) subclavian, 12 (1.9%) direct, 3 (0.5%) carotid and 232 (37.6%) apical TAVR. 71 (11%) patients required the implantation of a second valve for persistence of severe AR due to misplacement or migration of the first valve.

Mean LVEDd ranged from 52 ± 3 mm to 62 ± 2 mm [58.2 mm (95% CI 54.2–62.2 mm); Table 2]. Size of ascending aorta was reported in three studies and ranged from 36 ± 8 mm to 38 ± 6 [36 mm (95% CI 35–37 mm; I^2 0%)]. Valve sizes of specific TAVR devices were reported in 166 (26%) cases (Table 3).

30-day outcomes

Overall cohort

Overall, procedural success rate was 89.9% (95% CI 81.1–96.1%; I^2 80%). Major bleeding occurred in 6.4% (95% CI 2.9–10.8%; I^2 48%). All-cause mortality at 30 days was 10.4% (95% CI 7.1–14.2%; I^2 20%) for the overall group (Figs. 1 and 2). Myocardial infarction was reported in 0.1% (95% CI 0.0–0.9%; I^2 0%), acute kidney injury was reported in 6.6% (95% CI 2.5–11.9%; I^2 0%; data from six studies). Stroke occurred in 2.2% (95% CI 0.9–3.9%; I^2 0%). A permanent pacemaker was required in 10.7% (95% CI 7.3–14.6%; I^2 23%). At 30 days after TAVR, > trace AR post-interventional was observed in 11.5% (95% CI 2.9–23.6%; I^2 90%). A second valve was necessary in 7.0% (95% CI 2.3–13.3%; I^2 39%; data from eight studies), conversion to surgery in 1.5% (95% CI 0.3–3.2%; I^2 0%).

First-generation valves

In the first-generation group (CoreValve, $n = 223$; Sapien XT, $n = 24$; total 247 patients), mortality at 30 days was 15.6% (95% CI 10.6–21.3%; I^2 15%). Procedural success was 68.4% (95% CI 58.7–77.5%; I^2 53%). Stroke occurred in 2.3% (95% CI 0.5–4.9%; I^2 0%). Implantation of a pacemaker was necessary in 13.5% (95% CI 8.8–18.9%; I^2 0%). More than trace AR occurred in 37.5% of patients (95% CI 12.1–67.1%; I^2 94%). Major bleeding was reported in 12.4% (95% CI 6.1–20.3%; I^2 53%). Acute kidney injury (AKI) was reported in 8.4% (95% CI 4.5–13.3% I^2 10%; data from three studies). Conversion to surgery was necessary in

Table 3 Valve sizes of specific TAVR devices were reported in 166 (26%) cases

	Valve size						
	21 mm	23 mm	25 mm	26 mm	27 mm	29 mm	31 mm
CoreValve	n/a	n/a	n/a	$n = 14$	n/a	$n = 38$	$n = 14$
J valve	$n = 1$	$n = 2$	$n = 9$	n/a	$n = 3$	n/a	n/a
JenaValve	n/a	$n = 9$	$n = 20$	n/a	$n = 42$	n/a	$n = 3$
DirectFlow valve	n/a	n/a	$n = 2$	n/a	$n = 4$	$n = 5$	n/a

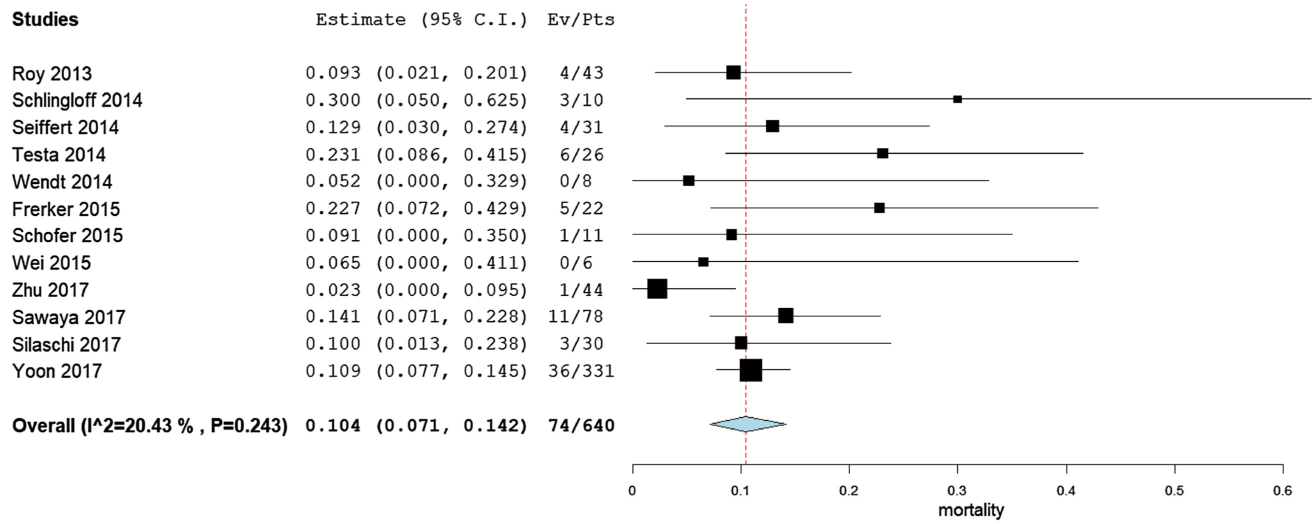
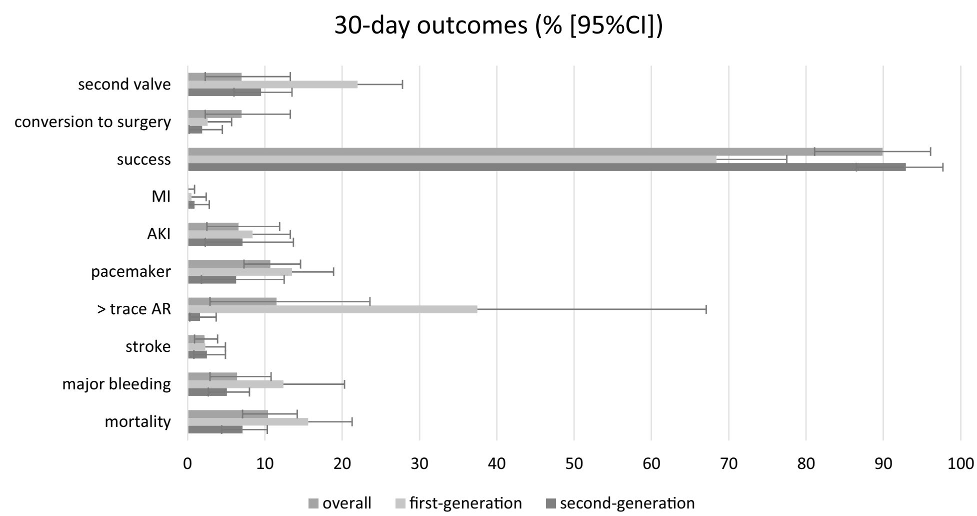


Fig. 1 Forest plot showing event rates for the primary endpoint (all-cause 30-day-mortality) in reported studies. Heterogenity was assessed by I^2 (20%)

Fig. 2 30-day outcomes in the overall cohort, and in the first- and second-generation subgroup; *MI* myocardial infraction, *AKI* acute kidney injury, *AR* aortic regurgitation



2.6% (95% CI 0.5–5.7%; I^2 0%). Myocardial infarction was reported in 0.5% (95% CI 0.0–2.4%; I^2 0%).

Second-generation valves

In the second device generation subgroup ($n = 393$), mortality was 7.1% (95% CI 4.4–10.3%; I^2 0%), stroke rate was 2.5% (95% CI 0.8–4.9%; I^2 0%) and permanent pacing was necessary in 6.3% (95% CI 1.8–12.5%; I^2 47%). Procedural success rate was 92.9% (95% CI 86.5–97.7%; I^2 57%). More than trace AR was present in 1.6% (95% CI 0.3–3.7%; I^2 0%). Major bleeding was reported in 5.1% (95% CI 2.7–8.0%; I^2 0%). AKI was reported in 7.1% (2.3–13.7%; I^2 36%; data from three studies) and myocardial infarction in 0.9% (0.0–2.8%; I^2 0%). Conversion to surgery was necessary in 1.9% (0.2–4.5%; I^2 0%).

"On-label" devices for TAVR for PAR: JenaValve and *J* valve

As the JenaValve and *J* valve share comparable features in design and are both certified for PAR, we combined the outcomes of these two valve prosthesis systems (Fig. 3). 208 (33%) patients were treated with either *J* valve or JenaValve. Procedural success rate was 93.0% (95% CI 85.9–98.1%; I^2 52%). 30-day-mortality was 9.1% (95% CI 3.7–16.0%; I^2 36%; data from six studies, Fig. 3). Stroke occurred in 2.8% (95% CI 0.4–6.5%; I^2 0%; data from five studies). More than trace AR was present in 2.8% (95% CI 0.1–7.6%; I^2 0%; data from five studies). Major bleeding rate was 3.0% (95% CI 0.4–7.2%; I^2 0%; data from five studies).

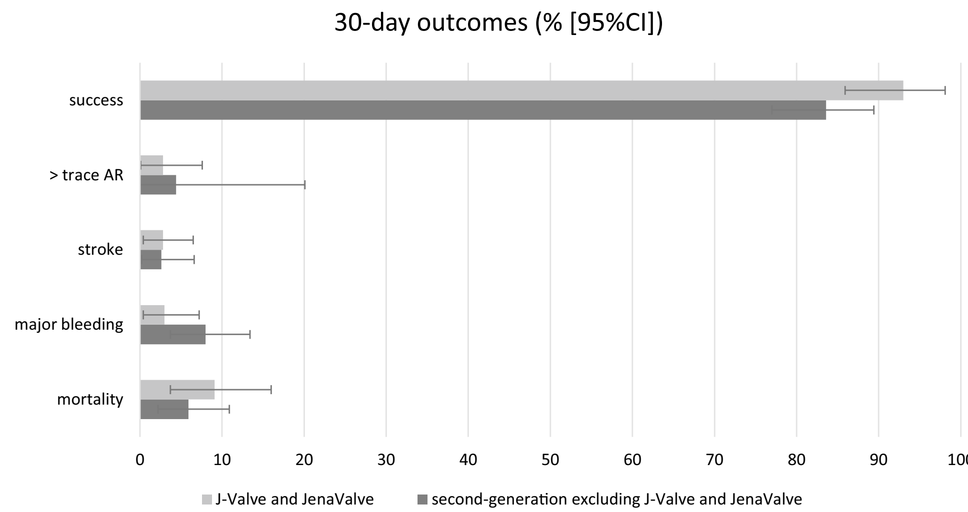


Fig. 3 30-day outcomes in the *J* valve and JenaValve subgroup and in the subgroup of patients treated with second-generation valves excluding *J* valve and JenaValve; *MI* myocardial infraction, *AKI* acute kidney injury, *AR* aortic regurgitation

"Off-Label": second-generation valves

In the subgroup of second-generation valves excluding *J* valve and JenaValve, data were available from three studies ([29, 31, 32]; $n = 167$; 26%). Procedural success rate was 83.6% (95% CI 77.0–89.4%; I^2 0%). Mortality rate was 5.9% (95% CI 2.2–10.9%; I^2 0%). More than trace residual AR rate was 4.4% (95% CI 0.0–20.1%; I^2 0%, data from two studies). Stroke occurred in 2.6% (95% CI 0.2–6.6%; I^2 0%). Rate of major bleeding was 8.0% (95% CI 3.7–13.4%; I^2 0%).

Meta-regression

Overall cohort

Neither sample size ($r = 0.00$; $p = 0.41$), nor LVEDd ($r = 0.02$; $p = 0.43$) nor age ($r = 0.03$; $p = 0.10$) nor STS score [$r = (-0.004)$; $p = 0.74$] nor EUROScore [$r = (-0.001)$; $p = 0.90$] nor annulus size ($r = 0.004$; $p = 0.89$) was associated with 30-day-mortality.

"On-label" TAVR versus "off-label" TAVR

Compared to other second-generation devices, the use of *J* valve or JenaValve was not associated with altered mortality ($r = 0.04$; $p = 0.50$) or rates of > trace residual AR ($r = -0.05$; $p = 0.65$) but with a significantly higher procedural success ($r = 0.15$; $p = 0.042$).

First-generation TAVR versus second-generation TAVR

Compared to first-generation devices, second-generation devices were associated with significantly lower 30-day-mortality ($r = -0.10$; $p = 0.02$), significantly lower rates of > trace residual AR ($r = -0.42$; $p < 0.001$) and significantly higher procedural success rates ($r = 0.28$; $p < 0.001$).

Discussion

Based on our review and analysis of available studies, (1) TAVR for PAR seems feasible and safe in selected patients unfit for SAVR with a procedural success rate of 90% in the overall group. (2) In accordance with previous studies, first-generation TAVR device were accompanied with higher mortality, higher rates of residual AR, more peri-procedural complications and significantly lower procedural success rates. (3) Lastly, compared to other second-generation valves, "on-label"-TAVR with *J* valve or JenaValve showed significantly higher procedural success rates.

Data from the European heart survey show that 30% of patients with a severe symptomatic valvular heart disease are not referred for surgical valve repair, mainly due to their comorbidities [17]. Medical management, however, is associated with a high morbidity and mortality in this cohort. Therefore, TAVR has evolved as standard of care for the treatment of severe symptomatic aortic stenosis in several indications, especially in high risk patients [38].

However, PAR is still considered a relative contraindication for TAVR, mainly due to a lack of valve calcification and the frequent presence of aortic root dilatation. But due to a large unmet need for treatment of high risk patients with PAR several registries have accumulated clinical and procedural data throughout the past years [29]. Franzone et al. published a well-conducted review of TAVR for PAR but ever since additional registry data has become available [29, 30, 35, 39, 40].

When referred to surgical treatment patients with PAR are usually younger than patients with severe symptomatic aortic stenosis [17]. Compared to the first study of TAVR in aortic stenosis, the PARTNER trial (mean age 83 years), to this analysis, the trend towards younger patients in TAVR for PAR can be affirmed with a mean age ranging from only 73 to 80 years in the present cohort [41]. Although relatively young, this patient cohort was at high risk reflected by both high logistic EuroSCORE and STS Scores.

We hereby confirm the results from Yoon et al. showing superiority of second-generation TAVR devices versus first-generation devices in TAVR for PAR. The use of second-generation valves is associated with fewer postinterventional complications including lower rates for need of permanent pacing and major bleeding [42]. Further, the use of first-generation valves was more often associated with a significant paravalvular leak requiring the implantation of a second TAVR device and to an only modest VARC defined success rate [28]. The limitations of these early devices were overcome by technical advances of second-generation devices, including the use of paravalvular skirts to prevent leakage and modified sizing strategies with the availability of larger valves [43].

Second generation devices specifically approved for the use in PAR (JenaValve and *J* valve) have introduced design features such as positioning elements to facilitate valve fixation independently of annular calcification. JenaValve has even been CE certified and *J* valve certified by China Food and Drug Administration for use in PAR [29, 44]. In our analysis, use of these "on-label" TAVR devices was associated with higher procedural success compared to second-generation valves. This significant trend observed in our analysis towards higher success rates in "on-label" TAVR devices compared to other second-generation valves suggests a potential benefit of valves with specific design features for use in PAR.

Until recently these "on-label" valves could be implanted only transapically which is associated with a higher rate of adverse events versus the transfemoral approach and might therefore also affect the outcome in the present study, leaving room for further improvement in "on-label" TAVR devices. Unfortunately, publicized data are not sufficient for comparing outcomes of different access routes [45]. Recently, the first case report described successful implantation of JenaValve via the transfemoral approach [46]. Therefore, the combination of specific valves with fixation mechanisms designed towards non-calcified valves and transfemoral approach could lead to even more favorable outcomes in TAVR for PAR.

PAR is frequently accompanied by a dilated aortic annulus and dilatation of ascending aorta. A relatively higher degree of device oversizing was associated with a reduction in postinterventional AR rates in one study in self-expanding valves [29]. Second-generation valves have a longer stent frame, a novel delivery system, new shapes with optimized radial force and the option for repositioning which allows a better deployment compared to first-generation valves. In this analysis, only patients with annular diameters ranging from 23 to 31 mm and without severe annular dilatation were treated with TAVR. Aortic annulus dilatation poses a contraindication for PAR in TAVR and limits future usage. In contrast, as second-generation devices anchor mainly in the aortic annulus, dilatation of the ascending aorta does not necessarily constitute a technical contraindication for TAVR in patients with PAR. In this regard, future studies investigating diameters, obtained by both echocardiography and computer tomography, and their impact on outcome with special emphasis on prosthesis design, mortality and post-interventional (paravalvular) aortic regurgitation are warranted and might help sizing TAVR device for PAR patients.

Furthermore, specific studies evaluating valve replacement in patients with poor prerequisites, as left ventricular dilatation or impaired left ventricular function, are needed. However, surgical valve replacement for PAR in patients with reduced left ventricular function was accompanied by favorable clinical outcomes and we certainly think that there is an unmet need for transcatheter treatments for PAR patients [47, 48].

Limitations

Although we included only peer-reviewed studies, none of these studies was a randomized control trial, hence limiting the quality of every meta-analysis in this field so far. Available studies focus on reporting feasibility and outcome of TAVR in patients with PAR and there is a lack of randomized controlled trials comparing interventional versus surgical treatment in patients with PAR. Further, although in 2017 three new trials added a lot of data in the field of PAR for TAVR, absolute patient numbers remain relatively low. Meta-analysis comparing transfemoral and transapical approach was not feasible due to lack of patient-level data. Available data does not allow identifying factors predicting the higher procedural success rate of "on-label" TAVR valves.

Conclusion

To the best of our knowledge, this review and meta-analysis constitute the largest patient collective of TAVR in PAR in the literature. We investigate "on-label" versus "off-label" TAVR for PAR for the first time. We show that TAVR seems to be feasible for patients suffering from PAR unfit for SAVR due to high perioperative risk. Future studies elucidating outcomes beyond one month after TAVR with special regards on left ventricular and aortic geometries as well as left ventricular function are necessary to refine possible indication criteria of TAVR for PAR. In patients suffering from PAR ineligible for SAVR, further evidence with respect to optimal timing and device selection could improve outcomes. We think that in TAVR for PAR a first-generation device should be avoided. There was a significant trend towards higher procedural success rates in "on-label" valves, and therefore, the use of those valves in TAVR for PAR should be preferred. Trials comparing "on-label" versus "off-label" TAVR for PAR are necessary.

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Data Availability All data relevant for this study will be given by the authors upon specific request without restriction.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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