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Meta-analysis

Corticosteroid Therapy and Vascular Complications in Patients Undergoing Transcatheter Aortic Valve Replacement: A Meta-analysis With Meta-regression

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ABSTRACT

Background: Corticosteroid use is associated with vascular fragility, prolonged wound healing, and infections. Therefore, we sought to compare outcomes between patients with aortic stenosis undergoing transcatheter aortic valve replacement who were using corticosteroids versus those who were not.

Methods: This is a study-level meta-analysis and meta-regression of observational studies. The primary end points of this study were rates of vascular complication (both major and minor), life-threatening bleeding, and 30-day mortality. Secondary end points included acute kidney injury rates, annular rupture, cardiac tamponade, closure device failure, coronary obstruction, periprocedural myocardial infarction, permanent pacemaker implantation, stroke, and specific vascular complications with its complementary therapy.

Results: Across the studies, patients were slightly predominantly female, older, and had a mean left ventricular ejection fraction of more than 50% with an intermediate Logistic EuroScore II. Significant differences were observed in the vascular complication rates between patients on corticosteroids and those who were corticosteroid-free (relative risk, 0.63; 95% CI, 0.35-0.90; $P < .001$), driven primarily by arterial occlusion, surgery, balloon angioplasty, and stenting (relative risk, 0.63; 95% CI, 0.32-0.93; $P < .05$). There was no difference in the 30-day mortality. No differences were seen in the length of corticosteroid therapies. For the secondary outcomes, there was an increased risk of annular rupture and cardiac tamponade in patients taking corticosteroids.

Conclusions: In conclusion, this is the first meta-analysis with meta-regression that showed a higher risk for vascular complications and life-threatening bleeding in patients on corticosteroid therapy undergoing transcatheter aortic valve replacement, despite no increase in the risk of 30-day mortality.

Based on the positive results of the PARTNER 3[1] and the Evolut Low Risk[2] trials, in 2019, the US Food and Drug Administration approved transcatheter aortic valve replacement (TAVR) for the treatment of severe aortic stenosis in low-risk patients, expanding its indication previously approved for patients with intermediate, high, and prohibitive risks. As a result, more patients with aortic stenosis are expected to undergo TAVR, including those with chronic conditions treated with steroids.[3] Regular steroid use is a well-known factor for tissue fragility, which can become an issue when dealing with large-bore vascular access for TAVR.[4] Patients treated with steroids have an increased risk of early death after cardiac surgery.[5] Therefore, the Society of Thoracic Surgeons score considers steroids when estimating the 30-day mortality after any cardiac surgical procedure.[6]

Transcatheter aortic valve replacement may be advantageous in preventing wound complications and life-threatening infections, thereby minimizing the risk of undesired events, compared with surgical aortic valve replacement in patients on chronic steroid therapy.[7] However, only a few studies have assessed corticosteroids in patients undergoing TAVR,

Abbreviations: AKI, acute kidney injury; MI, myocardial infarction; PPI, permanent pacemaker implantation; RR, relative risk; TAVR, transcatheter aortic valve replacement.

Keywords: corticosteroids; heart valve prosthesis implantation; meta-analysis; mortality; transcatheter aortic valve replacement; vascular complications.

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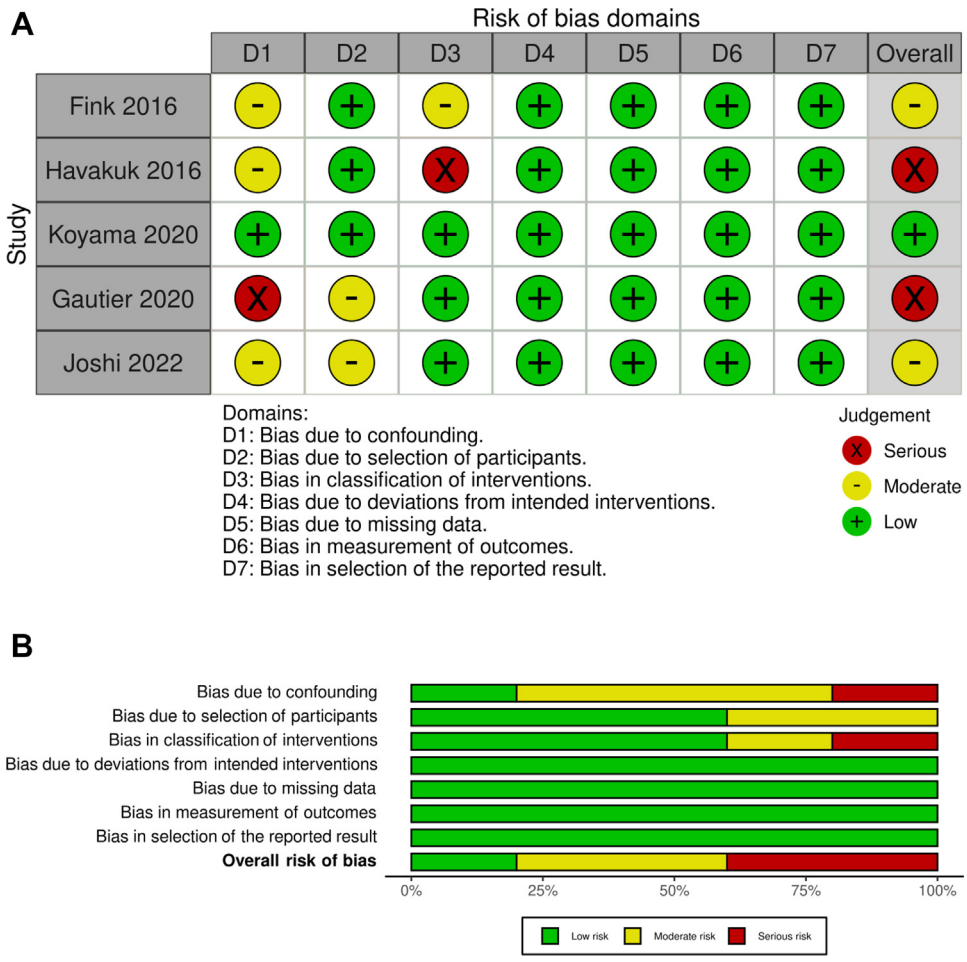


Figure 1. Risk of bias summary ROBINS-I tool with traffic lights (A) and summary plot (B).

and the link between corticosteroid use and vascular complications remains unclear. No randomized controlled trials have addressed this important clinical question to date.

The heart team needs to be aware of the potential challenges of TAVR, including its vascular complications. Because there is a paucity of data documenting the relationship and clinical effects of steroid therapy on vascular complications in patients who underwent TAVR, we performed this systematic review with a meta-analysis of studies examining the use of steroids and its clinical outcomes, mainly vascular-related complications, in patients who underwent TAVR.

Materials and methods

Eligibility criteria, databases, and search strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.[8] In addition, using the Population, Interventions, Comparison, Outcome, and Study (PICOS) design strategy, studies were included if the following criteria were fulfilled:

1. The population was comprised of patients who underwent TAVR.
2. In 1 arm, patients were receiving corticosteroids.
3. In the other arm, patients were not receiving corticosteroids.
4. Outcomes studied included any of the following: vascular complications and life-threatening bleeding clearly defined using a standardized end points definition[9,10]; etiology for the vascular complication with its treatment, acute kidney injury (AKI), annular rupture, acute coronary obstruction, cardiac tamponade, closure device failure, permanent pacemaker implantation (PPI), or periprocedural myocardial infarction (MI).
5. The study design was retrospective, prospective, randomized, or nonrandomized.

The following databases were searched for studies meeting our inclusion criteria and published by June 10, 2022: PubMed/MEDLINE, Embase, Cochrane Database, Google Scholar, ScienceDirect, and Web of Science. In addition, we searched for the following terms: ("transcatheter aortic valve implantation" OR "transcatheter aortic valve replacement" OR "TAVI" OR "TAVR" OR "aortic valve" OR "aortic valve stenosis" OR "aortic valve disease") AND ("steroid therapy" OR "corticosteroid therapy" OR "oral steroids" OR "systemic steroids") AND ("vascular complications" OR "vascular repair" OR "complications"). The following steps were taken for study selection: (1) identification of titles of records through database search; (2) removal of duplicates; (3) screening and selection of abstracts; (4) assessment for eligibility through full-text papers; and (5) final inclusion in the meta-analysis. Studies were selected by 2 independent reviewers (C.M. and F.M.). There were no language restrictions. The third/fourth reviewers arbitrated discrepancies to achieve consensus (T.P. and R.L.). This study was registered in PROSPERO (CRD42022339352).

End points, assessment of publication bias, and statistical analysis

The study's primary end points were vascular complications, life-threatening bleeding, and 30-day mortality, clearly defined using a standardized end points definition.[9,10] The secondary end points were

Table 1. Baseline characteristics.

Characteristic	Corticosteroid (n = 278)	No corticosteroid (n = 3969)	*P* value
Age, y	80.7 ± 2.5	82 ± 1.5	.23
Female sex	138 (49%)	2207 (55%)	.46
Hypertension	192 (69%)	1866 (47%)	.001
Hyperlipidemia	77/179 (43%)	766/2977 (25%)	.001
Diabetes mellitus	87 (31%)	1136 (28%)	.34
Chronic kidney disease	40 (14%)	806 (20%)	.02
Previous MI	27 (9.7%)	299 (7.5%)	.10
Previous stroke	52 (18%)	507 (12%)	.04
Peripheral vascular disease	33 (12%)	594 (15%)	.15
Coronary artery disease	97 (35%)	1442 (36%)	.70
Atrial fibrillation	114 (41%)	1357 (34%)	.02
EuroScore II[a]	5.2	4.6	.78
Ejection fraction, %	56 ± 6	56 ± 3.7	.90

Values are mean ± SD or n (%), unless otherwise noted.
MI, myocardial infarction.
[a] Median.

etiology for the vascular complication with its treatment, AKI, annular rupture, acute coronary obstruction, cardiac tamponade, closure device failure, and PPI or periprocedural MI.

The Risk of Bias in Nonrandomized Studies of Interventions tool was systematically used to assess included studies for risk of bias.[11] The papers and their characteristics were classified into a low, moderate, and severe risk of bias (P.V. and J.F.). Two independent reviewers (M.P.S. and B.R.) assessed the risk of bias. When there was a disagreement, the senior reviewers (T.P. and R.K.) checked the data and made the final decision.

Risk ratios with 95% CIs for the crude end points were calculated. The ratios were calculated as corticosteroid use versus non-corticosteroid use. For other comparative data, differences in means with 95% CIs and *P* values were considered. Forest plots were constructed to represent clinical outcomes. Chi-square and I^2 tests were performed for assessment of statistical heterogeneity.[12] Proportions were combined across the studies using a random-effects model.[13] A funnel plot was generated for each outcome to assess the publication bias, and it was statistically evaluated using the Begg and Mazumdar test[14] and Egger test,[15] if feasible. Sensitivity analyses on the primary end point, excluding the studies that were deemed to have an overall serious bias in Figure 1, were also performed. The major interest is how the meta-analytical point estimates the risk ratio difference between the meta-analysis when all studies are included versus the meta-analysis that excludes the potentially-severely-biased studies. A

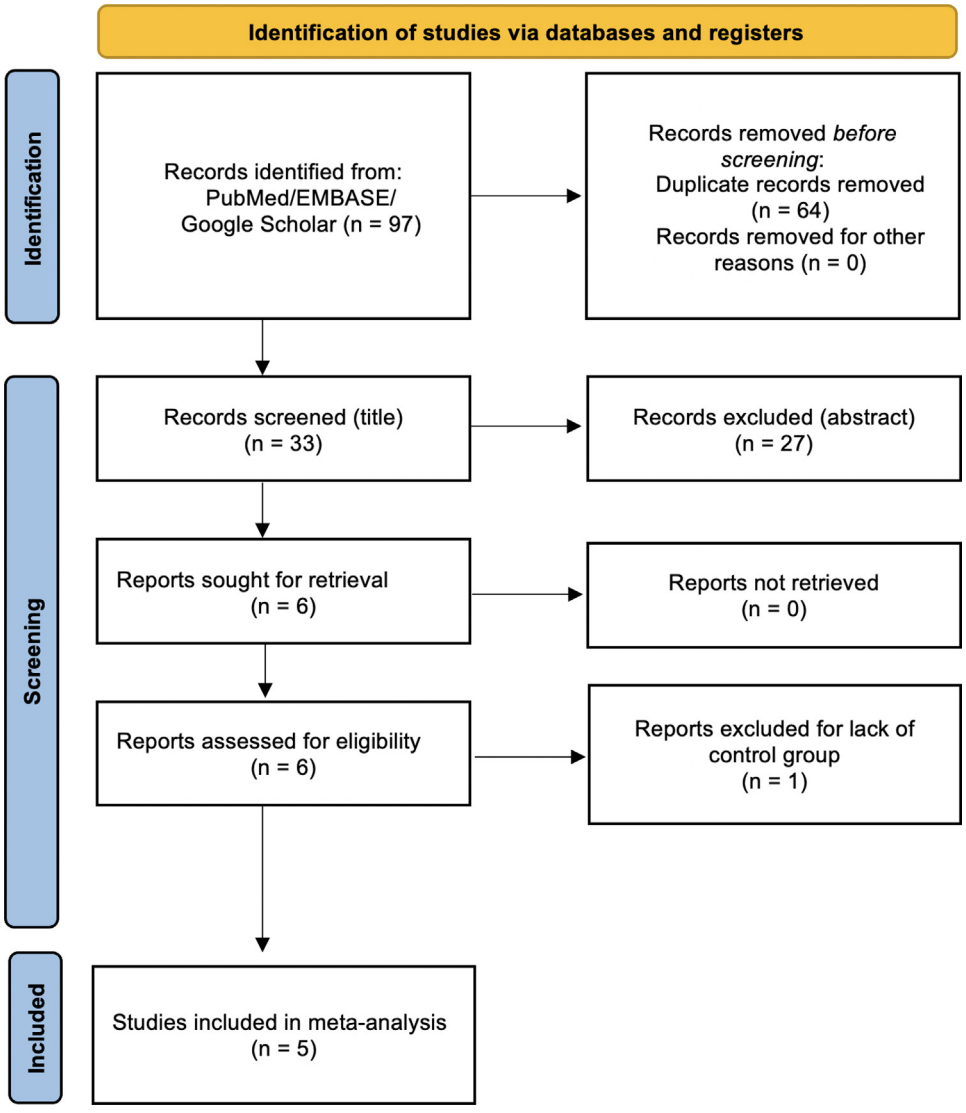


Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart.

Table 2. Summary of included studies.

Reference, year	Design	Country	N (total)/corticosteroid arm	Length of corticosteroid therapy prior to TAVR	Criteria used to define the primary vascular outcomes
Fink et al,[17] 2016	Nonrandomized; retrospective; single center	Israel	220/25 (11.3%)	1390 d (mean)/900 d (median)	VARC-2
Havakuk et al,[18] 2016	Nonrandomized; prospective; single center	Israel	324/39 (12%)	3 d	VARC
Koyama et al,[19] 2020	Nonrandomized; prospective; multicentric registry	Japan	1313/67 (5%)	At least more than 30 d	VARC-2
Gautier et al,[20] 2020	Nonrandomized; retrospective; single center	France	1299/48 (3.7%)	At least more than 30 d	VARC-2
Joshi et al,[21] 2022	Nonrandomized; retrospective; single center	United States	1091/99 (9%)	N/A	VARC-2

TAVR, transcatheter aortic valve replacement; VARC, Valve Academic Research Consortium.

meta-regression analysis was carried out to analyze the impact of corticosteroid duration on primary outcomes, aiming to assess whether time variability in the course of corticosteroid therapy could modulate the outcome. The *P* values for Table 1 were compared using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Statistical analyses were conducted using Jamovi 'built-in' R version 3.2 and Origin Pro 2020b. All values were 2-tailed, and $P < .05$ was set as the threshold for statistical significance.

Results

Patients characteristics

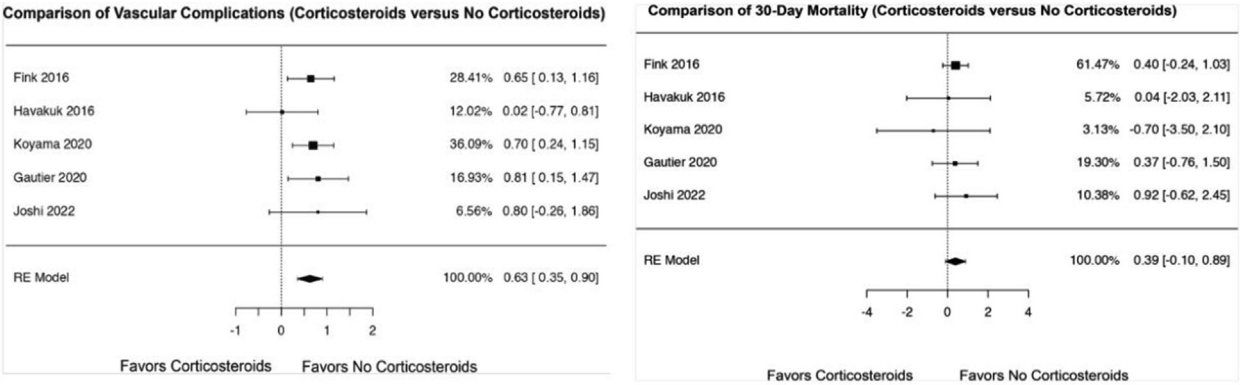
Our search retrieved 97 entries, which were reduced to 6 studies after an initial prescreening. Three studies were excluded based on the excluded criteria. In the eligibility assessment, 1 additional study was excluded because it compared corticosteroids in TAVR versus surgical aortic valve replacement, and there was no control group.[16] Finally, 5 studies[17–21] were available for the analysis (1 propensity-matched) with 4247 patients (corticosteroid users: 278; noncorticosteroid users: 3969). Our search strategy is displayed in Figure 2. All studies retrieved based on our search analysis and included in this study were nonrandomized. Of note, there are no randomized controlled trials on this subject. Table 2 includes the included studies with some important demographic and design details. Figure 1 shows the qualitative assessment of the studies with the Risk of Bias in Nonrandomized Studies of Interventions tool. There were some concerns regarding confounders in the analyses due to differences between the groups regarding the risk, age, sex, prevalence of chronic obstructive pulmonary disease, and kidney disease. These differences might lead to the effect of bias in the moderate- to high-risk range.

Baseline characteristics

Across studies, patients were slightly predominantly female, older, and had a mean left ventricular ejection fraction of more than 50% with an intermediate Logistic EuroScore II. The absolute number and percentages of patients with hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, previous MI, previous stroke, peripheral arterial disease, coronary artery disease, and atrial fibrillation were also available and are summarized in Table 1.

Primary outcomes

The analysis of this study's primary outcome, including the rates of vascular complications (both major and minor), life-threatening bleeding, and 30-day mortality, is shown in the Central Illustration and Figure 3A, respectively. There was a statistically significant difference in the vascular complication rates between patients on corticosteroids and those who were corticosteroid-free (relative risk [RR], 0.63; 95% CI, 0.35-0.90; $P < .001$). Heterogeneity within the included studies was low ($I^2 = 0\%$), as seen in the Central Illustration (left). The follow-up period for this outcome varied among the studies from 30 to 763 days. In our sensitivity analyses, after excluding the studies with a high risk of bias, as shown in Figure 1, the difference between groups was no longer observed (RR, 0.2; 95% CI, -0.63 to 1.04; $P = .057$), despite a higher heterogeneity ($I^2 = 64.75\%$). Life-threatening bleeding rates were also analyzed in 3969 patients from 5 studies (Figure 3A). There was a statistically significant difference in life-threatening bleeding rates between patients undergoing TAVR taking corticosteroids and those who were not (RR, 0.80; 95% CI, 0.36-1.25; $P = .003$). Heterogeneity within the included studies was low ($I^2 = 7.5\%$), and to further explore this finding and its association with mortality, an



Central Illustration. Left: Random-effects meta-analysis of vascular complications in patients who underwent transcatheter aortic valve replacement using corticosteroids versus those who were not. **Right:** Random-effects meta-analysis of 30-day mortality associated with transcatheter aortic valve replacement in patients using corticosteroids versus those who were not.

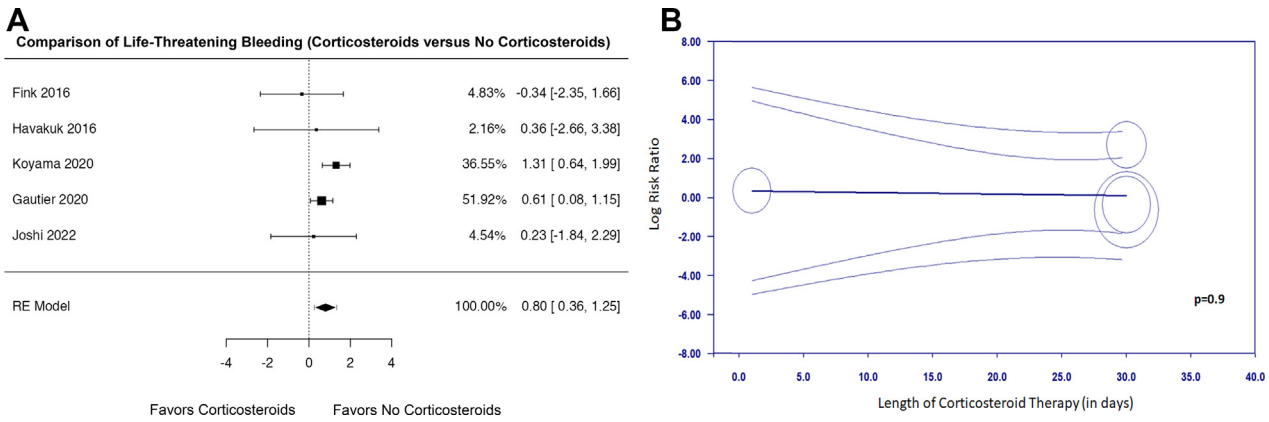


Figure 3. **(A)** Random-effects meta-analysis of life-threatening bleeding associated with transcatheter aortic valve replacement in patients using corticosteroids versus those who were not. (**B**) Random-effects meta-regression of life-threatening bleeding versus length of corticosteroid therapy in days. RE, random-effects.

analysis of 30-day mortality was carried out. There was no significant difference in the 30-day mortality between patients on corticosteroids and those not undergoing TAVR (RR, 0.39; 95% CI: -0.10 to 0.89; $P = .122$). Heterogeneity within the included studies was low ($I^2 = 0\%$). A meta-regression of the log risk ratio of vascular complications over the duration of corticosteroid therapy was not significant ($P = .06$, Figure 4), and the same finding was obtained for the log risk ratio of life-threatening bleeding over the course of corticosteroid therapy ($P = .9$, Figure 3B).

Secondary outcomes

Acute kidney injury, acute coronary obstruction, closure device failure, PPI, or periprocedural MI did not show any difference between patients undergoing TAVR who were on corticosteroids versus those who were not (Figure 5). The follow-up time for the secondary outcomes varied between 1 and 60 months in those studies that reported such analysis.[16,17,20] The studies that reported follow-up time for secondary outcomes this for this outcome varied among studies from 30 to 763 days. The noncorticosteroid arm had fewer vascular complications compared with the corticosteroid arm for femoral artery stenosis (RR, 1.14; 95% CI, 0.06-2.22), occlusion (RR, 2.05; 95% CI, 0.14-3.97), femoral artery surgery (RR, 0.88; 95% CI, 0.13-1.62), and femoral angioplasty or stenting (RR, 0.77; 95% CI, 0.10-1.43), as seen in the Central Illustration (right). In terms of cardiac-related complications, the noncorticosteroid arm had fewer annular ruptures (RR, 1.41; 95% CI, 0.43-2.38) and less cardiac tamponade (RR, 1.56; 95% CI, 0.67-2.45).

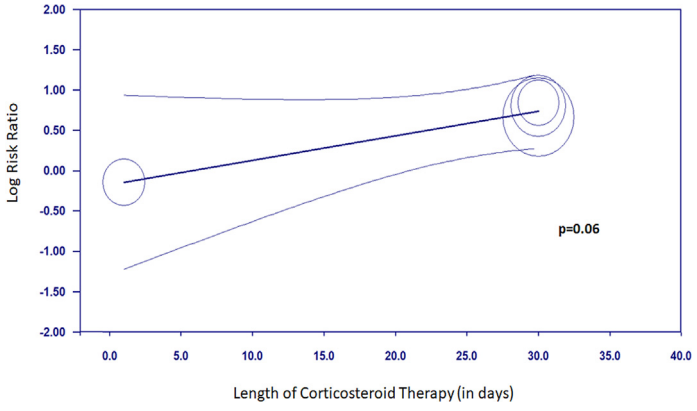


Figure 4. Random-effects meta-regression of vascular complications versus length of corticosteroid therapy in days. RE, random-effects.

Risk of bias across the studies (publication bias)

In a meta-analysis of a few studies (<10), the asymmetry test cannot distinguish random bias from true asymmetry. Therefore, our analysis could not statistically assess the presence of publication bias appropriately due to the insufficient number of studies in the medical literature (Supplemental Figures S1-S3). A sensitivity analysis for vascular complications was performed after excluding the studies with high risk of bias (Supplemental Figure S4)

Discussion

This is the first meta-analysis with meta-regression investigating the possible impact of corticosteroid therapy on vascular complications and major bleeding associated with TAVR. Our study suggests that treatment with corticosteroids is associated with an increase in the rate of vascular complications and life-threatening bleeding in patients undergoing TAVR. This was primarily driven by a statistically significant increase in femoral artery occlusion, stenosis, femoral artery surgery, and femoral artery angioplasty or stenting in the patients receiving corticosteroid therapy. A plausible theory is that corticosteroids have been shown to affect wound healing by inhibiting transforming growth factor-β and insulin-like growth factor 1.[7,22] Reductions in these cells' signaling hormones reduce hydroxyproline levels, a surrogate marker for collagen formation, leading to a less compliant arterial bed with poor elasticity.[22] Chronic therapy has also been further demonstrated to significantly suppress the proliferation of endothelial progenitor cells.[23] Endothelial progenitor cells participate in neovascularization and assist in wound healing by migrating to areas of injury and modulating the repair process by excreting proangiogenic factors.[24]

Our meta-regression did not find a statistically significant difference in vascular complication rates in patients with chronic versus acute corticosteroid use. Corticosteroid use was not associated with worse 30-day mortality despite an increased risk of vascular access and major bleeding complications. In addition, there was no statistically significant difference in the rates of AKI, closure device failure, PPI, periprocedural MI, or acute coronary obstruction on secondary outcomes. On the other hand, corticosteroid use was associated with worse cardiac-related complications, such as annular rupture and cardiac tamponade.

Our study found a statistically significant difference in vascular complications in patients on corticosteroid therapy versus those without (RR, 0.63; 95% CI, 0.35-0.90; $P < .001$). In subgroup analysis, most of these complications were related to the femoral artery's vascular access site used in TAVR. This finding correlates with prior research, which has demonstrated an increased risk of vascular complications in patients on

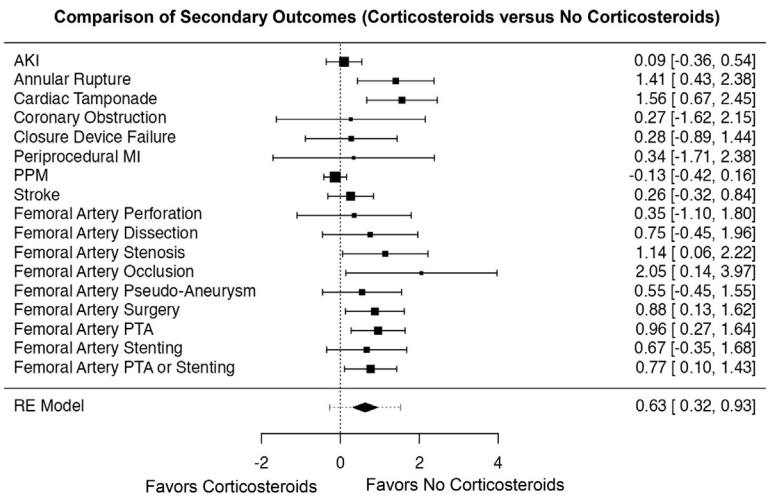


Figure 5. Random-effects meta-analysis of the secondary outcomes in patients who underwent transcatheter aortic valve replacement using corticosteroids versus those who were not. AKI, acute kidney injury; MI, myocardial infarction; PPM, permanent pacemaker; PTA, percutaneous transluminal angioplasty; RE, random-effects.

corticosteroid therapy following cannulation of the aorta during cardiac bypass.[25] The increased complication rate is presumed to result from the decreased effectiveness of intrinsic wound healing in patients on corticosteroid therapy, which can be more pronounced in patients with diabetes, leading to possible worse outcomes, which need to be confirmed in more extensive studies.[22]

Previous studies on wound healing after surgery in patients taking corticosteroids have demonstrated a deleterious effect on wound healing with long-term corticosteroid therapy and minimal effect with short-term therapy.[7,22,23] In our analysis, there was a trend toward increased risk of vascular complication with increased duration of corticosteroid therapy; however, it was not statistically significant. It is unclear if this trend would become significant with a larger sample size or if the long-term effects of corticosteroid use do not represent a deleterious effect in relation to TAVR. In addition, most of the patients in the studies included in our analysis were on low doses of corticosteroids, and further evaluation of dose-related impacts is warranted.

A single-center, observational study on patients receiving chronic corticosteroid therapy demonstrated increased vascular complications and major bleeding with an increased risk of coronary perforation[26] in patients undergoing percutaneous coronary intervention. Our analysis found similar findings in patients on corticosteroids regarding vascular complications, including life-threatening access-related bleeding (RR, 0.80; 95% CI, 0.36-1.25; $P = .003$), annular rupture (RR, 1.41; 95% CI, 0.43-2.38), and cardiac tamponade (RR, 1.56; 95% CI, 0.67-2.45), without an impact in the 30-day mortality (RR, 0.39; 95% CI, -0.10 to 0.89; $P = .122$), a reassuring finding. This latter finding may be related to the chronicity of therapy. A recent analysis of preoperative corticosteroid use in cardiac surgery found a decrease in bleeding rates following cardiac surgery.[27] Our study included patients with both short-term and long-term use of corticosteroid therapy. Our net result was no statistically significant increase in 30-day mortality after corticosteroid therapy against those who were not on corticosteroid therapy. It is unclear whether this is due to a net neutral effect because of long-term steroid therapy causing increased bleeding risks and short-term treatment causing decreased bleeding risks.

While our analysis adds to emerging evidence that corticosteroid use is associated with an increased risk of vascular complications and life-threatening bleeding, many factors remain to be investigated. Further studies on chronic versus acute corticosteroid use and the dose-effect relationship are warranted. The use of vascular closure devices should be controlled in these studies. Comorbidities are another aspect that is difficult to control, as patients with large-vessel vasculitis are often on chronic corticosteroid therapy and would be presumed to have a higher risk of vascular complications from their disease and not necessarily from the corticosteroids themselves.

Limitations

This study has several limitations, mainly because of the limited studies on the topic. The retrieved data are based on observational studies with limited follow-up and may not apply to different patient populations. Randomized controlled trials are needed to determine the role of corticosteroid therapy and vascular complications in patients undergoing procedures with large bore access. Meanwhile, in the absence of definitive evidence, careful evaluation of patients on an individual basis is of paramount importance to determine if these procedures can be safely carried out in those individuals who require steroid therapy.

Conclusion

In conclusion, this is the first meta-analysis with meta-regression that showed a higher risk for vascular complications and life-threatening bleeding in patients on corticosteroid therapy undergoing TAVR despite no increase in the 30-day mortality. Furthermore, in our secondary outcomes, those on corticosteroids are at increased risk for cardiac-related complications (annular rupture and cardiac tamponade) and access site complications requiring more peripheral interventions or surgical procedures.

Declaration of competing interest

Dr Pasala has received educational grants from Medtronic and is a speaker for Phillips Healthcare. Dr Villablanca is a consultant for Edwards, Teleflex, and Angiodynamic and a proctor for Edwards. Dr Kaple is a speaker for Abbott and Edwards. Dr Vieira is a speaker for Novartis and Boehringer Ingelheim-Lilly. Dr Ramlawi has received financial support from Medtronic, Corcym, and AtriCure. Dr Sá receives support from the Thoracic Surgery Foundation (the charitable arm of the Society of Thoracic Surgeons) through the TSF Every Heartbeat Matters Global Structural Heart Fellowship Award. Drs Macedo, Lago, and Mejia-Otero have no financial conflicts to disclose.

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Ethics statement

This study was exempted from the institutional review board's approval because it used study (not patient)-level data, publicly available in the literature.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2022.100446.

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