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REVIEW

Transcatheter aortic valve replacement in patients with pure native aortic valve regurgitation: A systematic review and meta-analysis

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This systematic review and meta-analysis sought to summarize the available evidence on the use of transcatheter aortic valve replacement (TAVR) in patients with Native Aortic Valve Regurgitation (NAVR) and compare outcomes between first and second generation valves. Owing to the improvements in transcatheter heart valve design and procedural success, TAVR has become increasingly performed in broader aortic valve pathologies. We searched Medline, Embase, Cochrane, and Scopus databases from 2007 to 2018 and performed a systematic review on reports with at least 10 patients with aortic valve regurgitation undergoing TAVR procedure. The main outcome of interest was all-cause mortality at 30 days. A total of 638 patients across 12 studies were included. Mean age ranged from 68 to 84. Society of Thoracic Surgeons score ranged from 5.4% to 13.1% and Logistic EuroSCORE ranged from 18.2% to 33%. The incidence rate of all-cause mortality at 30 days was found to be 11% (95% CI 7%-16%; I^2 = 20.86%). All-cause mortality at 30 days for first generation valves had an incidence rate of 15% (95% CI 10%-20%; I^2 = 10%) compared to 7% (95% CI 3%-13%; I^2 = 37%) in second generation valves with subgroup interaction analysis P = 0.059. Device success incidence rate in second generation valves was 92% (95% CI 83%-99%; I^2 = 67%) vs 68% (95% CI 59%-77%; I^2 = 53%) in first generation valves with P = 0.001. TAVR appears to be a feasible treatment choice for NAVR patients at high risk for surgical valve replacement. Second generation valves show promising results in terms of short-term outcomes.

KEYWORDS

aortic regurgitation, meta-analysis, systematic review, transcatheter aortic valve replacement

1 | INTRODUCTION

According to the Euro Heart Survey, approximately 13% of patients with native valve disease suffer from isolated aortic regurgitation (AR).[1] Surgical aortic valve replacement remains the standard of care in symptomatic patients, patients with left ventricular dilatation or decreased left ventricular function[2] and pharmacologic therapy is limited to symptomatic patients who are not candidates for surgery or to treat patients with severe AR in preparation for surgery.

Transcatheter aortic valve replacement (TAVR) has become the standard of care for the management of high-risk patients with aortic stenosis (AS). Since the first in human aortic valve replacement in 2002[3] and owing to the improvements in device design and procedural success, TAVR has become increasingly performed in broader aortic valve pathologies, other than aortic stenosis.[4–6] Limited data is available regarding the performance of TAVR in patients with native aortic valve regurgitation (NAVR).

Initial experiences with TAVR for AR patients using first generation valves, majority of which used CoreValve system, showed high risk for valve dislocation, residual AR and need for second valve implantation. Using second generation valves, such as Jenavalve, was found to overcome some of the technical challenges with early generation valves.

A systematic review and meta-analysis published in 2016 by Franzone et al has summarized the available evidence up to 15 February 2016.[7] There have been multiple studies published since then. Thus, we conducted this systematic review and meta-analysis as an update to the previous work and to compare the outcomes between first vs second generation valves.

2 | METHOD

This is systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8] A protocol was developed a priori by the authors and is available in Supporting information Appendix S1.

2.1 | Search strategy

A comprehensive search of several databases from 2007 to January 22nd 2018, English language was conducted. The databases included Ovid MEDLINE Epub Ahead of Print, Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for studies of TAVR for aortic valve regurgitation. The actual strategy is available in Appendix S2. Previous systematic reviews were also reviewed for cross-referencing.

2.2 | Study selection

Two reviewers screened the titles and abstracts of the identified references in an independent and blinded manner. The full-texts were then retrieved and evaluated for inclusion by the same independent blinded reviewers and establishing consensus solved disagreements. Studies were eligible if they met the following criteria: (a) Patients with pure native aortic regurgitation (AR); (b) studies including patients with pure degenerative AR within a larger cohort of patients undergoing TAVR because of severe aortic stenosis; (c) reports of a minimum of 10 patients; (d) abstracts or conference presentations reporting procedural characteristics, and clinical outcomes of interest; and (e) reports written in English language. We excluded case reports as well as reports with aortic valve replacement due to regurgitation in failed aortic prosthesis, endocarditis, aortic dissection, or in patients with left ventricular assist device (LVAD). When multiple publications reported results from one center, we identified the most comprehensive reports and used them to avoid inflation of our results.

2.3 | Data extraction

When reported, the following data were sought from included studies: patients' characteristics including number of patients included in the report, age, gender, New York Heart Association (NYHA) class, aortic regurgitation grade (moderate or severe), concomitant moderate or severe mitral stenosis, aortic annulus diameter and ascending aortic diameter, left ventricular ejection fraction, Society of Thoracic Surgeon and Logistic EuroSCORE, and comorbidities. Procedure characteristics including device type, size and access site were also extracted when available. Follow-up duration was also extracted when reported. Two reviewers extracted the data and disagreements were solved with establishing consensus.

2.4 | Outcomes of interest

Out main outcome of interest was all-cause mortality at 30 days. Other outcomes were extracted, when available, all-cause mortality at the end of follow-up period for each study, cardiovascular mortality at 30 days and end of follow up, cerebrovascular accidents, myocardial infarction, acute kidney injury, major bleeding, major vascular complication, pacemaker implantation, moderate or severe AR and paravalvular leak, second valve required, conversion to SAVR and devices success.[9]

2.5 | Risk of bias assessment

We planned to assess the risk of bias in randomized controlled trials and non-randomized comparative studies using the Cochrane Risk of Bias Tool[10] and the Newcastle Ottawa Scale,[11] respectively. For non-comparative studies and case series, we used the tool suggested by Murad et al.[12]

2.6 | Data synthesis

We extracted the number of events and total for each study arm to generate an incidence rate (event rate) and 95% confidence interval [CI] using the Freeman Turkey double arcsine method.[13] Incidence rates were pooled using a random effects model.[14] Heterogeneity between studies was assessed using the I^2 statistic.[15] All analyses were performed using STATA.[16]

3 | RESULTS

Our search protocol identified 2608 references. After screening titles and abstracts, 39 reports were selected for full-text evaluation. We were able to identify three reports that met our inclusion criteria but had to be excluded from the analysis due to study centers overlap with other included studies and the risk of data inflation.[17–19] Finally, 12 studies were identified as eligible and included in our systematic review[20–31] (Figure 1). In total, 638 patients with native pure aortic regurgitation identified across the 12 studies. Patients and procedural characteristics in addition to outcomes are summarized in Table 1. For more comprehensive summary of the included studies, with the excluded studies because of centers overlap, refer to the Table S1.

3.1 | Baseline characteristics

The mean age ranged from 68 to 84 ± 2.6. Society of Thoracic surgeons score was reported in eight studies with mean ranged from 5.4 ± 3.6 to 13.1 ± 2.0. Logistic EuroSCORE was reported in 11 of the included studies and it ranged from 18.2 ± 8.9 to 33 while Logistic EuroSCORE II was only reported in two studies with mean ranging

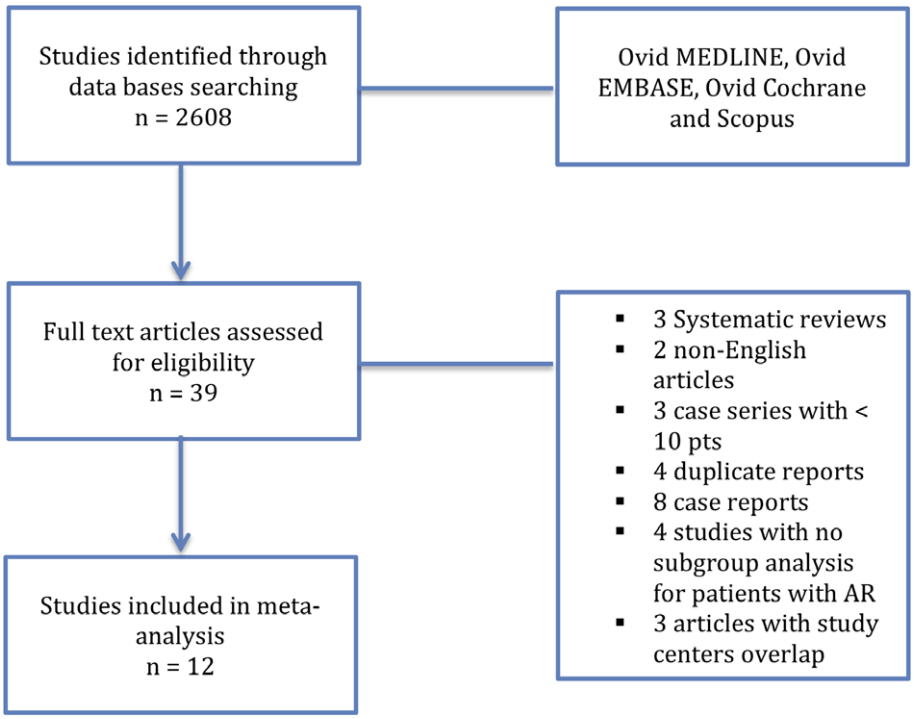

FIGURE 1 Flow chart of manuscript selection

from 9.3 ± 6.4 to 9.8 ± 10.7. Access site was reported in 540/638 patients, 9/12 studies, and consisted of 351 femoral, 154 apical, 20 subclavian, 12 aortic, and 3 carotid.

3.2 | Risk of bias assessment

The risk of selection and reporting biases were unclear in more than half of the included studies. The method of selecting patient patients for TAVR or the specific criteria they met to be eligible for this intervention was not reported in some of the included studies. All studies have reported at least outcomes at the end of the follow up period post valve replacement. Some studies failed to report outcomes according to Valve Academic Research Consortium-2 (VARC-2) criteria. Figure S1 summarizes the risk of bias for each individual study using the tool suggested by Murad et al.[12]

3.3 | Outcomes

Our main outcome of interest was all-cause mortality at 30 days. The incidence rate of patients who did not survive until the 30 days benchmark was 11% (95% confident interval (CI) from 7% to 16%; I^2 = 35%) (Figure 2). All-cause mortality at the end of the follow up period for all studies had incidence rate of 17% (95% CI from 11% to 24%; I^2 = 59%). Cardiovascular mortality at 30 days and at the end of follow-up period had incidence rates of 7% (95% CI, from 4% to 10%; I^2 = 35%) and 9% (95% CI, from 4% to 15%; I^2 = 67%), respectively. Incidence rate of cerebrovascular accidents, reported in nine studies, was 2% (95% CI, from 1% to 3%; I^2 = 0%). Device success was reported in eight studies with incidence rate of 84% (95% CI, from 75% to 91%; I^2 = 72%) and conversion to surgical aortic valve replacement had incidence rate of 2% (95% CI, from 0% to 3%; I^2 = 0%).

Other outcomes were extracted from the included studies, when reported, and are listed in Table 2.

3.4 | Baseline characteristics of patients that received first vs second device generations

We performed a subgroup analysis to compare outcomes between first vs second generation valves (Table 3) The mean age ranged from 73 ± 10 to 84 ± 2.6 in patients who had first generation valves implanted vs 68 to 79 ± 9 in patients with second generation valves implanted. The mean Logistic EuroScore ranged from 18.2 ± 8.9 to 33 in first generation compared to 18.5 ± 13.2 to 28.3 ± 17.1 in second generation valves. Logistic EuroScore II mean was 11.7 ± 12.9 in first generation valves compared to 8.9 ± 9.4 to 9.3 ± 6.4 in second generation valves. The mean STS score in second generation valves ranged from 5.4 ± 3.6 to 9.1 ± 3.6 compared to 7.6 ± 6.7 to 13.1 ± 2.0 in first generation valves.

The valve type was reported in all 638 patients underwent TAVR for NAVR. Out of these patients 44% received a first generation valve, CoreValve (265) and Sapien XT (14), and 56% had a second generation valve implanted, Acurate (5), Direct flow (52), Engager (7), Evolut R (55), JenaValve (138), J-Valve (45), lotus (12), Portico (3), and Sapien 3 (42).

3.5 | Outcomes of first vs second generation valves

Upon comparing all-cause mortality at 30 days between the two groups, the incidence rate was 15% (95% CI from 10% to 20%; I^2 = 10%) in first generation valves compared to 7% (95% CI from 3% to 13%; I^2 = 37%) in the second generation valves with subgroup interaction test P = 0.059.[32] The incidence rate of all-cause mortality at the end of the follow-up was found to be higher in first generation

TABLE 1 Main clinical, procedural and outcomes of included studies

Author, year	Patient (n)	Age (y)	Male (n)	Logistic euro-score (% ± SD)	Logistic euro-score II (% ± SD)	STS score (% ± SD)	Device	All cause mortality (30 d)	Device success	Pacemaker rate	Follow-up (mo)
Roy et al[21]	43	75.3 ± 8.8	20	26.9 ± 17.9	—	10.2 ± 5.3	Corevalve (43)	4	32	7	12
Koschyk et al[18]	10	68	7	26.1	—	—	JenaValve (10)	—	—	—	3-7
Rossi et al[20]	16	84 ± 2.6	9	33	—	—	CoreValve (16)	—	—	7	36
Schlingloff et al[23]	10	79 ± 9	6	28.3 ± 17.1	—	6.74 ± 11.1	JenaValve (10)	3	10	2	12
Seiffert et al[25]	31	73.8 ± 9.1	20	23.6 ± 14.5	9.3 ± 6.4	5.4 ± 3.6	JenaValve (31)	4	30	2	6
Testa et al[27]	26	73.0 ± 10.0	16	24.0 ± 8.0	—	13.1 ± 2.0	CoreValve (26)	6	20	3	12
Freker et al[17]	22	80.0 ± 5.6	12	25 ± 18.0	—	—	CoreValve (21) SapienXT (1)	5	18	6	12
Schofer et al[24]	11	74.7 ± 12.9	4	19.9 ± 7.1	—	8.84 ± 8.9	Direct flow (11)	1	11	1	1
Munoz-Garcia et al[19]	16	73.1 ± 17	—	18.2 ± 8.9	—	—	CoreValve (16)	1	—	—	36.5
Sawaya et al[22]	78	74 ± 10	46	20.4 ± 11.8	—	6.7 ± 4.8	CoreValve (33) Evolut R (5) JenaValve (23) direct flow (6) Lotus (6) SAPIEN XT (4) SAPIEN 3 (1)	11	55	12	1
Yoon et al[28]	331	74.4 ± 12.2	172	—	9.8 ± 10.7	6.7 ± 6.7	Sapien XT (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)	36	246	51	12
Zhu et al[29]	44	73.8 ± 5.6	31	25.4 ± 5.3	—	9.1 ± 3.6	J-valve (44)	1	—	2	6

Abbreviations: d, day; n, number; SD, standard deviation.

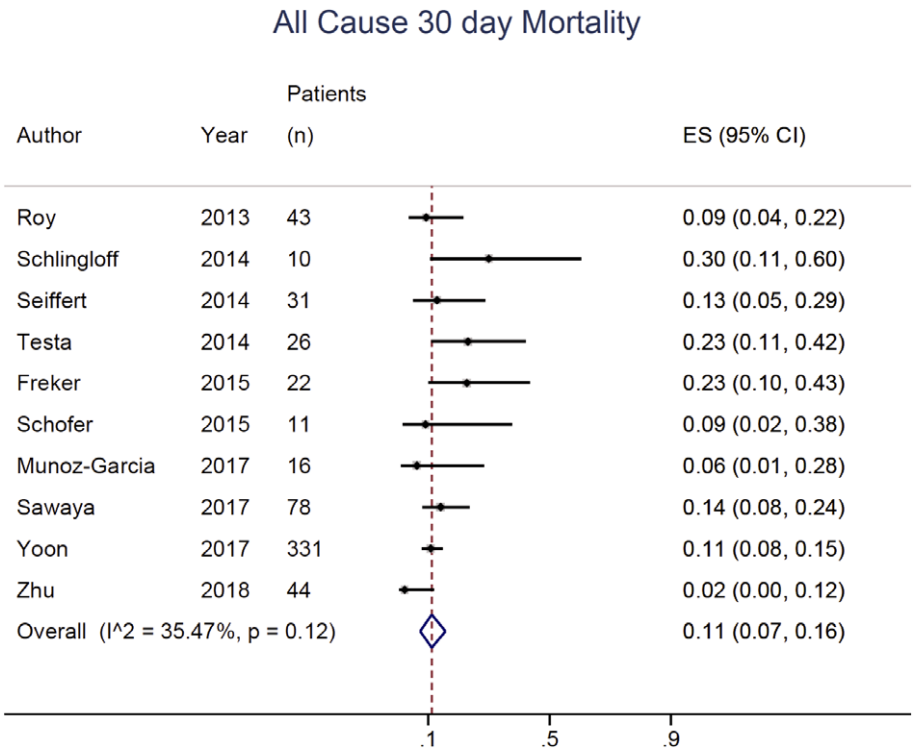

FIGURE 2 Forest plot with individual and pooled event rate for the all-cause mortality at 30 day

compared to second generation valves, 24% (95% CI from 19% to 29%; I^2 = 0.7%) vs 13% (95% CI from 5% to 22%; I^2 = 69%) with subgroup interaction analysis P = 0.052. While the difference between the incidence rates in the two groups was not statistically significant (P = 0.209) for cardiovascular mortality at 30 days, it was found to be significant at the end of follow-up period (P = 0.035) with incidence rates of 15% (95% CI from 8% to 24%; I^2 = 61%) vs 6% (95% CI from 3% to 10%; I^2 = 15%).

Conversion to SAVR was lower in second generation valves, 1% (95% CI from 0% to 4%; I^2 = 0%), compared to first generation valves, 2% (95% CI from 0% to 6%; I^2 = 17%), with interaction analysis P = 0.889. When comparing device success between first and second generation valves, we found that the incidence rate of success was higher in second generation, 92% (95% CI from 83% to 99%; I^2 = 67%) compared to first generation valves, 68% (95% CI from 59% to 77%; I^2 = 53%), with P value of 0.001. Comparisons of other outcomes of interest are listed in Table 3.

TABLE 2 Mata-analysis of TAVR in AR endpoints

Endpoints	No. of studies	No. of events	Incidence rate (95% CI)	I^2, %
All-cause mortality, 30 days	10	72/612	11% (7%-16%)	35.47
All cause mortality	12	130/638	17% (11%-24%)	59.17
Cardiovascular mortality, 30 days	6	45/553	7% (4%-10%)	34.61
Cardiovascular mortality	6	68/553	9%(4%-15%)	67.11
Cerebrovascular accidents	9	19/602	2% (1%-3%)	0
Acute kidney injury	6	49/549	9% (5%-14%)	55.01
Major bleeding	6	56/553	8% (3%-15%)	77.90
Major vascular complication	4	22/447	4% (2%-7%)	11.63
Myocardial infarction	5	0/160	0% (0%-1%)	0
Pacemaker implantation	10	93/612	14% (9%-20%)	45.70
Moderate or severe AR	5	54/484	14% (7%-21%)	61.06
> mild paravalvular leak	4	8/117	5% (0%-17%)	74.07
Second valve required	9	74/556	9% (4%-15%)	64.72
Conversion to SAVR	9	17/552	2% (0%-3%)	0
Device success	8	422/552	84% (75%-91%)	71.62

Abbreviation: CI, confidence interval.

4 | DISCUSSION

In the Euro Heart Survey on Valvular Heart Disease, AR comprises 13.3% of patients with single left-sided valve heart disease. The main three etiologies for aortic regurgitation were degenerative (50.3%), congenital (15.2%) and rheumatic (15.2%).[1] Despite that surgical aortic valve replacement remains the treatment of choice in patients with AR,[33–35] only 32% of patients with aortic regurgitation, as a single valve disease, underwent surgical replacement.[1] Comorbidities and advance age were the most frequent inhibitive factors from surgical intervention resulting in an annual mortality rate of 10% to 20%.[1,7]

Patients with predominant AR are not considered to be candidates for TAVR according to current guidelines.[33] However, advancement in valve technology and accumulated experiences lead to the experiment in the off-label use of TAVR to treat patients with valvular diseases other than severe aortic stenosis.[36]

Operative mortality in AR patients undergoing surgical valve replacement was reported at 3.4%.[1] Aortic stenosis patients included in

TABLE 3 Subgroups pooled proportion with interaction analysis

Endpoints	Early generation				New generation				Subgroup interaction analysis
	No. of studies	No. of events	Incidence rate (95% CI)	I^2, %	No. of studies	No. of events	Incidence rate (95% CI)	I^2, %	*P* value
All cause mortality, 30 days	6	40/263	15% (10%-20%)	9.95%	6	31/349	7% (3%-13%)	37.03%	0.059
All cause mortality	7	68/279	24% (19%-29%)	0.71%	7	60/359	13% (5%-22%)	68.60%	0.052
Cardiovascular mortality, 30 days	4	23/225	9% (4%-15%)	39.71%	4	20/328	6% (3%-9%)	0%	0.209
Cardiovascular mortality	4	40/225	15% (8%-24%)	61.04%	4	24/328	6% (3%-10%)	15.20%	0.035
Cerebrovascular accidents	6	6/263	1% (0%-4%)	0%	5	13/339	2% (0%-5%)	35.4%	0.921
Acute kidney injury	4	22/221	9% (5%-15%)	24.09%	4	27/328	9% (3%-18%)	73.14%	0.988
Major bleeding	4	31/225	12% (6%-20%)	53.27%	4	25/328	5% (0%-12%)	72.37%	0.095
Major vascular complication	4	12/194	5% (2%-9%)	0%	2	10/256	4% (1%-6%)	—	0.239
Myocardial infarction	3	0/85	0% (0%-2%)	—	2	0/75	0% (0%-3%)	—	0.894
Pacemaker implantation	5	40/226	19% (11%-29%)	52.4%	5	41/308	10% (5%-17%)	37.66%	0.109
Moderate or severe AR	5	45/231	19% (14%-24%)	0%	2	9/253	3% (1%-6%)	—	<0.001
> mild paravalvular leak	2	7/42	16% (6%-29%)	—	2	1/75	1% (0%-5%)	—	0.003
Second valve required	5	52/241	21% (16%-27%)	0%	6	34/315	9% (6%-13%)	0%	0.001
Conversion to SAVR	4	7/204	2% (0%-6%)	16.74%	6	10/318	1% (0%-4%)	0%	0.889
Device success	5	163/247	68% (59%-77%)	52.74%	5	258/305	92% (83%-99%)	66.81%	0.001

Abbreviation: CI, confidence interval.

PARTNER trial had all-cause mortality at 30 days of 3.4% with mean STS risk score reported at 11.4.[37] Our meta-analysis has shown that all-cause mortality at 30 days has an incidence rate of 11% with STS score ranging from 5.4 to 13.1%. The incidence rate of all-cause mortality at 30-days drops to 7% when using a second generation valve. The higher mortality in NAVR patients undergoing TAVR is speculated to be due to most patients included in this meta-analysis were deemed high surgical risk; had depressed LVEF, concomitant moderate or severe mitral regurgitation and dilated aortic diameter in AR patients.

The incidence rate of cerebrovascular accidents in our analysis was 2% with no significant difference between first and second generation valves, compared to 5% at 30 days and 7.8% at 1 year in PARTNER trial.[37] The rate of embolism, including transient ischemic attacks, post-surgical replacement in the Euro Heart Survey on Valvular Heart Disease was reported at 2.5%. The absence of aortic valve calcium and the rare need for valvuloplasty have potentially allowed for lower risk for thromboembolic events in AR patients undergoing TAVR.

Owing to its larger annular size, CoreValve was predominately used in first generation valves as most patients with pure AR have large annulus size. Second generation valves have offered features like self-positioning, repositionability, and fixation mechanism to improve anchoring, as seen in JenaValve and J-Valve clipping onto the native leaflets. These features have helped lowering the rate of second valve implantation, post implantation moderate or severe AR and paravalvular leak compared to what were observed when using a first generation valve.[18,24,30] Additionally, these features could explain the higher device success rate in second generation valves when compared to first generation, 92% vs 68%, respectively.

Finally, a systematic review and meta-analysis published in 2016 by Franzone et al[7] has summarized the available evidence up to 15 February 2016. There have been multiple studies published since then and by including them in our analysis we were able to include 638 patients, compared to 237 in the previous meta-analysis. We were able to perform a subgroup analysis to compare the outcomes between first and second generation valves and assess the quality of the evidence in this meta-analysis.

4.1 | Study limitations

Our systematic review and meta-analysis has multiple limitations. First, all the studies were observational single-arm studies without direct comparison to an alternative with an inherently high risk of bias. Second, the type of valves used varied in generation, design, features and implantation techniques, which could have led to heterogeneity among included studies. Third, the subgroup analysis results are based on indirect comparisons rather than direct head-to-head comparative studies and they should be interpreted with caution. Fourth, there was inconsistent reporting of baseline characteristics and outcomes between the studies. Fifth, longer follow up is needed to determine the durability of implanted valves and the rate of progression of trivial and mild post-implantation paravalvular leak or aortic regurgitation and their effect on the device outcomes. Sixth, our analysis has included different access sites without assessing outcomes per site. This was due to the included studies not reporting outcomes per access site and hence we were not able to perform a sensitivity analysis to test if this would affect the results, especially procedure related mortality rate. Seventh, up to our knowledge, the first published case report for TAVR in AR was in 2010[38] and there has been rapid evolution in the field over the past few years and growing operators experience which also might explain the improvement in outcomes with the second valve generation.[39] Finally, publication bias might have affected our report of published data as reports of negative outcomes or from small centers have higher likelihood of not being able to publish their results.[40]

5 | CONCLUSION

The present systematic review and meta-analysis is a comprehensive review of the literature with the largest number of patients with native aortic valve regurgitation undergoing TAVR. TAVR appears to be a viable option for high surgical risk or inoperable patients with NAVR.

CONFLICTS OF INTEREST

Dr. De Marchena is a local PI in Medtronic CoreValve trials. The other authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

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