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Clinical Outcomes After Transcatheter Aortic Valve Replacement Using Valve Academic Research Consortium Definitions

A Weighted Meta-Analysis of 3,519 Patients From 16 Studies

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Objectives This study sought to perform a weighted meta-analysis to determine the rates of major outcomes after transcatheter aortic valve replacement (TAVR) using Valve Academic Research Consortium (VARC) definitions and to evaluate their current use in the literature.

Background Recently, the published VARC definitions have helped to add uniformity to reporting outcomes after TAVR.

Methods A comprehensive search of multiple electronic databases from January 1, 2011, through October 12, 2011, was conducted using predefined criteria. We included studies reporting at least 1 outcome using VARC definitions.

Results A total of 16 studies including 3,519 patients met inclusion criteria and were included in the analysis. The pooled estimate rates of outcomes were determined according to VARC's definitions: device success, 92.1% (95% confidence interval [CI]: 88.7% to 95.5%); all-cause 30-day mortality, 7.8% (95% CI: 5.5% to 11.1%); myocardial infarction, 1.1% (95% CI: 0.2% to 2.0%); acute kidney injury stage II/III, 7.5% (95% CI: 5.1% to 11.4%); life-threatening bleeding, 15.6% (95% CI: 11.7% to 20.7%); major vascular complications, 11.9% (95% CI: 8.6% to 16.4%); major stroke, 3.2% (95% CI: 2.1% to 4.8%); and new permanent pacemaker implantation, 13.9% (95% CI: 10.6% to 18.9%). Medtronic CoreValve prosthesis use was associated with a significant higher rate of new permanent pacemaker implantation compared with the Edwards prosthesis (28.9% [95% CI: 23.0% to 36.0%] vs. 4.9% [95% CI: 3.9% to 6.2%], $p < 0.0001$). The 30-day safety composite endpoint rate was 32.7% (95% CI: 27.5% to 38.8%) and the 1-year total mortality rate was 22.1% (95% CI: 17.9% to 26.9%).

Conclusions VARC definitions have already been used by the TAVR clinical research community, establishing a new standard for reporting clinical outcomes. Future revisions of the VARC definitions are needed based on evolving TAVR clinical experiences. (J Am Coll Cardiol 2012;59:2317–26) © 2012 by the American College of Cardiology Foundation

Since the first transcatheter aortic valve replacement (TAVR) case in 2002 (1), >35,000 transcatheter aortic valve procedures have been performed worldwide. This has resulted in a substantial number of published case series, registries, and, lately, randomized controlled trials (2–13). Diversity in technique and study devices as well as disparity in the learning curve may potentially explain some of the discrepancies in outcomes that have been reported. However, the absence of standardized definitions may be the most significant factor to explain inconsistencies in the early literature. The recent publication of the Valve Academic Research Consortium (VARC) definitions has provided uniformity in outcome reporting after TAVR, which should ensure a more balanced inter-

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Abbreviations and Acronyms

AKI = acute kidney injury
AVA = aortic valve area
CI = confidence interval
MI = myocardial infarction
TAVR = transcatheter aortic valve replacement
TF = transfemoral
VARC = Valve Academic Research Consortium

pretation of clinical results (14). Currently, there is a growing body of literature applying these new VARC definitions. Therefore, we sought to perform a meta-analysis of all published studies reporting outcomes using VARC definitions after TAVR to evaluate current acceptance and use patterns and to determine whether future revisions are warranted.

Methods

Studies and endpoint definitions. All studies reporting outcomes using at least 1 VARC definition from January 1, 2011, to October 12, 2011, were selected and included in the current analysis. Only outcomes properly reported conforming to VARC definitions (clear mention in the paper) were included in the pooled analysis. Intrahospital 30-day and 1-year outcomes are reported conforming to the VARC definitions previously described (Online Appendix) (14).

Data source and study selection. Relevant studies were identified through PubMed, Cochrane, and EMBASE database searches, using the key words *trans-catheter aortic valve implantation*, *trans-catheter aortic valve replacement*, *percutaneous aortic valve implantation*, *percutaneous aortic valve replacement*, *transfemoral aortic valve implantation*, *transapical aortic valve implantation*, *transarterial aortic valve implantation*, *direct aortic valve implantation*, *aortic stenosis*, and *valve academic research consortium*. Two investigators (P.G., S.J.H.) independently reviewed the titles, abstracts, and studies to determine whether they met the inclusion criteria. Conflicts between reviewers were resolved by consensus.

Statistical analysis. Outcome rates were first presented as the minimum and maximum rates reported among selected articles. Cumulative rates for each VARC outcome were then obtained from a pooled analysis among selected studies. Given the high heterogeneity among reported rates, summary rate estimates and 95% confidence intervals (CIs) were obtained using a random-effects model, as described by DerSimonian and Laird (15). The random-effects model was chosen for its conservative summary estimate and incorporating both between and within study variance. To assess heterogeneity across trials, we used the Cochrane Q statistic (a p value ≤ 0.1 was considered significant). The I^2 statistic was also used to measure the consistency among studies with values of 25%, 50%, and 75% showing, respectively, low, moderate, and high heterogeneity.

Data collection, study selection, processing of the data, and reporting of the results were performed according to accepted principles related to systematic review and meta-analysis (16–19). The Mann-Whitney test was used to compare proportions, with a significance level of $p < 0.05$. Statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, North Carolina).

Results

Of 482 potentially relevant articles initially screened, 16 unique studies with 3,519 patients met the inclusion criteria and were included in the final pooled analysis (10,20–34) (Fig. 1). A total of 1,903 Edwards Lifesciences (Irvine, California) prosthesis (54.1%) and 1,186 Medtronic CoreValve (Minneapolis, Minnesota) prosthesis (33.7%) implantations were identified. The type of implanted device was not clearly reported by authors in 430 patients (12.2%). Basic study characteristics are shown in Table 1. The 30-day Society of Thoracic Surgeons score and logistic EuroSCORE were 8.7% (95% CI: 7.0% to 10.3%) and 22.8% (95% CI: 20.3% to 25.3%), respectively. Table 2 shows the proportion of articles that appropriately used and reported outcomes according to VARC definitions.

In-hospital and 30-day follow-up outcomes. Overall device success reported in the literature ranged from 80% to 100%, with a pooled estimate rate of 92.1% (95% CI: 88.7% to 95.5%) (Table 3). The most frequent modes of failure were moderate to severe aortic regurgitation (7.4%; 95% CI: 4.6% to 10.2%), aortic valve area (AVA) <1.2 cm^2 (4.8%; 95% CI: 3.0% to 6.6%), and failure of delivery or implantation of the valve in the correct position (3.5%; 95% CI: 2.2% to 5.6%) (Table 4).

All-cause 30-day mortality rates were reported between 1.7% and 14.3%, with a pooled estimate of 7.8% (95% CI: 5.5% to 11.1%). Cardiovascular death accounted for most of the 30-day mortality after TAVR, with a pooled estimate rate of 5.6% (95% CI: 3.7% to 8.3%) (Table 3, Fig. 2).

Myocardial infarction (MI) was reported as a complication of TAVR in 0% to 5.6% of studies, with a pooled estimate rate 1.1% (95% CI: 0.2% to 2.0%). Acute kidney injury (AKI) at all stages was a frequent complication, with a pooled estimate rate of 20.4% (95% CI: 16.2% to 25.8%). However, most of the AKI was at stage I (13.3%; 95% CI: 9.8% to 18.0%), whereas the AKI at stages II/III (significant AKI according to VARC criteria) was less frequent (7.5%; 95% CI: 5.1% to 11.4%).

Life-threatening bleeding and major vascular complications occurred at a pooled estimate rate of 15.6% (95% CI: 11.7% to 20.7%) and 11.9% (95% CI: 8.6% to 16.4%). All neurologic events (all strokes and transient ischemic attacks) were reported from 1.3% to 21.0% and occurred at a pooled estimate rate of 5.7% (95% CI: 3.7% to 8.9%), and all strokes (major and minor) were reported from 1.0% to 6.8%, with a pooled estimate rate of 4.0% (95% CI: 2.4% to 6.3%). The reported rates for a new permanent pacemaker implantation after TAVR range from 3.4% to 50%, with a pooled estimate rate of 13.9% (95% CI: 10.6% to 18.9%). Medtronic CoreValve prosthesis use was associated with a significantly higher rate of new permanent pacemaker im-

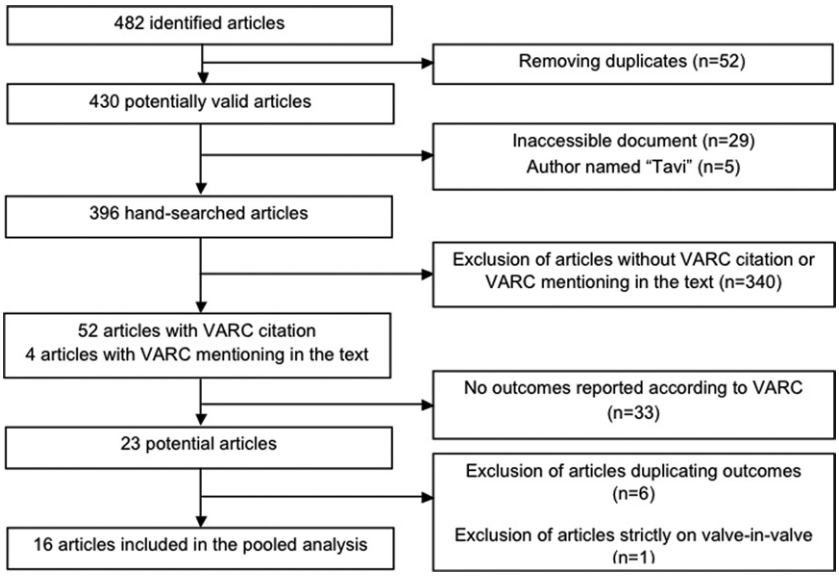

Figure 1 **Flow Diagram of the Study**

Among the 482 potentially relevant articles, 16 were included in the final pooled analysis. VARC = Valve Academic Research Consortium.

plantation compared with the Edwards prosthesis (28.9% [95% CI: 23.0% to 36.0%] vs. 4.9% [95% CI: 3.9% to 6.2%], $p < 0.0001$). Device-related outcomes and other complications are shown in Table 4.

Composite endpoint and 1-year follow-up outcomes. The 30-day safety composite endpoint was correctly reported in 6 studies (37.5%) (Table 2), with a pooled estimate rate of 32.7% (95% CI: 27.5% to 38.8%). The 1-year safety composite endpoint was reported in only 2 studies (12.5%), with a pooled estimate rate of 71.1% (95% CI: 65.6% to 76.0%). One-year all-cause mortality and cardiovascular mortality rates were reported in 7 studies (43.8%) and 4 studies (25.0%), respectively, with an associated pooled estimate rate of 22.1% (95% CI: 17.9% to 26.9%) and 14.4% (95% CI: 10.6% to 19.5%).

Discussion

The current report, which includes 3,519 patients from 16 unique studies, is the first pooled analysis reporting outcomes after TAVR according to the recently proposed VARC definitions. The main results of the current study are as follows: 1) VARC definitions have already been widely used by the TAVR community since their introduction earlier this year; 2) VARC definitions have established an important uniformity for outcomes after TAVR; 3) the pooled estimate outcomes after TAVR reported in this meta-analysis represent a new standard of quality for TAVR clinical research; 4) specific issues in the first version of the VARC definitions were identified; and 5) refinement and modifications of the current VARC definitions may be needed and are in progress.

VARC in the current literature. Since January 2011 (14), VARC definitions have been rapidly incorporated into clinical and research practice (Fig. 3). Although most of the VARC-related endpoints have been reported in high proportion among selected studies, the 30-day and 1-year composite endpoints and the 1-year mortality rates have been reported by only a few authors (Table 2). The relative complexity of the 2 hierarchical composite endpoints, the absence of all data fields required to compute the endpoints, and inadequate follow-up may explain the low reporting rates.

Not surprisingly, device-related outcomes, such as coronary obstruction, ventricular septal defect, annulus rupture, aortic rupture, aortic dissection, and left ventricle perforation, occurring less frequently after TAVR, were not systematically reported by authors (Table 4). However, considering that this technique is in its infancy, systematic reports of such complications (present or not) are strongly recommended to provide a complete understanding of the risks associated with TAVR procedures.

In-hospital, 30-day, and 1-year follow-up outcomes. The device success rate of the current pooled analysis appears to be lower than previously reported. This difference is mostly explained by the fact that VARC uses stricter definitions, with echocardiography-derived criteria not used before, such as AVA <1.2 cm^2 and residual moderate to severe prosthetic valve aortic regurgitation. Indeed, Gurvitch et al. (22) reported a relatively low success rate of 80% using VARC definitions and explained that the main reasons for "device failure" were a calculated AVA of <1.2 cm^2, a criterion that may not be reasonable for either a small

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Table 1 Selected Publications Reporting at Least 1 VARC Criterion in TAVR Population

First Author (Ref. #)	n	Approach	Device	Mean STS, %	Mean EuroScore, %	Mean Age, yrs	Female, n (%)	Mean Gradient, mm Hg	AVA, cm^2	NYHA Functional Class III/IV, %
D'Onofrio et al. (10)	504	TA	SAPIEN	11.0	26.3	81.2 ± 6.5	306 (60.7)	47.4 ± 15.4	0.53 ± 0.18	419 (83)
Buchanan et al. (20)	305	TF/SC/TAo	Mix*	8.6	24.2	79.4 ± 7.3	146 (48)	—	Inclusion <1.0	204 (67)
Grube et al. (21)	186	TF	CoreValve	—	23.4	81.4 ± 6.4†	104 (56)	47.1 ± 15.7†	0.7 ± 0.2†	146 (78)
Gurvitch et al. (22)	310	TF/TA	SAPIEN	9.4	—	82.2 ± 8.1	—	—	—	273 (88)
Hayashida et al. (23)	127	TF	100 SAPIEN, 27 CoreValve	—	25.8	83.3 ± 5.9	65 (51)	—	Inclusion ≤0.8	113 (89)
Lange et al. (24)	412	TF, TA, SC, TAo	129 SAPIEN, 283 CoreValve	5.6	20.2	80.3 ± 7.2	258 (63)	47.9 ± 16.3	0.67 ± 0.20	400 (97)
Mussardo et al. (25)	120	TF	SAPIEN and XT	7.2	24.9	80.2 ± 8.1	60 (50)	55.6 ± 17.4	Inclusion <1.0	84 (70)
Nuis et al. (26)	165	TF/SC	CoreValve	4.6	13.1‡	81 ± 7	82 (55)	46 ± 17	0.64 ± 0.20	118 (79)
Stahli et al. (27)	130	TF/TA	50 SAPIEN, 80 CoreValve	—	22.7	83 (78.8–86)	66 (51)	49 (38–57)	0.6 (0.5–0.7)	94 (72)
Wenaweser et al. (28)	256	TF/TA/SC	92 SAPIEN, 164 CoreValve	6.4†	24.8†	82.1 ± 6.0†	144 (56)	44.4 ± 17.0†	0.7 ± 0.2	2.6 ± 0.8
Ussia et al. (29)	143	TF/SC	7 SAPIEN, 36 CoreValve	7.9	23.4	81.0 ± 6.0	85 (59)	56.6 ± 17.4	0.59 ± 0.19	92 (64)
Bagur et al. (30)	64	TF/TA	SAPIEN	7.5	21.0	80 ± 8	21 (33)	43 ± 17	0.60 ± 0.15	64 (100)
Dehédin et al. (31)	125	TF/SC	Mix*	13.0	24.0	83 (78–87)	57 (46)	47 (39–61)	0.39 (0.31–0.46)	103 (82)
Gotzmann et al. (32)	145	TF/SC	CoreValve	—	21.0	79.1 ± 6.4	—	47.8 ± 13.6	Inclusion ≤1.0	117 (96)
Leon et al. (33)	179	TF	SAPIEN	11.2	26.4	83.1 ± 8.6	97 (54)	44.5 ± 15.7	0.6 ± 0.2	165 (92)
Smith et al. (34)	348	TF/TA	SAPIEN	11.8	29.3	83.6 ± 6.8	147 (42)	42.7 ± 14.6	0.7 ± 0.2	328 (94)
Pooled estimate rate (95% CI)	3,519	—	—	8.7 (7.0–10.3)	22.8 (20.3–25.3)	81.5 (80.8–82.2)	52.0 (46.4–57.6)	47.6 (45.7–49.5)	0.61 (0.54–0.69)	82.0 (77.5–86.5)

Values are mean ± SD or ranges. *The rate of SAPIEN and CoreValve implantation was not reported. †Mean was reported from 2 groups. ‡Median EuroSCORE. The mean reported here is calculated as $[(\text{mean} \cdot n_1) + (\text{mean} \cdot n_2)]/(n_1 + n_2)$.
AVA = aortic valve area; CI = confidence interval; NYHA = New York Heart Association; SC = subclavian; STS = Society of Thoracic Surgeons; TA = transaortic; TAo = transaortic; TAVR = transcatheter aortic valve replacement; TF = transfemoral; VARC = Valve Academic Research Consortium.

Table 2 Proportion of Studies Reporting Outcomes Using Appropriate VARC Definitions

Device success	10/16 (62.5)
30-day mortality	15/16 (93.8)
30-day cardiovascular mortality	12/16 (75.0)
1-year mortality	7/16 (43.8)
1-year cardiovascular mortality	4/16 (25.0)
Myocardial infarction ≤72 h	14/16 (87.5)
Acute kidney injury	9/16 (56.3)
Bleeding	7/16 (43.8)
Transfusions	7/16 (43.8)
Vascular complications	14/16 (87.5)
Stroke at 30 days	14/16 (87.5)
Permanent pacemaker	14/16 (87.5)
Composite endpoint: safety, 30 days	6/16 (37.5)
Composite endpoint: efficacy, 1 year	2/16 (12.5)
Failure to deliver or implantation of the valve in the correct position	10/16 (62.5)
Multiple valves implanted	9/16 (56.3)
Aortic valve area ≤1.2 cm^2	2/16 (12.5)
Mean gradient ≥20 mm Hg	4/16 (25.0)
Moderate to severe aortic regurgitation	11/16 (68.8)
Valve embolization	10/16 (62.5)
Valve in valve	8/16 (50.0)
Conversion to open surgery	10/16 (62.5)
Repeat procedure for valve dysfunction	8/16 (50.0)
Unplanned cardiopulmonary bypass use	3/16 (18.8)
Coronary obstruction	7/16 (43.8)
Left ventricular perforation	3/16 (18.8)
Tamponade	6/16 (37.5)
Annulus rupture	3/16 (18.8)
Aortic dissection	2/16 (12.5)
Aortic rupture	2/16 (12.5)
Endocarditis	3/16 (18.8)
Valve thrombosis	2/16 (12.5)
Left ventricular outflow tract rupture	1/16 (6.3)
Ventral septal defect	1/16 (6.3)

Values n/N (%).
VARC = Valve Academic Research Consortium.

annulus or low body weight patients. Despite this low success rate, clinical and symptomatic improvement in these patients was dramatic, with 97% of patients with procedural AVA <1.2 cm^2 improving to New York Heart Association functional class I or II. Ikeda et al. (35) also reported some concerns with the 1.2 cm^2 criterion for device success, especially in small body size populations, such as Asian patients, in whom an indexed valve area may be more appropriate. Until now, no evidence has been shown that patients with an AVA <1.2 cm^2 after TAVR have a worse outcome. Conversely, Ewe et al. (36) recently showed that patients with prosthesis–patient mismatch after TAVR, defined as an indexed effective orifice area ≤0.85 cm^2/m^2, had a slower and smaller reduction in mean transaortic gradient, limited left ventricular mass regression, and a higher proportion of patients not improving in New York Heart Association functional class compared with patients without mismatch. Moreover, no standardized method for

Table 3 30-Day and 1-Year VARC Outcomes After TAVR

Outcome	Reported Rate Min, Max, %	Cumulative Rate	I^2, %	Cochran's Q	p Value Heterogeneity	Pooled Estimate Rate, %	95% CI
Device success	80.0, 100.0	1,748/1,899	93.2	133.2	<0.0001	92.1	88.7–95.5
30-day mortality	1.7, 14.3	258/3,465	74.1	61.7	<0.0001	7.8	5.5–11.1
30-day CV mortality	1.7, 11.5	142/2,645	72.5	40.0	<0.0001	5.6	3.7–8.3
1-year mortality	15.3, 30.7	336/1,530	78.3	27.6	0.0001	22.1	17.9–26.9
1-year CV mortality	14.3, 19.6	113/800	85.2	20.2	0.0002	14.4	10.6–19.5
MI ≤72 h	0.0, 5.6	34/3,018	88.9	117.8	<0.0001	1.1	0.2–2.0
AKI							
I	3.2, 24.6	149/1,150	91.1	45.1	<0.0001	13.3	9.8–18.0
II	0.8, 5.3	29/1,150	64.9	11.3	0.02	2.7	1.5–5.3
III	1.0, 10.2	98/1,929	73.0	25.9	0.0005	5.3	3.5–8.2
II-III	3.0, 15.0	93/1,275	80.9	26.2	<0.0001	7.5	5.1–11.4
I-II-III	6.5, 34.1	232/1,150	94.8	76.6	<0.0001	20.4	16.2–25.8
Bleeding							
Life threatening	7.0, 25.9	207/1,350	86.1	43.2	<0.0001	15.6	11.7–20.7
Major	2.9, 47.0	298/1,363	96.6	177.2	<0.0001	22.3	17.8–28.3
Minor	3.0, 16.0	95/987	81.9	22.1	0.0002	9.9	6.9–14.3
All	26.8, 77.0	408/987	98.4	257.6	<0.0001	41.4	35.5–47.6
Transfusion ≥1 U	6.3, 80.0	386/906	85.3	34.0	<0.0001	42.6	19.8–62.4
Vascular complications							
Major	5.0, 23.3	282/2,417	81.3	64.1	<0.0001	11.9	8.6–16.4
Minor	5.6, 28.3	203/2,142	88.8	88.9	<0.0001	9.7	6.7–14.0
All	9.5, 51.6	511/2,740	92.6	176.6	<0.0001	18.8	14.5–24.3
Stroke 30-day							
Major	0.8, 9.0	84/2,730	70.7	37.5	<0.0001	3.2	2.1–4.8
Minor	0.0, 1.7	12/1,450	54.6	15.4	0.03	1.0	0.5–1.9
TIA	0.0, 12.0	18/1,826	83.4	42.1	<0.0001	1.2	0.0–2.3
Major + minor	1.0, 6.8	68/1,706	67.4	18.4	0.005	4.0	2.4–6.3
All	1.3, 21.0	103/1,892	72.8	29.3	0.0003	5.7	3.7–8.9
PPM	3.4, 50.0	396/2,914	95.9	323.2	<0.0001	13.9	10.6–18.9
Composite endpoint: safety at 30 days	17.0, 61.8	420/1,286	96.6	146.6	<0.0001	32.7	27.5–38.8
Composite endpoint: efficacy at 1 year	70.2, 72.2	209/294	0.0	0.3	0.58	71.1	65.6–76.0

AKI = acute kidney injury; CV = cardiovascular; Max = maximum; MI = myocardial infarction; Min = minimum; PPM = permanent pacemaker; TIA = transient ischemic attack; other abbreviations as in Table 1.

echocardiographic measurement of the left ventricular outflow tract diameter after TAVR has been validated. Therefore, AVA may vary considerably, depending on where the left ventricular outflow tract measurement is performed after TAVR (37). These issues will be addressed in future versions of VARC definitions.

The 30-day mortality rate in the current report is similar to the mortality rate reported in the early registries (4,5,7,8), reflecting the use of first-generation devices, early experience of operators, and a population of patients at high or prohibitive risk of surgery. Interestingly, the 30-day mortality rate pooled estimate of our report (7.8%; 95% CI: 5.5% to 11.1%) is similar to the 30-day predicted mortality rate by the Society of Thoracic Surgeons score (8.7%; 95% CI: 7.0% to 10.3%). Considering that the population of the current report represents a mix of several approaches (transapical, transfemoral [TF], subclavian) and different devices, this finding underlines the high-risk profile of the patients included in this meta-analysis.

The cardiovascular mortality rate, both at 30 days and 1 year, represents >65% of the total mortality in the present study. Although such results might be expected in a population of high-risk patients who underwent a major cardiac procedure, some authors have challenged the clinical relevance to systematically attribute unknown death to cardiovascular death and, consequently, its relationship to the device and underlying aortic pathology (38). In fact, according to the current VARC definitions, unknown deaths should be considered as cardiovascular in origin. Although VARC suggests the use of all-cause mortality as the primary endpoint of choice and cardiovascular mortality as a secondary endpoint, ascertainment and adjudication of cardiovascular death remain a challenge.

Periprocedural MI (≤72 h after TAVR) occurred at a rate of 1.1% (95% CI: 0.2% to 2.0%) after TAVR in the current analysis. Although coronary obstruction is a potential cause, other factors such as global ischemia due to hypotension, rapid pacing, microembolism induced by device delivery or implantation, myocardial tissue compression by the device expansion, and direct trauma of the apex during transapical access must also be considered. VARC proposed the use of a relatively conservative definition for MI, for which

Table 4 VARC: Prosthesis-Related Complications

Outcomes	Reported Rate, Min, Max, %	Cumulative Rate	I^2, %	Cochran's Q	p Value Heterogeneity	Pooled Estimate Rate, %	95% CI
Failure to deliver or implantation of the valve in the correct position	0.8, 5.6	79/2,383	53.8	19.5	0.02	3.5	2.2–5.6
Multiple valve implanted	0.6, 4.1	38/2,208	62.1	21.1	0.0069	1.8	1.1–3.1
AVA ≤1.2 cm^2	0.0, 9.7	30/814	98.2	55.0	<0.0001	4.8	3.0–6.6
Mean gradient >20 mm Hg	0.0, 2.9	11/1,064	85.2	20.2	0.0002	1.0	0.0–2.1
Moderate to severe AR	0.0, 30.0	167/2,601	95.3	213.5	<0.0001	7.4	4.6–10.2
Valve embolization	0.0, 5.6	45/2,329	85.9	63.6	<0.0001	1.7	0.2–3.3
Valve in valve	0.0, 9.0	43/2,014	80.9	36.7	<0.0001	2.3	1.3–4.5
Conversion to open surgery	0.0, 5.6	23/2,189	84.1	56.7	<0.0001	1.3	0.0–2.6
Repeat procedure for valve dysfunction	0.0, 4.1	31/1,920	51.7	14.5	0.04	1.8	1.0–3.7
Unplanned CPB	0.0, 1.9	15/1,081	78.0	9.1	0.01	1.3	0.3–2.2
Coronary obstruction	0.0, 3.0	13/1,984	54.1	13.1	0.04	0.7	0.4–1.1
LV perforation	0.2, 0.8	3/702	0.0	0.6	0.43	0.4	0.1–1.5
Tamponade	0.6, 4.6	29/1,097	74.4	19.5	0.0015	2.7	1.7–4.2
Annulus rupture	0.3, 0.8	3/560	0.0	0.5	0.77	0.5	0.2–1.7
Aortic rupture	0.8, 1.0	5/539	0.0	0.1	0.82	0.9	0.4–2.2
Aortic dissection	0.9, 1.7	5/468	0.0	0.7	0.40	1.1	0.4–2.5
Endocarditis	0.3, 1.1	5/832	0.0	1.9	0.39	0.6	0.2–1.4
Valve thrombosis	0.0, 2.7	2/380	93.5	15.3	<0.0001	1.2	0.3–2.2
LVOT rupture	0.6	1/165	—	—	—	0.6	0.1–4.3
VSD	0.6	1/165	—	—	—	0.6	0.1–4.3

AR = aortic regurgitation; AVA = aortic valve area; CPB = cardiopulmonary bypass; LV = left ventricular; LVOT = left ventricular outflow tract; VSD = ventricular septal defect; other abbreviations as in Tables 1 and 3.

the recommended biomarker is the creatine kinase-myocardial band isoenzyme, and not troponin and clinical signs of infarction. This may explain the low rate of MI reported after TAVR. Conversely, Rodes-Cabau et al. (39) were the first to report the incidence and implication of troponin increase after TAVR, in which 97% of TF patients and 100% of the transapical patients showed some degree of troponin increase. After multivariate analysis, a greater magnitude of troponin T increase (15 times the upper normal range) was shown to be an independent predictor of mortality at a mean follow-up of 9 months as well as a factor correlated with lesser degrees of improvement in left ventricular ejection fraction. However, the inclusion of troponin as a criterion for MI after TAVR is still a matter of debate, and more data and validation are needed.

AKI was reported according to the VARC definition in 9 studies (56.3%). However, less than one-third of the authors

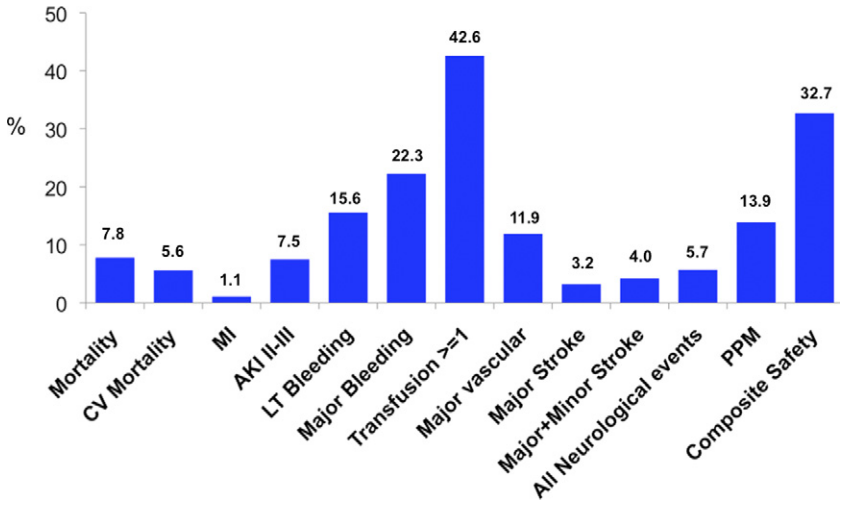

Figure 2 30-Day Event Rates of Major VARC-Related Outcomes

AKI = acute kidney injury; CV = cardiovascular; LT = life-threatening; MI = myocardial infarction ≤72 h after procedure; PPM = permanent pacemaker; VARC = Valve Academic Research Consortium.

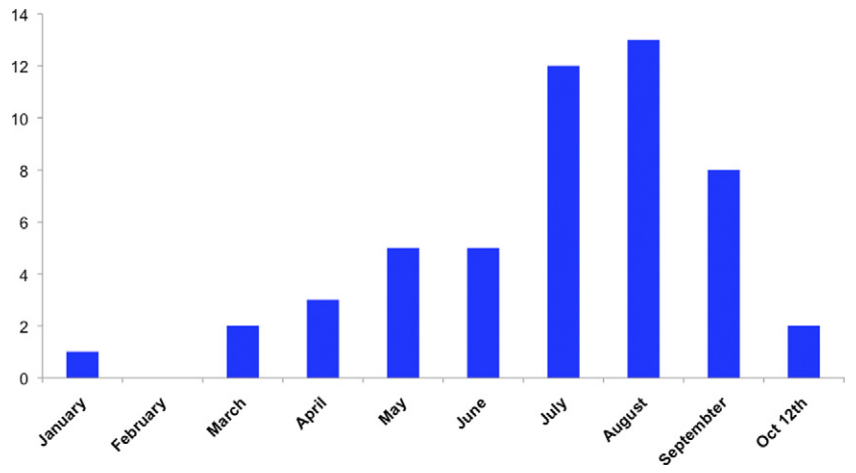

Figure 3 **VARC-Related Publications Since Original Publication in January 2011**

Early after its publication in January 2011, VARC definitions were already in use and incorporated into clinical research, showing acceptance by the TAVR community. TAVR = transcatheter aortic valve replacement; VARC = Valve Academic Research Consortium.

appropriately reported AKI stage II or III, which is the proposed stage to be reported according to VARC definitions. Most of the AKIs were stage I, and the frequency of stage II/III was 7.5%. Noticeably, the rate of AKI stage I reported in the literature was as high as 24.6% in 1 study (Table 3). This may be explained by the low threshold chosen by the first VARC committee, in which any increase of >0.3 mg/dl is considered AKI stage I.

Life-threatening and major bleeding after TAVR occurred in 15.6% (95% CI: 11.7% to 20.7%) and 22.3% (95% CI: 17.8% to 28.3%), respectively (Table 3). These rates appear higher compared with previous reports. However, bleeding complications have been inconsistently reported and likely even underreported in the early literature (5,11,40,41). Among the 16 studies in our analysis, transfusion rates were reported by 7 authors (43.8%), with a pooled estimate rate of needing 1 or more transfusions after TAVR of 42.6% (95% CI: 19.8% to 62.4%). VARC strongly recommended reporting the rate of transfusions after TAVR. However, Gurvitch et al. (22) previously reported that a significant proportion of patients received blood transfusions without an obvious source of bleeding, in whom anemia was pre-existent or the cause of the hemoglobin decrease was unclear. Généreux et al. (42) also reported that among the 25% of patients who needed red blood cells after TAVR, 57% of the transfusions given were not directly related to the procedure (gastrointestinal bleeding, genitourinary bleeding, or no obvious source). Such findings may warrant a possible separate category in future revised VARC criteria so that a clear distinction can be made between procedure-related blood loss and nonprocedural bleeding.

Major vascular complications occurred in 11.9% (95% CI: 8.6% to 16.4) of patients in the current study. Before VARC definitions, vascular complications were inconsistently reported, and when they were, it was mostly reported by site and according to the investigator definitions. Moreover, classification of severity was rarely done. Piazza et al. (5) reported their early data using the TF approach with the Medtronic CoreValve device with a low rate (1.9%) of vascular complications, whereas Eltchaninoff et al. (11) reported a much higher rate (7.5%) using the same device and the same access route. Similarly, early studies using the Edwards device via the TF route reported 30-day vascular complication rates ranging from 6.3% (11) to 22.9% (8). The TA approach has been associated with a lower rate of vascular complications than the TF route (8,40,43).

Moreover, further clarification of the current VARC criteria may be needed because the TF approach is moving toward a full-percutaneous procedure. Also, inclusion of "new" alternative access sites, such as the subclavian-axillary artery (41,44,45) and direct transaortic access (46), should be considered in the elaboration of new definitions.

Stroke has emerged as one of the major foci of attention after TAVR. The major stroke rate reported in our study is 3.2% (95% CI: 2.1% to 4.8%). Interestingly, minor strokes and transient ischemic attacks were less frequently reported, underlying the difficulty to adequately identify such post-procedural events, especially in a population of elderly sick patients.

Before VARC definitions, the 30-day stroke rates had been variably reported, ranging from 1.5% (40) to 4.2% (11) for the Edwards device and 0% (11,47) to 10% (4) for the Medtronic device. These were mostly self- or site-reported results and nonadjudicated events. VARC emphasizes the necessity to confirm the diagnosis by neuroimaging technique (computed tomography and/or magnetic resonance imaging) and to classify the severity of stroke using conventional neurological assessment tools. VARC recommended

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the modified Rankin Scale score at 30 and 90 days for the stroke assessment. However, Ikeda et al. (35) suggested that the National Institutes of Health Stroke Scale should also be used, and the time point of the evaluations should also cover event onset (acute phase). Given the different level of invasiveness and pattern of recovery after surgical aortic valve replacement and TAVR, assessment and comparison of stroke rates between these 2 approaches has become challenging. Early recognition of events, use of an appropriate scoring system (National Institutes of Health Stroke Scale and the modified Rankin Scale), neuroimaging tools, and adjudication by a neurology specialist will provide a more accurate comparison of stroke frequency between different therapies.

The permanent pacemaker insertion rate in the current analysis is 13.9% (95% CI: 10.6% to 18.9%), resulting from the pooling of data including both devices (Medtronic CoreValve system and Edwards Lifesciences device). It is generally accepted that the self-expandable CoreValve, because of its higher and longer lasting radial force as well as the deeper implantation site in the left ventricular outflow tract, has a higher rate of pacemaker requirement than the Edwards valve. Current evidence shows that ~20% to 30% of patients after CoreValve implantation and 3% to 5% of patients after Edwards valve placement will require a new permanent pacemaker. An additional analysis was performed, pooling data from centers where TAVR were done with 1 type of device, showing similar results (Edwards valve, 4.9% [95% CI: 3.9% to 6.2%] vs. CoreValve, 28.9% [95% CI: 23.0% to 36.0%], $p < 0.0001$). However, differences between operator and institution relating to the threshold for permanent pacemaker insertion must also be considered.

Another important focus has been the higher incidence of paravalvular leak after TAVR compared with surgical aortic valve replacement. The pooled estimate for residual moderate or severe aortic regurgitation after TAVR was 7.4% (95% CI: 4.6% to 10.2%) in this report. Currently, however, there are no standardized methods to grade paravalvular regurgitation after TAVR. Whereas the current VARC definition suggests criteria such as jet density, jet width, and jet deceleration time for central aortic regurgitation, paravalvular leak assessment is based on the percentage of the circumferential extent of paraprosthetic aortic regurgitation, which has not been validated in a TAVR population. Uniformity and a standardized echocardiographic definition for paravalvular leak after TAVR is mandatory for the next version of VARC definitions.

As mentioned earlier, many authors have not reported composite endpoints. However, among those reporting the 30-day composite endpoint, disparity seems to exist, with rates ranging from 17.8% to 68%. Although differences in population risk profiles may explain a portion of this discrepancy, correct interpretation of the hierarchical order and use of proper echocardiographic findings are mandatory with this composite endpoint.

The 1-year safety endpoint rate was reported by 2 studies and occurred in ~70% of patients. The high rate of this endpoint is explained by the inclusion of recurrent heart failure requiring admission as a component of this outcome. Although important, this component can introduce "background noise," reflecting more on the presence of suboptimal heart failure management, multiple comorbidities, or different severities of left ventricular depression, despite a perfectly functioning valve. In a recent comment, Ikeda et al. (35) also underlined the possible bias by each country's medical care setting, where thresholds for hospitalization would vary from country to country, according to local culture.

Study limitations. Several important limitations of the present analysis warrant discussion. This report represents a study-level pooled analysis of 16 TAVR articles. A patient-level analysis would have been preferable. We pooled data that were clearly reported in each article. Authors may not have reported outcomes simply because they did not occur, which may have led to some overestimation of events in our analysis. Reported outcomes from the 16 studies were mainly self- or site reported, with only 2 studies adequately reporting adjudicated events (33,34). This is likely to have contributed significantly to the high heterogeneity that is observed in this report. Different devices and approaches were used in the selected studies, and no systematic comparison of the devices or approaches has been attempted thus far. Although unlikely, a publication bias is always possible. The aim of this meta-analysis was to evaluate the performance and the use of the VARC definitions among the most recent TAVR literature. A patient-level pooled analysis comparing the different devices and access approaches was beyond the scope of this paper.

Conclusions

VARC definitions have already been used successfully in the literature and are being rapidly adopted by the TAVR community. However, slight modifications are needed and may improve their application in the future. Although VARC definitions have brought uniformity and standardization in reporting outcomes after TAVR, appropriate recognition and ascertaining, reporting and adjudication of outcomes should be reinforced and will ensure that TAVR study results are a valid reflection of "real-world" clinical events.

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Key Words: aortic stenosis ■ TAVI ■ TAVR ■ VARC.

APPENDIX

For supplementary tables, please see the online version of this article.