Meta-Analysis for Impact of Statin on Mortality After Transcatheter Aortic Valve Implantation

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To determine whether statin (hydroxymethylglutaryl-CoA reductase inhibitor) therapy is associated with better midterm survival after transcatheter aortic valve implantation (TAVI), the first meta-analysis of currently available studies was performed. To identify all observational comparative studies and randomized controlled trials (RCTs) of statin versus control (no statin) therapy or cohort studies investigating statin treatment as one of covariates in patients undergoing TAVI, PubMed, Web of Science, and Google Scholar were searched through March 2019. Adjusted (if unavailable, unadjusted) hazard ratios (HRs) with their confidence interval (CIs) of midterm (≥1 year) all-cause mortality after TAVI for statin therapy were extracted from each study. Study-specific estimates were combined by means of inverse variance-weighted averages of logarithmic HRs in the random-effects model. Eight eligible studies with a total of 5,170 TAVI patients were identified and included in the present meta-analysis. The primary meta-analysis (including HRs for high intensity statin from 3 studies together with other HRs) demonstrated that statin treatment was associated with significantly lower midterm mortality (HR, 0.74; 95% CI, 0.60 to 0.91; p = 0.005). The secondary meta-analysis (including HRs for low/moderate intensity statin from 3 studies together with other HRs) also indicated an association of statin therapy with significantly lower midterm mortality (HR, 0.80; 95% CI, 0.69 to 0.93; p = 0.005). No funnel plot asymmetry for the primary meta-analysis (p = 0.64) was identified, which suggested probably no publication bias. In conclusion, statin therapy is associated with better midterm survival after TAVI. **(Am J Cardiol 2019;124:920−925)**

It has been well-known that statin (hydroxymethylglutaryl-CoA reductase inhibitor) therapy is associated with better survival after repair of abdominal aortic aneurysm.[1−5] Statin treatment also may be associated with lower early all-cause mortality[6−8] and midterm mortality from myocardial infarction (MI)[9] after cardiac surgery[6] and coronary artery bypass grafting.[7−9] After surgical aortic valve replacement (SAVR), however, a meta-analysis[10] of only 4 studies demonstrated no significant difference in early all-cause mortality between statin and control groups. Impact of statin on mortality after transcatheter aortic valve implantation (TAVI) has been less investigated. Our aim was to determine whether statin therapy is associated with better midterm survival after TAVI, performing the first meta-analysis of currently available studies.

Methods

To identify all studies reporting impact of statin on midterm mortality after TAVI, PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Web of Science (http://www.webofknowledge.com/wos), and Google Scholar (https://scholar.google.com) were searched through March 2019. Search terms included *transcatheter; aortic valve; implantation* or *replacement*; and *statin, hydroxymethylglutaryl-CoA reductase inhibitor, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin*, or *simvastatin*. Studies meeting the following criteria were included in the present meta-analysis: the design was an observational comparative study and a randomized controlled trial (RCT) of statin versus control (no statin) therapy or a cohort study investigating statin treatment as one of covariates; the study population was patients undergoing TAVI; outcomes included midterm (≥1 year) all-cause mortality.

Adjusted (if unavailable, unadjusted) hazard ratios (HRs) with their confidence interval (CIs) of mortality for statin therapy were extracted from each study. Study-specific estimates were combined by means of inverse variance-weighted averages of logarithmic HRs in the random-effects model. Funnel plot asymmetry (indicating publication bias) was mathematically assessed by use of the linear regression test. All analyses were performed using Review Manager version 5.3 (available from http://tech.cochrane.org/revman) and Comprehensive Meta-Analysis version 3 (Biostat, Englewood, New Jersey).

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See page 924 for disclosure information.

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Results

Eight eligible studies[11–18] with a total of 5,170 TAVI patients (Table 1) were identified and included in the present meta-analysis. None was an RCT, 4[14–16,18] were observational comparative studies (including 1 propensity score matched study[17]) of statin versus no statin therapy, and 4[11–13,17] were cohort studies investigating statin treatment as one of covariates. Statin prescribe was defined at baseline in all[11–17] but one[18] (at discharge) studies. The follow-up duration was 1 year in 3 studies,[11,13,17] 2 years in 3 studies,[12,15,18] and 5 years in 2 studies.[14,16] Three studies[14,16,18] reported adjusted HRs using the multivariate Cox proportional hazards regression analysis[14,16] and the propensity score matching analysis.[18] In 3 studies,[11–13] statin therapy was not entered into the multivariate analysis because the unadjusted HR derived from the univariate analysis was not statistically significant ($p \geq 0.05$), and accordingly only unadjusted HRs were available. From 2 studies,[15,17] unadjusted risk ratios (RRs) were extracted and pooled together with HRs because any HRs were unavailable (Table 2). Huded et al[14] and Merdler et al[16] reported adjusted HRs for high intensity statin and for low/moderate intensity statin separately, and unadjusted RRs for high intensity statin versus no statin and for low/moderate intensity statin versus no statin were severally extracted from a study by Klinkhammer et al[15] These estimates for high intensity statin were combined in the primary meta-analysis, and those for low/moderate intensity statin were pooled in the secondary meta-analysis.

The primary meta-analysis demonstrated that statin treatment was associated with significantly lower midterm mortality (HR, 0.74; $p = 0.005$; Figure 1). The secondary meta-analysis also indicated an association of statin therapy with significantly lower midterm mortality (HR, 0.80; $p = 0.005$; Figure 2). High intensity statin treatment, however, was not associated with lower midterm mortality compared with low/moderate intensity statin therapy (HR, 0.70; $p = 0.11$; Figure 3). A number of sensitivity analyses for the primary meta-analysis were performed. First, excluding a study by Peri-Okonny et al[18] with the highest weight (25.2%), in which statin prescribe was defined at discharge, brought about significant benefit for statin treatment (HR, 0.77; $p = 0.04$). Second, exclusion of 2 studies[14,16] with 5-year follow-up resulted in significant advantage favoring statin therapy (HR, 0.80; $p = 0.03$). Third, excluding RRs from 2 studies[15,17] leaded to significant benefit for statin treatment (HR, 0.74; $p = 0.02$). No funnel plot asymmetry for the primary meta-analysis ($p = 0.64$) was identified (Figure 4), which suggested probably no publication bias.

Discussion

The present meta-analysis suggests that statin therapy is associated with better midterm survival after TAVI, which was robust in sensitivity analyses without publication bias. Because no study included in the present meta-analysis unfortunately performed subgroup analyses, it remains unclear whether there are specific patients who are more likely than others to benefit from statin treatment. Hence, we could not recommend whether statin should be

Table 1
Baseline patient characteristics

Study	Region	Statin	Patient number				Age (year)*				Men (%)				STS-PROM (%)*				
			Statin				Statin				Statin				Statin				
			HI†	L/MI	Total	No statin	HI†	L/MI	Total	No statin	Total	HI†	L/MI	Total	No statin	Total	HI†	L/MI	Total	No statin	Total
Debonnaire 2015[11]	Netherlands, Italy	Baseline	N/A		247	264		N/A		N/A	82 (77–86)		N/A		N/A	38.0		N/A		N/A	16.6 (12.5–22.1)
Franzone 2017[12]	Switzerland	Baseline	N/A		231	238		N/A		N/A	82.3 ± 5.5		N/A		N/A	43.7		N/A		N/A	6.9 ± 4.5
Honda 2018[13]	Japan	Baseline		N/A		N/A	969		N/A		84 ± 5			N/A		31.0		N/A		N/A	6.7 (4.6–9.3)
Huded 2017[14]	US	Baseline	41	173	214	80	294	80.9 ± 6.9	83.3 ± 8.0	82.8	83.6 ± 7.5	56.1	55.5	55.6	40.0	51.4	8.8 ± 4.1	9.0 ± 4.5	9.0	8.1 ± 3.3	8.8 ± 4.2
Klinkhammer 2018[15]	US	Baseline	50	193	243	99	342	77.3 ± 8.8	79.9	79.4 ± 8.4	79.3 ± 10.2	79.4	72.0	57.0	59.7	46.5	55.8	6.2 ± 3.1	7.2	7.0 ± 4.0	6.2 ± 4.4	6.8
Merdler 2019[16]	Israel	Baseline	254	667	921	317	1238	80.8 ± 6.3	82.8 ± 5.6	82.2	83.9 ± 6.1	82.7	52	44	46	40	45	3.9 ± 3.4	4.2 ± 2.9	4.1	4.3 ± 3.2	4.2
Okuno 2019[17]	Japan	Baseline	N/A		48	47	95		N/A		N/A	84 (81–88)		N/A		N/A	29.5		N/A		N/A	5.18 (3.96–7.12)
Peri-Okonny 2019[18,‡]	US, Canada	Discharge	N/A		626	626	1252		N/A	84 (78–87)	84 (80–88)	84 (79–88)	N/A		49.0	48.4	48.7		N/A		N/A	6.1 (4.7–8.5)

HI = high intensity; HR = hazard ratio, L/MI = low/moderate intensity; N/A = not available; STS-PTOM = Society of Thoracic Surgeons Predicted Risk of Mortality.
* Mean, mean ± standard deviation, or median (interquartile range).
† Rosuvastatin 20 to 40 mg/day or atorvastatin 40 to 80 mg/day.
‡ Propensity score matching.

Table 2
Relative risk estimates

Study	Follow-up (years)				Relative risk estimate [95% CI]
Debonnaire 2015[11]	1	Unadjusted*	HR		1.19 [0.76, 1.84]
Franzone 2017[12]	2	Unadjusted*	HR		0.91 [0.63, 1.31]
Honda 2018[13]	1	Unadjusted*	HR		0.67 [0.41, 1.08]
Huded 2017[14]	5	Adjusted	HR	for HI statin	0.358 [0.143, 0.900]†
			HR	for L/MI statin	0.622 [0.359, 1.078]‡
Klinkhammer 2018[15]	2	Unadjusted	RR§	for HI vs no statin	0.70 [0.31, 1.59]†
		Unadjusted	RR§	for L/MI vs no statin	0.96 [0.61, 1.50]‡
Merdler 2019[16]	5	Adjusted	HR	for HI statin	0.59 [0.37, 0.96]†
			HR	for L/MI statin	0.82 [0.57, 1.18]‡
Okuno 2019[17]	1	Unadjusted	RR§		0.78 [0.22, 2.74]
Peri-Okonny 2019[18,¶]	2	Adjusted	HR		0.65 [0.49, 0.87]

CI = confidence interval; HI = high intensity; HR = hazard ratio, L/MI = low/moderate intensity; RR = risk ratio.

* The multivariate analysis was conducted. Statin therapy, however, was not entered into the multivariate analysis because the unadjusted HR derived from the univariate analysis was not statistically significant ($p \geq 0.05$).

† Pooled in the primary meta-analysis.

‡ Pooled in the secondary meta-analysis.

§ The RR was extracted instead of the unavailable HR.

¶ Propensity score matching.

prescribed to all patients undergoing TAVI or to specific patients with no indication for statin therapy.

The following findings may strength the present result. Peri-Okonny et al[18] reported, in their propensity score matched study, that statin treatment was associated with lower 2-year cardiovascular (HR, 0.66; p = 0.030) and non-cardiovascular mortality (HR, 0.64; p = 0.045) after TAVI. Although, in the same study,[18] there was no difference in

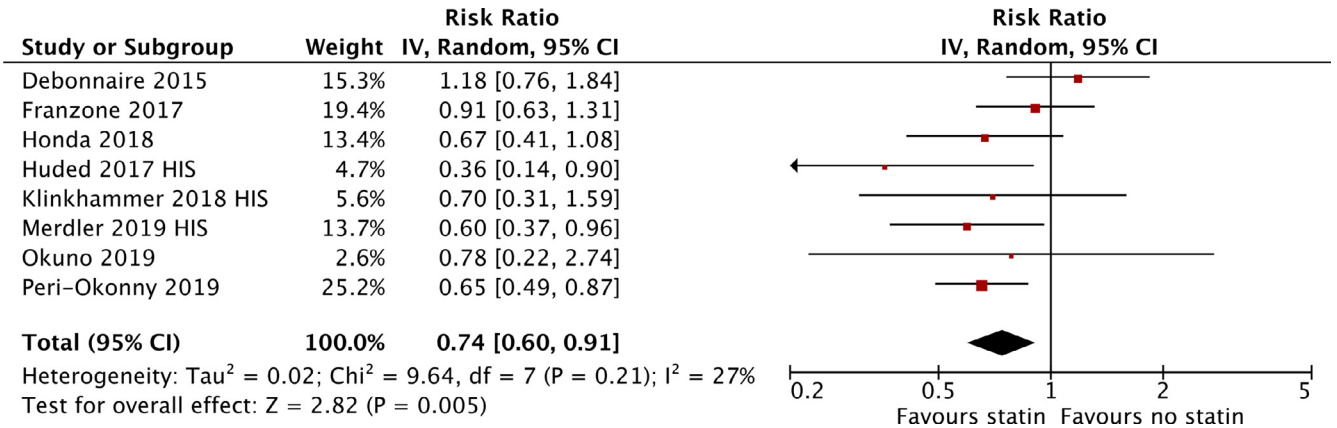

Figure 1. Primary meta-analysis (q.v. text) of midterm all-cause mortality for statin therapy versus no statin. CI = confidence interval; HIS = high intensity statin; IV = inverse variance.

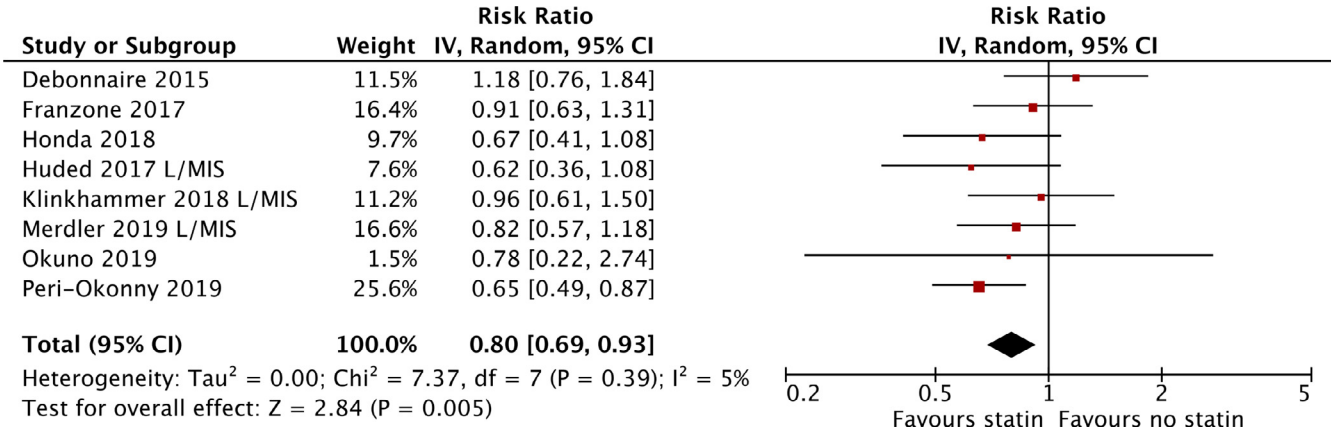

Figure 2. Secondary meta-analysis (q.v. text) of midterm all-cause mortality for statin therapy versus no statin. CI = confidence interval; IV = inverse variance; L/MIS = low/moderate intensity statin.

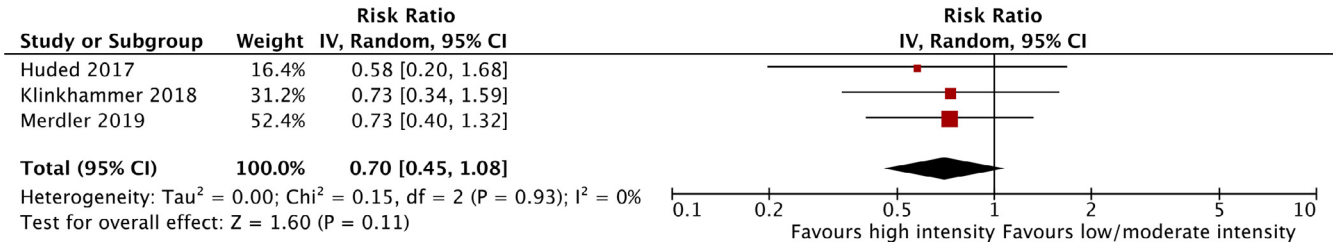

Figure 3. Meta-analysis of midterm all-cause mortality for high versus low/moderate intensity statin therapy. CI = confidence interval; IV = inverse variance.

2-year incidence of MI (HR, 1.89; p = 0.031) between the stain and no statin groups. Furthermore, Klinkhammer et al[15] provided no differences in incidence of MI in all the periods of in-hospital (0.8% vs 0%; p = 0.412), discharge to 30 days (1.6% vs 0%; p = 0.663), 30 days to 6 months (1.2% vs 0%; 0.639), and 6 months to 1 year (0.8% vs 2.0%; p = 0.070) after TAVI between the any and no statin groups. Interestingly, despite the present finding, there was no difference in 2-year mortality between the statin and no stain groups (HR, 1.21; p = 0.41) among patients referred for but not undergoing TAVI in a study by Kang et al[19]

A number of meta-analyses[6–9] suggest associations of statin treatment with lower early all-cause mortality[6–8] and midterm mortality from MI[9] after cardiac surgery[6] and coronary artery bypass grafting.[7–9] After SAVR, however, statin therapy may not associate with lower early

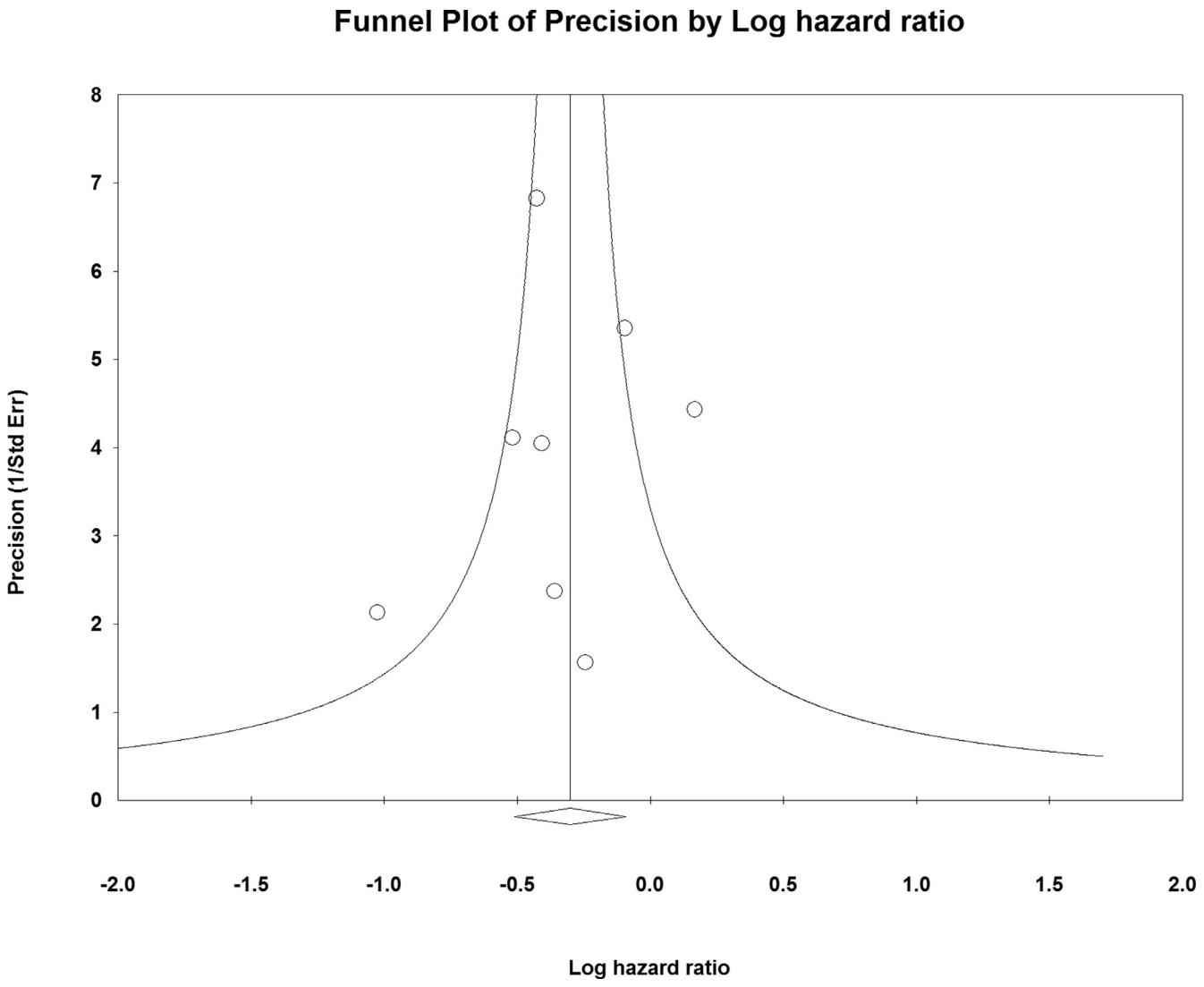

Figure 4. Funnel plot of precisions by logarithmic hazard ratios of midterm all-cause mortality for statin therapy versus no statin in the primary meta-analysis (q.v. text).

mortality.[10] The meta-analysis by Kuhn et al[10] of only 4 observational studies with 3,091 patients undergoing SAVR reported no statistically significant difference in early incidence of all-cause death (OR, 0.72; p = 0.14), MI (OR, 1.02; p = 0.97), stroke (OR, 0.77; p = 0.34), and renal failure (OR, 0.68; p = 0.12) between statin and control groups.

The present result favoring statin therapy for midterm mortality after TAVI may not be owing to reduced ischemic events, because of no difference in 2-year incidence of MI in the propensity score marched study by Peri-Okonny et al[18] Hence, the present finding may be explicated by the anti-inflammatory and/or pleiotropic influence of stains. In statins, not only anti-inflammatory functions but also both lipid-lowering dependent and independent functions certainly exist, the latter of which include functions requiring cholesterol synthesis (e.g. regulation of the membrane function), those involving protein prenylation (e.g. by farnesyl pyrophosphate or geranylgeranyl pyrophosphate), or those not requiring interaction with hydroxymethylglutaryl-CoA reductase (e.g. by direct interaction with proinflammatory mediators such as leukocyte-function antigen-1 and T-cell receptor).[20] Without lipid-lowering effects, statins regulate vascular repair after injury, which are associated with reductions in cellular proliferation, leukocyte accumulation, and platelet-derived growth factor-induced phosphorylation of the survival factor Akt and an increase in apoptosis after injury.[21] Statin-induced Kruppel-like factor 2 expression may provide favorable effects in endothelial cells, because reduced Kruppel-like factor 2 expression diminishes statin-mediated accumulation of endothelial NO synthase and thrombomodulin levels.[22]

The present finding should be interpreted with caution because of the following limitations. First, the present result was drawn from nonrandomized studies (observational and cohort studies), in which attrition is often worse and inadequately provided, intervention and outcome evaluation are seldom practiced in accordance with standard protocols, and outcomes are rarely blinded.[23] Second, statin prescribe was defined at baseline[11–17] or discharge[18] in the studies included in the present meta-analysis. It was unclear that statin prescribe was continued during the follow-up period after discharge. Third, publication bias favoring statin therapy may affect the present finding. Nonsignificant covariates in the univariate analysis are usually not entered into the multivariate analysis and seldom reported. The present statistical assessment of the funnel plot, however, did not detect asymmetry, which suggests minimal publication bias.

In conclusion, statin therapy is associated with better midterm survival after TAVI, which warrants a large-size RCT with longer term follow-up.

Disclosures

The authors have no conflicts of interest to disclose.

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