Incidence, Predictors, and Outcomes of Aortic Regurgitation After Transcatheter Aortic Valve Replacement

Meta-Analysis and Systematic Review of Literature

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Objectives   This study was designed to establish the incidence, impact, and predictors of post-transcatheter aortic valve replacement (TAVR) aortic regurgitation (AR).

Background   AR is an important limitation of TAVR with ill-defined predictors and unclear long-term impact on outcomes.

Methods   Studies published between 2002 and 2012 with regard to TAVR were identified using an electronic search and reviewed using the random-effects model of DerSimonian and Laird. From 3,871 initial citations, 45 studies reporting on 12,926 patients (CoreValve [Medtronic CV Luxembourg S.a.r.l., Tolochenaz, Switzerland] n = 5,261 and Edwards valve [Edwards Lifesciences, Santa Ana, California] n = 7,279) were included in the analysis of incidence and outcomes of post-TAVR AR.

Results   The pooled estimate for moderate or severe AR post-TAVR was 11.7% (95% confidence interval [CI]: 9.6 to 14.1). Moderate or severe AR was more common with use of the CoreValve (16.0% vs. 9.1%, p = 0.005). The presence of moderate or severe AR post-TAVR increased mortality at 30 days (odds ratio: 2.95; 95% CI: 1.73 to 5.02) and 1 year (hazard ratio: 2.27; 95% CI: −1.84 to 2.81). Mild AR was also associated with an increased hazard ratio for mortality, 1.829 (95% CI: 1.005 to 3.329) that was overturned by sensitivity analysis. Twenty-five studies reported on predictors of post-TAVR AR. Implantation depth, valve undersizing, and Agatston calcium score (r = 0.47, p = 0.001) were identified as important predictors.

Conclusions   Moderate or severe aortic regurgitation is common after TAVR and an adverse prognostic indicator of short- and long-term survival. Incidence of moderate or severe AR is higher with use of the CoreValve. Mild AR may be associated with increased long-term mortality. Therefore, every effort should be made to minimize AR by a comprehensive pre-procedural planning and meticulous procedural execution.   (J Am Coll Cardiol 2013;61:1585–95) © 2013 by the American College of Cardiology Foundation

Transcatheter aortic valve replacement (TAVR) is a rapidly evolving technology that has been shown to be a durable alternative to surgical aortic valve replacement in patients with severe, symptomatic aortic stenosis considered a high or prohibitive operative risk. In the randomized PARTNER (Placement of AoRTic TraNscathetER Valve Trial) trial (1,2), TAVR exceeded expectations by decreasing mortality and improving quality of life in patients at prohibitive risk of surgical aortic valve replacement. Fueled by these results that had earlier been replicated in large prospective registries (3–5), there has been an exponential increase in TAVR procedures across the globe with speculations of its extension to a low-risk population. However, despite the progress made, there remain several potential TAVR limitations that need to be minimized before implementing this approach in low-risk patients.

**Abbreviations
and Acronyms**

AR = aortic regurgitation

CI = confidence interval

HR = hazard ratio

OR = odds ratio

TAVR = transcatheter
aortic valve replacement

TEE = transesophageal
echocardiography

3D = 3-dimensional

TTE = transthoracic
echocardiography

VARC = Valve Academic
Research Consortium

Aortic regurgitation (AR) remains a frequent complication of TAVR, with yet unexplained determinants and clinical consequences. Depending on the method of assessment (angiography vs. echocardiography, quantitative vs. semiquantitative), the reported prevalence of AR after TAVR varies from 40% to 67% (6–8) for trivial to mild leaks and from 7% to 20% (3,6–8) for moderate to severe leaks. What constitutes clinically significant valve regurgitation after TAVR is not fully established and is currently a matter of utmost importance. Earlier reports suggested that mild AR is benign and well tolerated (9). However, a recent study (10) revealed that even mild paravalvular leak is an adverse prognostic indicator. The limited yet concerning evidence against AR emphasizes the need for further investigation and to identify variables that can be modified to minimize paravalvular leak.

The objective of our meta-analysis was to identify all currently published literature to establish the incidence of post-procedural AR, its impact on outcomes after TAVR, and its predictors.

Methods

Study selection. We conducted a systematic review of the published literature on post-TAVR AR following the QUOROM (Quality of Reporting of Meta-Analysis) (11) and MOOSE (Meta-Analysis of Observational Studies in Epidemiology) (12) guidelines. We performed a computerized search to identify all relevant studies published from January 1, 2002, to May 5, 2012, in the PubMed database. We chose 2002 because that was the year that Dr. Cribier in Rouen, France, performed the first-in-human TAVR (13). The following search terms were used: *TAVI, percutaneous valves, transcutaneous aortic valve,* and *transcatheter aortic valve.* Citations were screened at the title and abstract level and retrieved as a full report if they reported on outcomes after TAVR. The search term *regurgitation* was then used in each retrieved paper to single out papers reporting data on post-procedural AR. Limiting the search parameters to the English language was applied subsequently. The full texts and bibliography of all potential articles also were reviewed in detail (G.A.) to seek additional relevant studies.

Inclusion criteria. Studies were included if the following criteria applied: 1) reported data on post-TAVR AR severity or predictors of AR or mortality outcomes based on AR severity; 2) reported to have enrolled consecutive patients; 3) performed a minimum of 30 successful TAVR procedures; and 4) enrollment for TAVR was based on existing and accepted guidelines. When 2 similar studies were reported

from the same institution or author, the most recent publication or the publication with the most information on post-TAVR AR was included in the analysis.

Exclusion criteria. Studies were excluded if any of the following criteria applied: 1) duplicate publication, overlap of patients, subgroup studies of a main study; 2) lack of data on post-TAVR AR severity; 3) outcome of interests was not clearly reported or was impossible to extract or calculate from the published results; 4) they were studies on valve-in-valve procedure; and 5) a valve other than the CoreValve (Medtronic CV Luxembourg S.a.r.l., Tolochenaz, Switzerland) or Edwards valve (Edwards Lifesciences, Santa Ana, California) was used.

Definitions. POST-PROCEDURAL AR. For the purpose of the current analysis, post-procedural AR included AR reported immediately after the procedure, AR at discharge, or AR at 30-day follow-up. AR: none = 0/4, mild = 1/4, moderate = 2/4, severe = 3 to 4/4.

COREVALVE OR EDWARDS VALVE. A study that performed 80% or more of the TAVR procedures with either valve was subcategorized to the respective group. Studies with less than 80% predominance of either valve were excluded from the analysis of CoreValve versus Edwards valve. Individual data where provided were incorporated in the analysis irrespective of valve predominance.

Data extraction. Relevant information was collected and included but was not limited to first author, year and journal of publication, study design, inclusion exclusion criteria, definition of primary and secondary endpoints, number of subjects included, subjects undergoing successful TAVR, type of device and approach used, study population demographics, echocardiographic parameters post-TAVR, follow-up period, and primary and secondary outcomes.

DATA EXTRACTION: MILD AR. To date, only 2 studies (10,14) have reported data on the long-term outcome of mild AR post-TAVR. Therefore, to investigate the outcome of mild AR, we corresponded with trial authors and invited participation in our study. We contacted study authors who reported the outcome of AR post-TAVR. Authors from 4 groups responded. The responding authors analyzed their data and provided us with the hazard ratio (HR) of 1-year mortality for mild AR compared with no AR post-TAVR (4,14–16).

Study endpoints. The primary endpoints evaluated were: 1) overall incidences of moderate or severe AR post-TAVR; 2) effect of post-TAVR AR on 30-day and long-term mortality; and 3) predictors of AR. Secondary endpoints of interest were AR incidence stratified by valve used (CoreValve vs. Edwards valve) and by individual grades (none mild, moderate, or severe).

Statistical analysis. DerSimonian and Laird's random-effects model was used to pool the estimates of post-TAVR AR from individual studies and subgroups. A random-effects model also was used to obtain a single pooled

estimate of the HRs, odds ratios (ORs), and correlation from the individual studies. The effect across subgroups was compared using a Q test based on analysis of variance. The odds function, where appropriate, was converted to a correlation. The HRs were estimated from the survival curves when not reported by the method proposed by Parmar et al. (17). Statistical significance was set at p < 0.05 (2-tailed). Heterogeneity, which was anticipated to be significant, was assessed by a Q-statistic and I^2 test. Significant heterogeneity was considered present for p values <0.10 or an I^2 >50%. Sensitivity analysis was performed by deleting one study at a time and switching from a random-effects to a fixed-effects analysis. Data analysis was performed using Comprehensive Meta Analysis Software Version 2 (18).

Results

Through a search by keywords, 3,871 reports were identified and reviewed at title and abstract level (Fig. 1). Initial evaluation identified 1,180 publications that were further evaluated using the search term *regurgitation*. This narrowed the selection to 158 potential publications. Manual search of the bibliographies further identified 8 relevant publications. When the inclusion and exclusion criteria were applied, 45 publications remained for assessment (3–5,10,14–16) (Online Refs. 1–38) of incidence and outcomes of post-TAVR AR and 25 publications remained for predictors of AR (15) (Online References 9,12,13,39–59). The 45 included pub-

lications had 2 randomized comparisons (10) (Online Ref. 25) and 43 observational studies (3–5,14–16) (Online Refs. 1–4,26–38).

All the studies included in the analysis were published between 2008 and 2012 (Table 1). Analysis was performed on 12,926 patients, the transfemoral/subclavian approach was used in 8,408 patients (65.1%), and the transapical/aortic approach was used in 3,995 patients (30.9%). The approach used was unavailable in 523 patients (4%) (14,16). The self-expanding CoreValve was implanted in 5,261 patients (40.7%), and the balloon-expandable Edwards valve was implanted in 7,279 patients (56.3%). Of the 45 publications, 42 studies (3–5,10,14–16) (Online Refs. 1–32,36–38) provided enough details on the primary endpoint of moderate or severe AR post-TAVR. The remaining 3 studies (Online Refs. 33–35) did not provide details on moderate AR but reported the incidence of severe AR post-TAVR.

The pooled estimate for overall incidence of moderate or severe AR was 11.7% (95% confidence interval [CI]: 9.6 to 14.1, I^2 = 91.22, Q = 467.37) (Fig. 2). The Valve Academic Research Consortium (VARC) definitions were used in 12 papers (14,15) (Online Refs. 2,7,15,19, 21,22,28,34,35,37). Pooled estimate of moderate or severe AR from papers that reported on the basis of VARC was 13.9% (95% CI: 9.8 to 19.3, I^2 = 92.63, Q = 122.09) and without VARC definitions was 10.8% (95% CI: 8.5 to 13.7, I^2 = 90.4, Q = 322.71). Papers that did not report on the basis of VARC failed to report the grading method or used the Sellers angiographic criteria or the American Society of
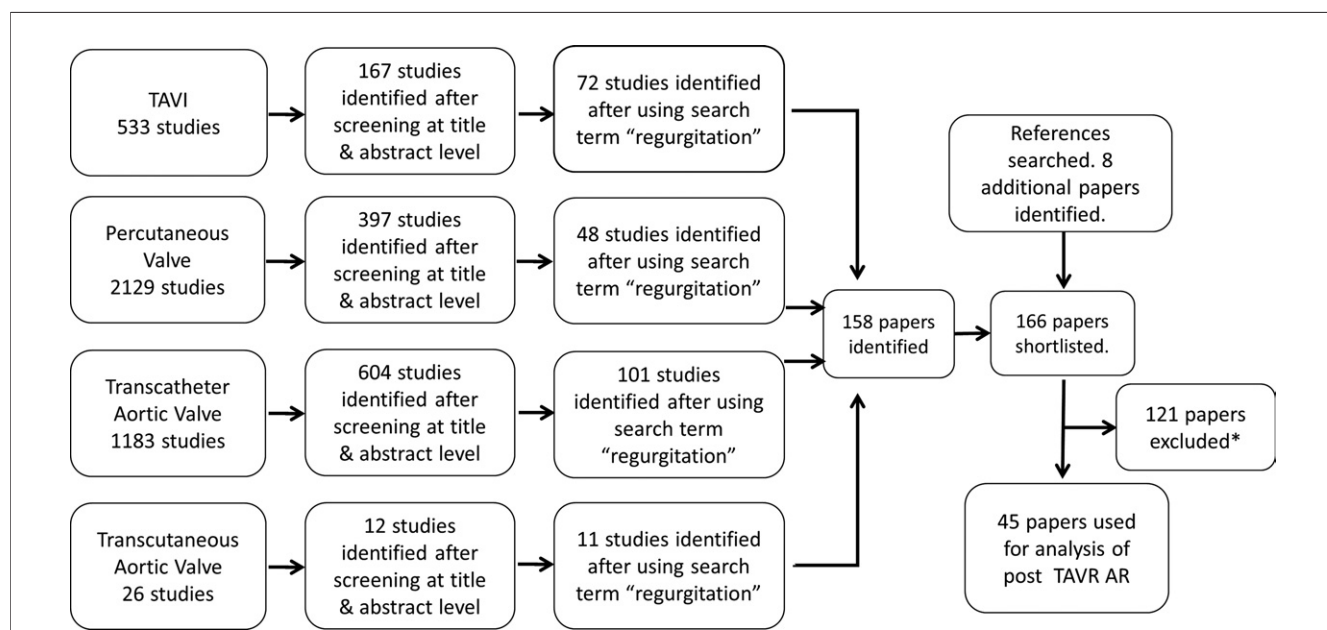
Figure 1 **Flow Chart Showing Selection of Studies**

*Different valve, n = 2; nonconsecutive patients, n = 8; <30 patients, n = 19; insufficient data, n = 23; duplicates/overlaps/same center studies, n = 63.
AR = aortic regurgitation; TAVI = transcatheter aortic valve implantation; TAVR = transcatheter aortic valve replacement.

| Table 1 | Selected Studies on the Incidence of AR Post-TAVR |

First Author (Ref. #)	Center	Year	n	Approach	Valve	Follow-Up
Rodés-Cabau et al. (3)	Canada (multicenter)	March 2010	339	TF/TA	ES	1 yr
Tamburino et al. (4)	Italy (multicenter)	January 2011	663	TF/SC	MC	1 yr
Moat et al. (5)	UK (multicenter)	November 2011	870	TF/TA	ES/MC	2 yrs
Kodali et al. (10)	USA	March 2012	348	TF/TA	ES	2 yrs
Lemos et al. (14)	Sao Paulo, Brazil	May 2012	79		MC	1 yr
Sinning et al. (15)	Bonn, Germany	March 2012	146	TF/SC	MC	1 yr
Fraccaro et al. (16)	Italy (multicenter)	April 2012	384	TF/SC/TA	ES/MC	1 yr
Bagur et al. (Online Ref. 1)	Quebec, Canada	February 2011	100	TA	ES	6 months
Gurvitch et al. (Online Ref. 2)	Vancouver, Canada	May 2011	310	TF/TA	ES	30 days
Lefevre et al. (Online Ref. 3)	International multicenter	January 2011	130	TF/TA	ES	1 yr
Eltchaninoff et al. (Online Ref. 4)	France (multicenter)	September 2010	244	TF/TA	ES/MC	30 days
Attias et al. (Online Ref. 5)	France (multicenter)	April 2010	83	TF	ES/MC	1 yr
Tchetche et al. (Online Ref. 6)	Toulouse, France	January 2010	45	TF	ES/MC	30 days
Hayashida et al. (Online Ref. 7)	Massy, France	February 2012	260	TF/TA/SC	ES/MC	1 yr
Abdel-Wahab et al. (Online Ref. 8)	Germany (multicenter)	March 2011	690	TF/TA/SC/AA	ES/MC	30 days
Unbehaun et al. (Online Ref. 9)	Berlin, Germany	January 2012	358	TA	ES	2 yrs
Conradi et al. (Online Ref. 10)	Hamburg, Germany	January 2012	82	TF/TA	ES	30 days
Lange et al. (Online Ref. 11)	Munich, Germany	January 2012	415	TF/TA/SC/AA	ES/MC	6 months
Leber et al. (Online Ref. 12)	Munich, Germany	December 2011	68	TF	MC	1 yr
Chorianopoulos et al. (Online Ref. 13)	Heidelberg, Germany	April 2012	70	TF	MC	1 yr
Grube et al. (Online Ref. 14)	Siegburg, Germany	December 2008	136	TF/SC/IL	MC	1 yr
Grube et al. (Online Ref. 15)	International multicenter	July 2011	60	TF	MC	30 days
Walther et al. (Online Ref. 16)	Germany (multicenter)	February 2012	299	TA	ES	3 yrs
Stohr et al. (Online Ref. 17)	Aachen, Germany	December 2011	175	TF/TA	MC/ES	30 days
Sherif et al. (Online Ref. 18)	Germany (multicenter)	November 2010	56	TF	MC	30 days
Puls et al. (Online Ref. 19)	Göttingen, Germany	February 2012	180	TF/TA	ES/MC	1 yr
Gotzmann et al. (Online Ref. 20)	Bochum, Germany	August 2011	145	TF/SC	MC	6 months
Amabile et al. (Online Ref. 21)	France and USA	March 2012	126	TF/TA	ES/MC	1 yr
Buchanan et al. (Online Ref. 22)	Milan, Italy	September 2011	305	TF/TA/AX/AA	ES/MC	30 days
D'Onofrio et al. (Online Ref. 23)	Italy (multicenter)	August 2011	504	TA	ES	2 yrs
Ewe et al. (Online Ref. 24)	International multicenter	October 2011	104	TF/TA	ES	30 days
Makkar et al. (Online Ref. 25)	USA	March 2012	179	TF	ES	2 yrs
Munoz-Garcia et al. (Online Ref. 26)	Málaga, Spain	April 2011	141	TF/SC	MC	6 months
Goncalves et al. (Online Ref. 27)	Madrid, Spain	May 2011	74	TF/TA	MC/ES	6 months
Wenaweser et al. (Online Ref. 28)	Bern, Switzerland	November 2011	257	TF/TA/SC	ES/MC	2.5 yrs
Dworakowski et al. (Online Ref. 29)	London, UK	August 2010	151	TF/TA	ES	30 days
Jabbour et al. (Online Ref. 30)	London, UK	November 2011	87	TF	ES/MC	—
Piazza et al. (Online Ref. 31)	International multicenter	August 2008	646	TF	MC	30 days
Buellesfeld et al. (Online Ref. 32)	International multicenter	April 2011	126	TF/SC	MC	2 yrs
Thomas et al. (Online Ref. 33)	International multicenter	April 2010	1,038	TF/TA	ES	1 yr
van der Boon et al. (Online Ref. 34)	Rotterdam, Netherlands	January 2012	230	TF/SC	MC	30 days
Stahli et al. (Online Ref. 36)	Bern, Switzerland	August 2011	130	TF/TA	ES/MC	1 yr
Kodali et al. (Online Ref. 36)	USA	March 2011	55	TF	ES	1 yr
Gilard et al. (Online Ref. 37)	France	May 2012	3,195	TF/SC/TA/TC/AA	ES/MC	1 yr
Wendler et al. (Online Ref. 38)	International multicenter	April 2012	120	TA	ES	1 yr

AA = transaortic; AX = transaxillary; ES = Edwards valve; IL = transiliac; MC = Medtronic CoreValve; N = number of patients; SC = subclavian; TA = transapical; TC = transcarotid; TF = transfemoral.

Echocardiography/European Society of Endocrinology guidelines for transthoracic echocardiography (TTE). The incidence of AR reported by these reports did not differ significantly from reports using the VARC guidelines (Q = 1.35, p = 0.25).

The incidence of moderate or severe AR after CoreValve implantation was 16.0% (95% CI: 13.4 to 19.0, I^2 = 74.81, Q = 59.56). The incidence of moderate or severe AR after

Edwards valve implantation was 9.1% (95% CI: 6.2 to 13.1, I^2 = 93.63, Q = 313.72). Moderate or severe AR was seen more often with the use of the self-expanding CoreValve (Q = 7.71, p = 0.005) (Fig. 3).

The overall pooled estimate was 1.6% (95% CI: 1.1 to 2.4, I^2 = 80.48, Q = 194.63) for severe AR, 10.5% (95% CI: 8.4 to 13.1, I^2 = 89.53, Q = 324.84) for moderate AR, 45.9% (95% CI: 40.8 to 51.0, I^2 = 95.32, Q = 705.78) for

Study name	Statistics for each study					Event rate and 95% CI
	Event rate	Lower limit	Upper limit	Z-Value	Total	
Lemos	0.038	0.012	0.111	-5.491	3 / 79	
Cabau	0.059	0.038	0.090	-12.014	20 / 339	
Bagur	0.005	0.000	0.074	-3.741	0 / 100	
Gurvitch	0.055	0.034	0.086	-11.412	17 / 310	
Lefe`vre	0.469	0.385	0.555	-0.701	61 / 130	
Eltchaninoff	0.094	0.063	0.138	-10.327	23 / 244	
Attias	0.193	0.122	0.292	-5.147	16 / 83	
Tchetche	0.089	0.034	0.214	-4.443	4 / 45	
Hayashida	0.308	0.255	0.366	-6.035	80 / 260	
Wahab	0.172	0.146	0.202	-15.563	119 / 690	
Unbehaun	0.006	0.001	0.022	-7.308	2 / 358	
Sinning	0.151	0.101	0.218	-7.475	22 / 146	
Conradi	0.012	0.002	0.081	-4.368	1 / 82	
Lange	0.063	0.043	0.090	-13.356	26 / 415	
Leber	0.118	0.060	0.218	-5.353	8 / 68	
Chorianopoulos	0.229	0.145	0.341	-4.273	16 / 70	
Grube	0.199	0.140	0.274	-6.492	27 / 136	
Grube E	0.067	0.025	0.165	-5.099	4 / 60	
Walther	0.033	0.018	0.061	-10.458	10 / 299	
Stohr	0.029	0.012	0.067	-7.772	5 / 175	
Sherif	0.232	0.140	0.360	-3.779	13 / 56	
Puls	0.072	0.042	0.120	-8.866	13 / 180	
Gotzmann	0.172	0.119	0.243	-7.135	25 / 145	
Tamburino	0.130	0.106	0.158	-16.468	86 / 663	
Amabile	0.103	0.061	0.170	-7.384	13 / 126	
Buchanan	0.266	0.219	0.318	-7.846	81 / 305	
D'Onofrio	0.001	0.000	0.016	-4.888	0 / 504	
Ewe	0.202	0.136	0.290	-5.626	21 / 104	
Makkar	0.128	0.087	0.186	-8.571	23 / 179	
Kodali	0.109	0.080	0.147	-12.212	38 / 348	
Garcia	0.229	0.168	0.305	-6.118	33 / 144	
Goncalves	0.068	0.028	0.152	-5.667	5 / 74	
Wenaweser	0.280	0.229	0.338	-6.794	72 / 257	
Moat	0.132	0.111	0.156	-18.799	115 / 870	
Dworakowski	0.040	0.018	0.086	-7.645	6 / 151	
Jabbour	0.195	0.125	0.292	-5.234	17 / 87	
Piazza	0.001	0.000	0.012	-5.064	0 / 646	
Buellesfeld	0.087	0.049	0.151	-7.437	11 / 126	
Wendler	0.025	0.008	0.075	-6.266	3 / 120	
Girald	0.165	0.149	0.182	-26.337	316 / 1915	
Fraccaro	0.185	0.149	0.227	-11.286	71 / 384	
REVIVAL	0.345	0.232	0.479	-2.254	19 / 55	
All	**0.117**	**0.096**	**0.141**	**-18.217**	**1,445/11,528**	

Event rate and 95% CI axis: -0.25   -0.13   0.00   0.13   0.25
Decreased Risk ← | → Increased Risk

Figure 2 **Forest Plot Showing the Individual and Pooled Event Rates for Moderate or Severe AR After TAVR From the Included Studies**

AR = aortic regurgitation; CI = confidence interval; TAVR = transcatheter aortic valve replacement.

mild/trivial AR, and 35.8% (95% CI: 30.0 to 42.0, I^2 = 96.82, Q = 1,037.78) for none.

Our search for predictors of TAVR identified several publications on 3 major culprits (Table 2). The computed tomography-derived mean Agatston calcium score positively correlated with the development of post-TAVR moderate or severe AR with a pooled estimate of correlation being r = 0.47 (95% CI: 0.30 to 0.61, p = 0.001, I^2 = 76.24, Q = 12.63). The other 2 predictive factors that were reported could not be pooled because of limited studies and variable reporting.

The overall 1-year mortality was unfavorable in patients with moderate or severe AR with an HR of 2.27 (95% CI: 1.84 to 2.81, p = 0.001, I^2 = 26.02, Q = 10.81) (Fig. 4). The OR of 30-day mortality was increased in patients with moderate or severe AR post-TAVR, 2.95 (95% CI: 1.73 to 5.02, p = 0.001, I^2 = 0, Q = 2.663). Mild AR post-TAVR was associated with significant mortality, with an HR of 1.829 (95% CI: 1.005 to 3.329, p = 0.048, I^2 = 75.28, Q =
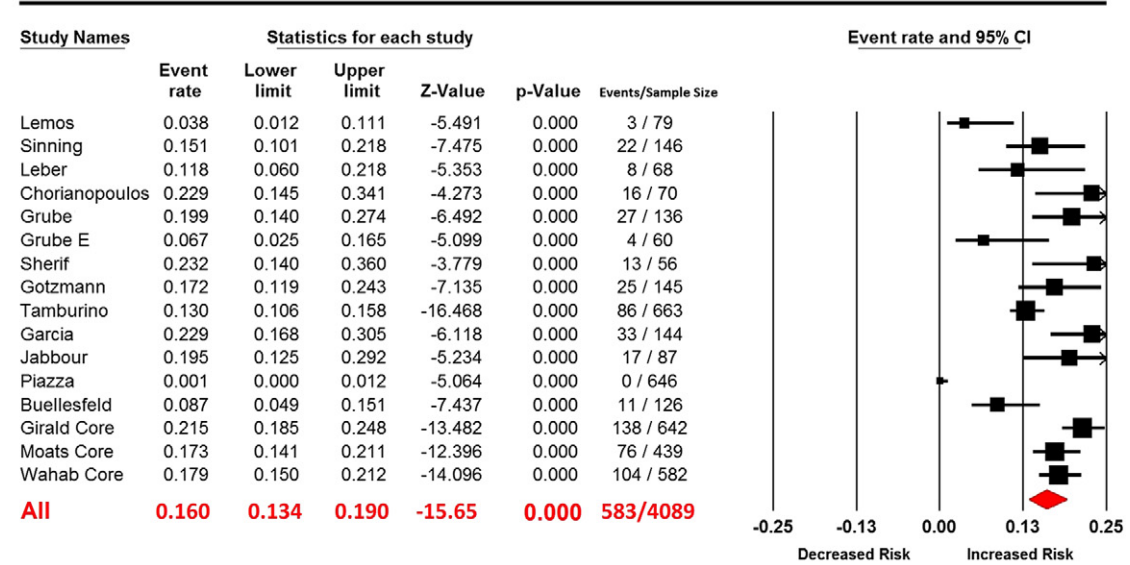
16.18) (Fig. 5). The analysis was performed on 1,620 patients across 5 individual studies.

We explored the robustness of our findings by omitting one study at a time or outlier studies and switching our meta-analysis model from a random- to a fixed-effects analysis. There was no change in the summary effects by either analysis other than for mild AR. The pooled HR for mortality with mild AR became insignificant on removal of the studies by Lemos et al. (14), Kodali et al. (10), Sinning et al. (15), and Fraccaro et al. (16) (Fig. 6). Nevertheless, there was a trend toward increased mortality.
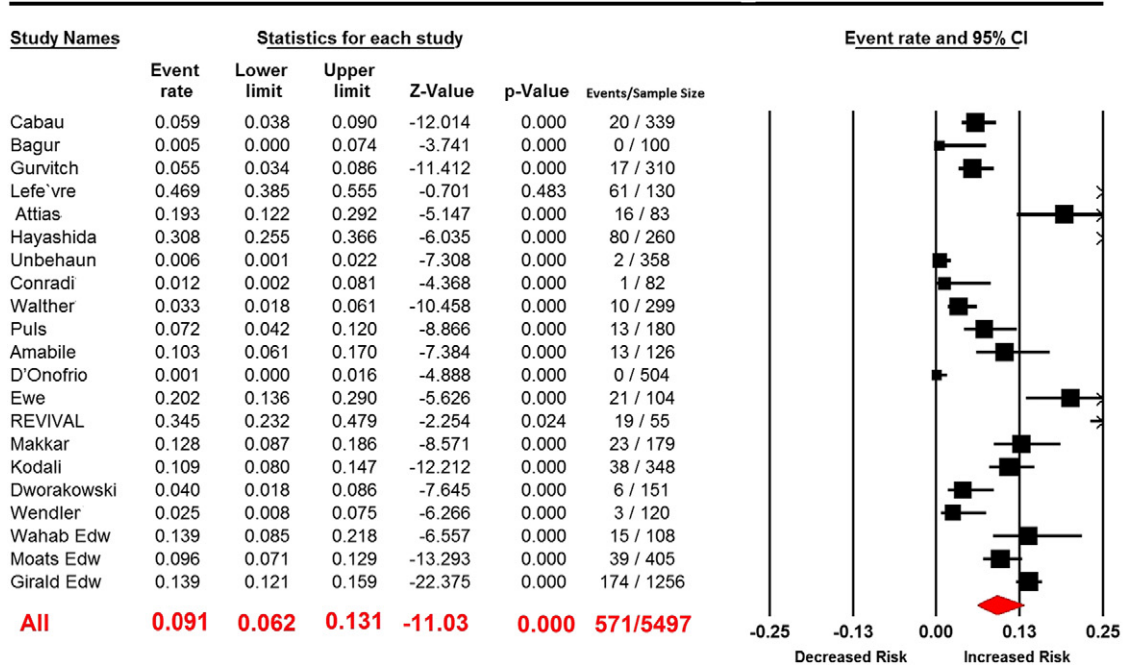
Discussion

AR after TAVR. The impact of mild AR on long-term outcomes has yielded conflicting results. In our pooled analysis, mild AR was associated with a 1-year hazard of 1.940 (95% CI: 1.090 to 3.452). However, the conclusions changed when studies were removed from the analysis set

A   Moderate or Severe AR Post TAVR: CoreValve

Study Names	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Events/Sample Size
Lemos	0.038	0.012	0.111	-5.491	0.000	3 / 79
Sinning	0.151	0.101	0.218	-7.475	0.000	22 / 146
Leber	0.118	0.060	0.218	-5.353	0.000	8 / 68
Chorianopoulos	0.229	0.145	0.341	-4.273	0.000	16 / 70
Grube	0.199	0.140	0.274	-6.492	0.000	27 / 136
Grube E	0.067	0.025	0.165	-5.099	0.000	4 / 60
Sherif	0.232	0.140	0.360	-3.779	0.000	13 / 56
Gotzmann	0.172	0.119	0.243	-7.135	0.000	25 / 145
Tamburino	0.130	0.106	0.158	-16.468	0.000	86 / 663
Garcia	0.229	0.168	0.305	-6.118	0.000	33 / 144
Jabbour	0.195	0.125	0.292	-5.234	0.000	17 / 87
Piazza	0.001	0.000	0.012	-5.064	0.000	0 / 646
Buellesfeld	0.087	0.049	0.151	-7.437	0.000	11 / 126
Girald Core	0.215	0.185	0.248	-13.482	0.000	138 / 642
Moats Core	0.173	0.141	0.211	-12.396	0.000	76 / 439
Wahab Core	0.179	0.150	0.212	-14.096	0.000	104 / 582
All	**0.160**	**0.134**	**0.190**	**-15.65**	**0.000**	**583/4089**

Event rate and 95% CI

-0.25   -0.13   0.00   0.13   0.25
Decreased Risk   Increased Risk

B   Moderate or Severe AR Post TAVR: Edward Valve

Study Names	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Events/Sample Size
Cabau	0.059	0.038	0.090	-12.014	0.000	20 / 339
Bagur	0.005	0.000	0.074	-3.741	0.000	0 / 100
Gurvitch	0.055	0.034	0.086	-11.412	0.000	17 / 310
Lefe`vre	0.469	0.385	0.555	-0.701	0.483	61 / 130
Attias	0.193	0.122	0.292	-5.147	0.000	16 / 83
Hayashida	0.308	0.255	0.366	-6.035	0.000	80 / 260
Unbehaun	0.006	0.001	0.022	-7.308	0.000	2 / 358
Conradi	0.012	0.002	0.081	-4.368	0.000	1 / 82
Walther	0.033	0.018	0.061	-10.458	0.000	10 / 299
Puls	0.072	0.042	0.120	-8.866	0.000	13 / 180
Amabile	0.103	0.061	0.170	-7.384	0.000	13 / 126
D'Onofrio	0.001	0.000	0.016	-4.888	0.000	0 / 504
Ewe	0.202	0.136	0.290	-5.626	0.000	21 / 104
REVIVAL	0.345	0.232	0.479	-2.254	0.024	19 / 55
Makkar	0.128	0.087	0.186	-8.571	0.000	23 / 179
Kodali	0.109	0.080	0.147	-12.212	0.000	38 / 348
Dworakowski	0.040	0.018	0.086	-7.645	0.000	6 / 151
Wendler	0.025	0.008	0.075	-6.266	0.000	3 / 120
Wahab Edw	0.139	0.085	0.218	-6.557	0.000	15 / 108
Moats Edw	0.096	0.071	0.129	-13.293	0.000	39 / 405
Girald Edw	0.139	0.121	0.159	-22.375	0.000	174 / 1256
All	**0.091**	**0.062**	**0.131**	**-11.03**	**0.000**	**571/5497**

Event rate and 95% CI

-0.25   -0.13   0.00   0.13   0.25
Decreased Risk   Increased Risk

Figure 3   **Forest Plot Showing the Individual and Pooled Event Rates for Moderate or Severe AR After TAVR From the Included Studies**

With use of the CoreValve **(A)** and Edwards valve **(B)**. Q between the 2 subgroups (CoreValve vs. Edwards valve) was 10.66 and statistically significant (p = 0.000), meaning that the event rate was related to the type of valve implanted. Abbreviations as in Figure 2.
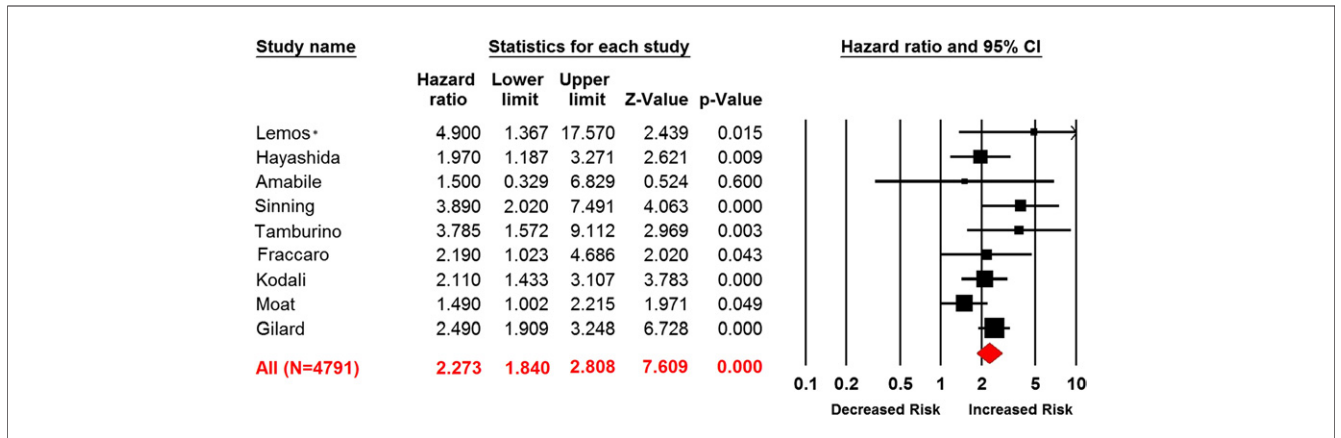
one at a time. This discrepancy in outcomes may be related in part to the challenges in identification and quantification of post-TAVR AR. Post-TAVR AR is frequently paravalvular, created by multiple eccentric jets that are nonparallel and irregular in shape (9,19). The eccentric jets in turn are frequently entrained along the LV wall with fanning of jets as they regurgitate. This makes the assessment of AR severity difficult and more subjective. Acoustic shadowing from the calcifications, reverberations, and Doppler attenuation from the prosthesis can further obscure significant regurgitant jets and result in underestimation of its severity (9). Various echocardiographic techniques (19,20) and

Table 2	Selected Studies on Predictors of AR Post-TAVR		
Predictor	First Author (Ref. #)	Variable	Association With Post-TAVR Moderate or Severe AR
Valve undersizing	Detaint et al. (Online Ref. 39)	Cover index	Low cover index was associated with mild or greater AR; OR: 1.22 (95% CI: 1.03–1.51, p = 0.02)
	Sinning et al. (15)	Cover index	Low cover index was associated with mild or greater AR (p < 0.001)
	Samim et al. (Online Ref. 40)	Cover index	High cover index associated with absence of AR
	Haensig et al. (Online Ref. 41)	Prosthesis mismatch (annulus > prosthesis)	Undersizing associated with mild or greater AR (p = 0.002)
	Willson et al. (Online Ref. 42)	Prosthesis mismatch (prosthesis – mean annulus diameter) <1 mm	Undersizing associated with mild or greater AR: OR: 9.4 (95% CI: 2.15–88.8, p < 0.01)
	Buzzatti et al. (Online Ref. 43)	Prosthesis mismatch (prosthesis – D_{mean})/D_{mean}	Undersizing associated with mild or greater AR (p = 0.0006)
		Larger annulus size	D_{max} (p = 0.0003), D_{min} (p = 0.0113), D_{mean} (p = 0.001)
	Schultz et al. (Online Ref. 44)	Larger annulus size	D_{max} (p < 0.05), D_{min} (p < 0.05), D_{CSA} (p < 0.01) associated with mild or greater AR
	Takagi et al. (Online Ref. 45)	Prosthesis mismatch (annulus > prosthesis)	Association with mild or greater AR (p = 0.056)
		Larger annulus size	OR: 1.78 (95% CI: 1.25–2.55, p = 0.002)
	Altiok et al. (Online Ref. 46)	Annulus size: 2D TEE vs. 3D TEE vs. DSCT	Significant difference in measurement of AV annulus by 2D TEE vs. DSCT (average bias = 1.7 mm; p = 0.001); strong correlation between 3D TEE and DSCT
	Jilaihawi et al. (Online Ref. 47)	Annulus size: CT vs. TEE	CT annular assessment superior to TEE (p = 0.045)
	Husser et al. (Online Ref. 48)	Annulus size: 2D TEE vs. 3D TEE	Mean AV diameters significantly larger in 3D TEE vs. 2D TEE (23.4 ± 2.2 mm vs. 22.1 ± 2.6 mm; p < 0.001)
	Kalavrouziotis et al. (Online Ref. 49)	Annulus size <20 mm	Only 2.9% incidence of mild or greater AR after implantation of 23-mm valve
Aortic valve calcification	Shultz et al. (Online Ref. 50)	Agatston score	Higher with mild or greater AR (p < 0.05)
	Koos et al. (Online Ref. 51)	Agatston score	r = 0.50, p < 0.001
		Morphological risk	No association identified
	Delgado et al. (Online Ref. 52)	Agatston score	Higher with moderate or severe AR post-TAVR (p = 0.005)
		Morphological risk	Aortic valve commissure
	John et al. (Online Ref. 53)	Agatston score	r = 0.254, p = 0.011
		Morphological risk	LVOT and aortic valve – DLZ
	Unbehaun et al. (Online Ref. 9)	Agatston score	OR = 1.09 (95% CI: 1.01–1.17), p = 0.029
		Morphological risk	DLZ calcification OR: 4.90
	Haensig et al. (Online Ref. 41)	Agatston score	OR = 11.38 (95% CI: 2.33–55.53), p = 0.001
		Morphological risk	Calcification at right and left coronary cusps
	Colli et al. (Online Ref. 54)	Echocardiographic calcium score	OR = 8.5 (95% CI: 1.2–58.9); p = 0.0001
		Morphological risk	Aortic commissures and valve cusp
	Ewe et al. (Online Ref. 55)	Morphological risk	Aortic wall calcification: AUC: 0.93 (p < 0.001)
			Valve commissure calcification: AUC: 0.94
	Leber et al. (Online Ref. 12)	Calcium mass score	r = 0.33, p < 0.002
	Wood et al. (Online Ref. 56)	Agatston score	No association with AR (p = 0.35)
	Staubach et al. (Online Ref. 57)	Visual estimation of valve calcification	No association with AR
Implantation depth	Sherif et al. (Online Ref. 58)	Depth from NCC	Least at depth ~10 mm; deep and shallow implantation increased AR
	Jilaihawi et al. (Online Ref. 59)	Depth from NCC	Implantation >15 mm associated with mild or greater AR (p = 0.032)
	Chorianopoulos et al. (Online Ref. 13)	Depth*	OR: 1.3 (95% CI: 1.1–1.6, p = 0.0098)
	Sinning et al. (15)	Depth from LCC	Significantly higher in moderate or greater AR (p = 0.029)
	Takagi et al.(Online Ref. 45)	Low implantation ≥3 struts below annulus	OR = 3.67 (95% CI: 1.01–13.35, p = 0.049)
	Schultz et al. (Online Ref. 50)	Implantation depth	No association with AR

Implantation depth was determined by calculating the distance between an imaginary line joining basal attachment points of aortic valve leaflets with the line connecting the right and left lower prosthesis skits.

AR = aortic regurgitation; AUC = area under the curve; AV = aortic valve; CI = confidence interval; CT = computed tomography; DLZ = device landing zone; Dmax = maximum aortic annulus diameter; Dmean = mean aortic annulus diameter; Dmin = minimum aortic annulus diameter; DSCT = dual-source computed tomography; LCC = left coronary cusp; LVOT = left ventricular outflow tract; NCC = noncoronary cusp; OR = odds ratio; r = correlation coefficient; TAVR = transcatheter aortic valve replacement; 2D TEE = 2-dimensional transesophageal echocardiography; 3D TEE = 3-dimensional transesophageal echocardiography.

Study name	Statistics for each study					Hazard ratio and 95% CI
	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	
Lemos*	4.900	1.367	17.570	2.439	0.015	
Hayashida	1.970	1.187	3.271	2.621	0.009	
Amabile	1.500	0.329	6.829	0.524	0.600	
Sinning	3.890	2.020	7.491	4.063	0.000	
Tamburino	3.785	1.572	9.112	2.969	0.003	
Fraccaro	2.190	1.023	4.686	2.020	0.043	
Kodali	2.110	1.433	3.107	3.783	0.000	
Moat	1.490	1.002	2.215	1.971	0.049	
Gilard	2.490	1.909	3.248	6.728	0.000	
All (N=4791)	**2.273**	**1.840**	**2.808**	**7.609**	**0.000**	

Figure 4   **Forest Plot Showing the HRs of Moderate or Severe AR on Overall Mortality**

*Includes mild AR in the analysis of HR. HR = hazard ratio; other abbreviations as in Figure 2.

grading schemes (grades 1 to 4, none to severe) have been proposed to measure the severity of post-TAVR AR; however, none of these techniques have been validated and the grading system has not been clearly defined (difference between mild, trivial, or trace, mild vs. moderate, moderate vs. severe). Therefore, the assessment of post-TAVR AR remains controversial and imprecise (21).

Sherif et al. (22) demonstrated an underestimation of the AR severity after implantation of the Core Valve by current echocardiography criteria compared with cardiac magnetic resonance. The VARC (23), which was developed to propose standardized consensus definitions to report post-TAVR complications, failed to adequately address paravalvular leak in its current report. The VARC did not propose standard terminologies or new diagnostic criteria for assessment of AR, but merely elaborated on the work done by others and summarized by Zoghbi et al. (20). The lack of core laboratory assessment of AR severity in the included studies and the absence of published standards for post-TAVR AR may have affected the quality of the reported data. This issue of imprecision is a major limitation in comparing echocardiographic studies performed in different laboratories and likely contributed to the discordant results on the outcome of mild AR. To develop standard criteria to achieve uniformity and accurate

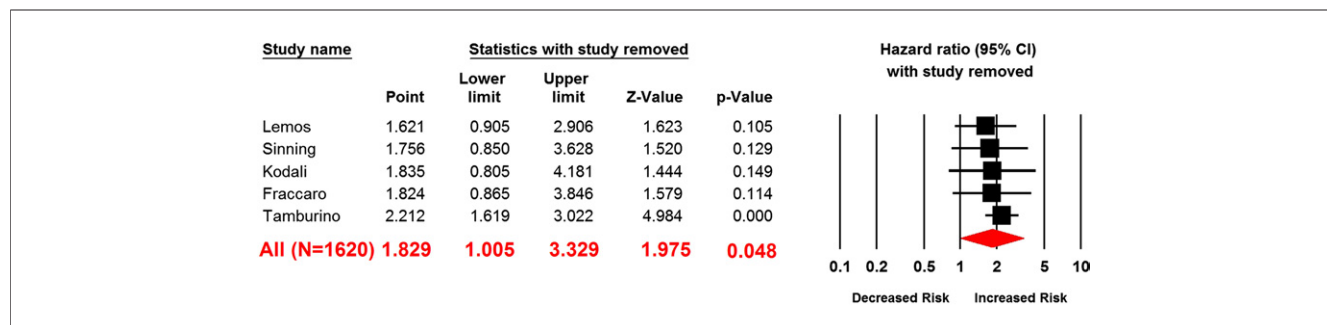grading of paravalvular AR post-TAVR is therefore a pressing necessity.

To complicate the matter further, it is possible that AR is a surrogate for an underlying cause, such as severe valve calcification or sicker patients. The role of other confounding variables, such as pre-procedural AR, left ventricle function, and mitral regurgitation, remains unclear at present. However, the impact of moderate to severe AR is more apparent with a pooled 30-day OR for mortality of 2.95 (95% CI: 1.73 to 5.02) and a long-term HR of 2.27 (95% CI: 1.84 to 2.89).

CoreValve versus Edwards valve. Regardless of the valve type, post-TAVR AR was a frequent complication in reported studies. Nevertheless, implantation of the CoreValve carried a higher risk of post-TAVR AR (16.0% vs. 9.1%, p = 0.005). Concerns have been raised over the radial strength of the nitinol frame of the self-expanding CoreValve in highly calcific lesions (Online Refs. 13,26,51). Incomplete device expansion and resultant impaired apposition of the Core Valve to the native annulus and the left ventricular outflow tract have been implicated in these cases. Another possible cause for AR after core valve implantation is the extreme angulation between the left ventricular outflow tract and the ascending aorta, which reduces the ability of the self-expanding prosthesis to form a tight seal to close the

Study name	Statistics for each study					Hazard ratio and 95% CI
	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	
Lemos	10.080	1.229	82.673	2.152	0.031	
Sinning	2.342	1.066	5.145	2.119	0.034	
Kodali	2.110	1.433	3.107	3.782	0.000	
Fraccaro	2.064	0.968	4.400	1.876	0.061	
Tamburino	0.780	0.499	1.218	-1.092	0.275	
All (N=1620)	**1.829**	**1.005**	**3.329**	**1.975**	**0.048**	
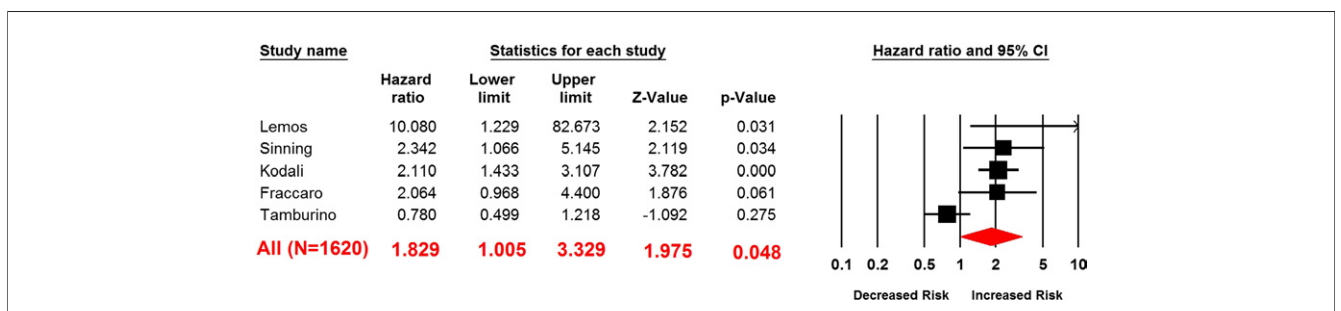
Figure 5   **Forest Plot Showing the HRs of Mild AR on Overall Mortality**

Study name						Hazard ratio (95% CI) with study removed
	Point	Lower limit	Upper limit	Z-Value	p-Value	
Lemos	1.621	0.905	2.906	1.623	0.105	
Sinning	1.756	0.850	3.628	1.520	0.129	
Kodali	1.835	0.805	4.181	1.444	0.149	
Fraccaro	1.824	0.865	3.846	1.579	0.114	
Tamburino	2.212	1.619	3.022	4.984	0.000	
All (N=1620)	**1.829**	**1.005**	**3.329**	**1.975**	**0.048**	

Figure 6   Sensitivity Analysis Performed by Excluding One Study at a Time for HRs of Mild AR on Overall Mortality

HR for all-cause mortality was statistically insignificant on removal of the papers by Lemos et al. (14), Kodali et al. (10), Sinning et al. (15), and Fraccaro et al. (16), with a shift of the overall HR to the **left** and crossing 1, thereby indicating no increased risk of mild AR. Abbreviations as in Figures 2 and 4.

paravalvular space. Balloon post-dilation and a greater oversizing as opposed to the Edwards valve may overcome the underexpansion of the CoreValve in these situations. However, balloon post-dilation has been associated with increased stroke risk (24). Another factor that is important for reducing AR when the CoreValve is used is the height of implantation. Because of the noncylindrical shape of the valve, the depth of implantation determines the effective diameter of the valve in the annulus. Particularly in larger annuli, the sealing of the CoreValve at the level of the virtual ring is dependent on a high implantation to take advantage of the diameter of the lower part of the valve.

Predictive factors and potential management strategies. Mismatch of the valve annulus and prosthesis diameter sizes, aortic root calcification, and suboptimal device implantation were identified as the major causes for post-TAVR AR in our search.

Valve undersizing. Undersizing of the prosthesis relative to the annulus size is the central cause for most paravalvular leaks after TAVR. Detaint et al. (Online Ref. 39) studied the effect of undersizing using the cover index [$100 \cdot$ (prosthesis diameter − transesophageal echocardiography [TEE] annulus diameter)/prosthesis diameter]. A low cover index was found to be an independent predictor of moderate or severe AR post-TAVR. This has been replicated in 2 other studies (15) (Online Ref. 40). Appropriate cover index for each valve may be different and requires more studies to clearly define this.

Therefore, precise annulus sizing by appropriate aortic imaging pre-TAVR is fundamental to prevent AR (25). The aortic annulus was initially sized by 2-dimensional measurements obtained from TTE, but there are several limitations to annulus sizing using TTE. TTE has been shown to underestimate the annulus size from anywhere between 1.4 mm and 1.7 mm (26) (Online Ref. 42). Similar underestimation may occur with TEE (1.2 mm) (26). Jilaihawi et al. (Online Ref. 47) showed that computed tomography−guided annular sizing reduced paravalvular AR compared with a TEE-guided approach in patients receiving an Edwards SAPIEN valve (7.5% vs. 21.9%).

Willson et al. (Online Ref. 42) and Schultz et al. (Online Ref. 44) also showed the superiority of multidetector computed tomography annular measurements. A high correlation between multidetector computed tomography and 3-dimensional (3D) TEE measurements of annulus size have been demonstrated in experienced hands. Therefore, it is fair to conclude that 3D imaging for annulus sizing holds the key to better sizing the valves and decreasing paravalvular leaks.

Aortic valve calcium score. Aortic root calcium is thought to hinder uniform valve expansion and tight sealing. However, existing data on this topic are conflicting. In the analysis of the German TAVI registry on 1,365 patients, Staubach et al. (Online Ref. 57) found that the extent of aortic valve calcification did not influence the severity of post-TAVR AR, which is similar to that reported by Wood et al. (Online Ref. 56). Other investigators found that an Agatston score >3,000 predicted moderate or severe AR after initial release of the CoreValve (Online Refs. 41,50,52) and the need for post-dilation. Likewise, other quantitative calcium scores also have been shown to correlate positively with the occurrence of post-TAVR AR (Online Refs. 54,55). Despite the conflicting evidence, precise quantitation of the extent and location of calcification in the aortic root may allow the identification of patients with asymmetric heavy calcification that may increase the risk of AR.

Implantation depth. Post-procedural AR is influenced significantly by the implantation depth. Valve positioning currently is based mainly on fluoroscopy and angiography with or without echocardiographic guidance. Choosing the correct fluoroscopic plane is critical. When misplaced high or low, the skirt of the prosthetic valve does not provide an adequate seal around the annulus, resulting in AR. The unequal geometry of the CoreValve with a narrow and tapered midsection further contributes to paravalvular leak from an inadequate seal when misplaced. Takagi et al. (Online Ref. 45) showed that low CoreValve implantation increased the OR of moderate or severe AR, 3.67 (95% CI: 1.01 to 13.35). Sherif et al. (Online Ref. 58) and Jilaihawi et al. (Online Ref. 59) showed that a 9.5-mm and 5- to

10-mm device depth, respectively, from the noncoronary cusp minimized the risk of moderate or severe AR for the CoreValve. Improvements in imaging technology to provide real-time 3D imaging, increasing experience and modifications in delivery systems, will likely improve the precision of valve deployment.

Clinical implications and future perspective. Moderate or severe AR post-TAVR is common but can be prevented by accurate annulus measurements with 3D techniques and adequate valve sizing. Accurate positioning of the valves may reduce the risk of paravalvular AR. Post-TAVR AR is difficult to quantitate with any single currently available imaging technique and should be accurately quantified using multimodality imaging with hemodynamic data. The next generation of transcatheter aortic valves designed to minimize paravalvular leak will have a major role to play in the future of TAVR.

Study limitations. The studies pooled in the analysis were observational studies with post-TAVR AR not being a primary outcome of interest. The included studies used different methods and grading schemes for assessment of AR severity, thereby introducing limitations in quality and completeness of data. There was significant heterogeneity across studies for all outcomes analyzed. Because of incomplete/unequal reporting of data, not all studies were pooled for all outcomes, which could lead to publication bias. Selection bias was introduced in the evaluation of the prognostic value of mild AR by our method of contacting authors. Precise distinction between paravalvular and valvular AR was not made. AR varies with time; therefore, our definition of post-procedural AR may not be precise. Expansion of the CoreValve over time was not taken into account, a fact that may have biased the results of post-procedural AR in favor of the Edwards valve (however, at present there are no data to indicate that expansion of the CoreValve caused by radial forces in the inflow portion reduces AR over time). Despite these limitations, the large sample size and robustness of our findings clearly demonstrate the need for ongoing critical evaluation of this problem.

Conclusions

Moderate or severe AR is common after TAVR and an adverse prognostic indicator of short- and long-term survival. Every effort should be made to predict and minimize post-procedural AR. Underestimation of paravalvular AR with currently used imaging modalities may be significant, and some patients with reported mild AR post-TAVR may have moderate or even severe AR. Sizing of the annulus is a key step to prevent post-procedural AR where sizing with 3D imaging is superior to 2-dimensional imaging techniques. Innovations designed to improve sealing, improvement in the range of available device sizes, accurate annular sizing, and precise positioning will help minimize AR after TAVR.

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REFERENCES

1. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011; 364:2187–98.
2. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.
3. Rodés-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol 2010;55:1080–90.
4. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation 2011;123:299–308.
5. Moat NE, Ludman P, de Belder MA, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J Am Coll Cardiol 2011;58: 2130–8.
6. Webb JG, Pasupati S, Humphries K, et al. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. Circulation 2007;116:755–63.
7. Walther T, Simon P, Dewey T, et al. Transapical minimally invasive aortic valve implantation: multicenter experience. Circulation 2007; 116:I240–5.
8. De Jaegere PP, Piazza N, Galema TW, et al. Early echocardiographic evaluation following percutaneous implantation with the self-expanding CoreValve Revalving System aortic valve bioprosthesis. EuroIntervention 2008;4:351–7.
9. Raffa GM, Malvindi PG, Settepani F, et al. Aortic valve replacement for paraprosthetic leak after transcatheter implantation. J Card Surg 2012;27:47–51.
10. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–95.
11. Moher D, Liberati A. [Reporting systematic reviews and meta-analyses: asking authors, peer reviewers, editors and funders to do better]. Med Clin (Barc) 2010;135:505–6.
12. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
13. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006–8.
14. Lemos PA, Saia F, Mariani J Jr., et al. Residual aortic regurgitation is a major determinant of late mortality after transcatheter aortic valve implantation. Int J Cardiol 2012;157:288–9.
15. Sinning JM, Hammerstingl C, Vasa-Nicotera M, et al. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. J Am Coll Cardiol 2012;59:1134–41.
16. Fraccaro C, Al-Lamee R, Tarantini G, et al. Transcatheter aortic valve implantation in patients with severe left ventricular dysfunction: immediate and mid-term results, a multicenter study. Circ Cardiovasc Interv 2012;5:253–60.
17. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815–34.
18. Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-analysis Version 2. Englewood, NJ: Biostat, 2005.
19. Zamorano JL, Badano LP, Bruce C, et al. EAE/ASE recommendations for the use of echocardiography in new transcatheter inter-

ventions for valvular heart disease. J Am Soc Echocardiogr 2011;24:
937–65.

20. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations
for evaluation of prosthetic valves with echocardiography and
Doppler ultrasound: a report From the American Society of
Echocardiography's Guidelines and Standards Committee and the
Task Force on Prosthetic Valves, developed in conjunction with the
American College of Cardiology Cardiovascular Imaging Commit-
tee, Cardiac Imaging Committee of the American Heart Associa-
tion, the European Association of Echocardiography, a registered
branch of the European Society of Cardiology, the Japanese Society
of Echocardiography and the Canadian Society of Echocardiogra-
phy, endorsed by the American College of Cardiology Foundation,
American Heart Association, European Association of Echocardi-
ography, a registered branch of the European Society of Cardiol-
ogy, the Japanese Society of Echocardiography, and Canadian
Society of Echocardiography. J Am Soc Echocardiogr 2009;22:
975–1014; quiz 1082–4.

21. Tarantini G, Gasparetto V, Napodano M, Fraccaro C, Gerosa G,
Isabella G. Valvular leak after transcatheter aortic valve implantation:
a clinician update on epidemiology, pathophysiology and clinical
implications. Am J Cardiovasc Dis 2011;1:312–20.

22. Sherif MA, Abdel-Wahab M, Beurich HW, et al. Haemodynamic
evaluation of aortic regurgitation after transcatheter aortic valve im-

plantation using cardiovascular magnetic resonance. EuroIntervention
2011;7:57–63.

23. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint
definitions for Transcatheter Aortic Valve Implantation clinical trials:
a consensus report from the Valve Academic Research Consortium.
J Am Coll Cardiol 2011;57:253–69.

24. Nombela-Franco L, Rodés-Cabau J, Delarochelliere R, et al. Predic-
tive factors, efficacy, and safety of balloon post-dilation after trans-
catheter aortic valve implantation with a balloon-expandable valve.
J Am Coll Cardiol Intv 2012;5:499–512.

25. Bloomfield GS, Gillam LD, Hahn RT, et al. A practical guide to
multimodality imaging of transcatheter aortic valve replacement. J Am
Coll Cardiol Img 2012;5:441–55.

26. Babaliaros VC, Liff D, Chen EP, et al. Can balloon aortic valvulo-
plasty help determine appropriate transcatheter aortic valve size? J Am
Coll Cardiol Intv 2008;1:580–6.

Key Words: CoreValve ■ mild AR ■ post-TAVR AR ■
predictors of AR post-TAVR ■ TAVI.

▶ **APPENDIX**

For a list of the additional references, please see the online version of this article.