Efficacy and safety of antithrombotic therapy with non-vitamin K antagonist oral anticoagulants after transcatheter aortic valve replacement: a systematic review and meta-analysis

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Abstract

Objective: A meta-analysis was performed to compare the efficacy and safety of antithrombotic therapy with non-vitamin K antagonist oral anticoagulants (NOACs) *versus* standard care in patients after successful transcatheter aortic valve replacement (TAVR).

Methods: A systematic search of PubMed, Cochrane Central Register of Controlled Trials, and EMBASE databases and ClinicalTrials.gov website (through 21 October 2020) was performed. Risk ratios (RRs) with 95% confidence intervals (CIs) for all outcomes were calculated using random-effects models.

Results: Twelve studies (two studies were randomized controlled trials) comprising 6943 patients were included (5299 had indications for oral anticoagulation (OAC) and 1644 had none). No significant differences were found between NOACs and the standard care in the incidences of all stroke, a composite endpoint, and major/life-threatening bleeding. NOACs were associated with lower all-cause mortality than vitamin K antagonists (VKAs) in post-TAVR patients with indications for OAC after more than 1 year of follow-up [RR = 0.64; 95% CI, (0.42, 0.96); $p = 0.03$], whereas NOACs exhibited poor outcomes than antiplatelet therapy (APT) in patients without indications for OAC [RR = 1.66; 95% CI, (1.12, 2.45); $p = 0.01$]. In the prevention of valve thrombosis, NOACs and VKAs were not significantly different in patients with indications for OAC [RR = 0.66; 95% CI, (0.24, 1.84); $p = 0.43$], whereas NOACs were better than APT in patients without indications for OAC [RR = 0.19; 95% CI, (0.04, 0.83); $p = 0.03$].

Conclusions: In patients with indications for OAC, post-TAVR antithrombotic therapy with NOACs was more favorable due to its lower all-cause mortality after more than 1 year of follow-up. In those without indications for OAC, NOACs presented poorer outcomes due to its higher all-cause mortality.

Keywords: APT, meta-analysis, NOACs, TAVR, VKAs

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Introduction

In patients with severe symptomatic aortic stenosis (AS), transcatheter aortic valve replacement (TAVR) is the standard of care for those who are at moderate to high surgical risk,[1] and on 16 August 2019, the U.S. Food and Drug Administration approved expanding the indication for TAVR to low-risk patients.[2]

Thromboembolic complications, such as stroke, systemic embolism, valve thrombosis, and venous thromboembolism, have been reported after

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TAVR,[3] and subclinical leaflet thrombosis may be associated with an increased incidence of cerebrovascular disease.[4] Therefore, an optimal antithrombotic regimen after TAVR is urgently needed; however, the recent antithrombotic regimen remains controversial and empirically based. According to current American guidelines, aspirin 75–100 mg daily is reasonable (class of recommendation IIa, level of evidence B-R), whereas treatment with low-dose rivaroxaban (10 mg daily) plus aspirin (75–100 mg) is contraindicated (III, B-R) based on the Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes (GALILEO) trial in TAVR patients without indications for oral anticoagulation (OAC). In patients with atrial fibrillation (AF) and other indications for OAC (such as venous thromboembolism), vitamin K antagonists (VKAs) therapy with a continuation of aspirin has been considered as standard of care and should be administered on the basis of the patient's CHA2DS2-VASc score (Supplementary Table 1). Patients with a low bleeding risk may be administered with 3- to 6-month dual antiplatelet therapy (DAPT) with aspirin 75 to 100 mg and clopidogrel 75 mg (IIb, B-NR) or anticoagulation with a VKAs to achieve an international normalized ratio (INR) of 2.5 for at least 3 months after TAVR (IIb, B-NR). European guidelines are slightly different, endorsing DAPT for 3 to 6 months after TAVR (IIa, C) or single-antiplatelet therapy in patients with high bleeding risk (IIb, C).[1,5–7] According to European guidelines, non-vitamin K antagonist oral anticoagulants (NOACs) may have more advantages than warfarin, but the sample is too small to draw a definite conclusion.[8]

NOACs have been demonstrated to reduce the incidence of thromboembolism in different clinical settings.[9] However, the need for its routine use to prevent thromboembolic events in post-TAVR patients without indications for OAC is not well documented. Moreover, in those with indications for OAC, whether using NOACs or VKAs as anticoagulants in antithrombotic therapy remains unclear and is actively debated, despite the more favorable efficacy profile of NOACs than VKAs in patients with non-valvular AF.[10] This study aimed to compare the efficacy and safety of antithrombotic therapy with NOACs *versus* standard care after TAVR and to identify the optimal antithrombotic therapy.

Methods

A systematic review and meta-analysis were carried out under the prespecified protocol (PROSPERO: CRD42020215578) and standards in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[11] The ethical approval was not applicable because this meta-analysis was not associated with ethics.

Search strategy

PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE databases and ClinicalTrials.gov websites were searched for relevant studies from the conception of the study to 21 October 2020. The reference lists of all included studies were independently screened to search for additional studies that were omitted in the primary search. The full details of the search strategy are presented in Supplementary Table 2.

Study selection

Two investigators (Q.A. and S.S.) selected the studies manually and independently using EndNote X9.3.3 software. Study inclusion was based on the PICOS criteria (participants/disease, intervention/exposure, comparison/control, outcomes/endpoints, and study design): (1) participants/disease, post-TAVR patients both with and without indication for long-term OAC; (2) intervention/exposure, utilized NOACs for antithrombotic therapy; (3) comparison/control, used VKAs or APT without NOACs for antithrombotic therapy; (4) outcomes/endpoints, all-cause mortality as the primary outcome; and (5) study design, randomized controlled trials (RCTs), controlled (nonrandomized) clinical trials (CCTs), and cohort studies. The secondary outcomes were categorized into two parts. One was the efficacy outcome, composed of all stroke, valve thrombosis (reduced leaflet motion (⩾50% reduction) or the presence of hypoattenuated leaflet thickening (HALT)), and a composite endpoint that was defined as the composite of death, stroke, or thromboembolic events. The other outcome was the safety outcome, including

major/life-threatening bleeding. All recorded outcomes were defined according to the Valve Academic Research Consortium-2 (VARC-2) criteria.[12] Studies that were not completed or presented with only an abstract were excluded.

Data extraction and quality assessment

Two investigators (Q.A. and S.S.) independently extracted data from the eligible studies using the predesigned data extraction tables in Microsoft Excel, which consisted of study characteristics (first author, publication year, and study design), whether anticoagulant indications exist or not, baseline clinical characteristics (patient demographics, CHA2DS2-VASc score, and HAS-BLED score (Supplementary Table 3)), and data on outcomes of interest (total number, occurrence number, and mean/median follow-up time).

Two investigators (Q.A. and S.S.) independently assessed the methodological quality of the included studies. The quality of the RCTs, CCTs, and cohort studies were assessed according to the Cochrane Collaboration Risk of Bias Tool (ROB), Methodological Index for Non-randomized Studies (MINORS), and Newcastle–Ottawa Scale (NOS), respectively.[13–15] Any disagreement in all processes mentioned above was resolved by an additional researcher (Q.Z.).

Data analysis

The measure of effect for all outcomes was the risk ratio (RR) with 95% confidence intervals (CIs). Data were pooled using the Mantel–Haenszel random-effects model, and statistical significance was set at $p < 0.05$. An analysis of patients with and without an indication for long-term OAC was conducted, respectively, due to the difference in risk profiles and the need for antithrombotic drugs between the two cohorts. The heterogeneity between studies was evaluated using Cochran's Q test and I^2 index ($I^2 \geqslant 50\%$ indicates heterogeneity and $p \leqslant 0.1$ shows significant difference). Subgroup analysis according to follow-up time ($>$ 1 year) was applied to the pooled outcomes with existing heterogeneity. Only if no less than 10 studies were included could we employ meta-regression and contour-enhanced funnel plots to inspect the source of heterogeneity and possible publication bias. Significant publication bias was further explored using Egger's test. Sensitivity analysis was used to judge the stability of the ultimate results. When there was high heterogeneity ($I^2 \geqslant 50\%$), cumulative analyses with O'Brien–Fleming sequential monitoring boundaries were supplemented, and the Baujat plot was used to explore the source of heterogeneity. RevMan 5.4.1 was utilized to pool the data, perform subgroup analysis, and assess the quality of the included RCTs. STATA 16.0 was utilized to perform meta-regression, perform sensitivity analysis, and assess publication bias. Trial Sequential Analysis (TSA).jar and R x64 3.6.3 were used to perform cumulative analyses and the Baujat plot.

Results

Selection of studies and evaluation of quality

The primary search identified 2171 records after excluding duplicates. Subsequently, 45 records were left after excluding 2126 records by carefully reviewing the titles and abstracts according to the PICOS principle. After reading the full text, 33 records were excluded for specific reasons listed in Figure 1. Finally, 12 studies with 6943 patients met the inclusion criteria, which included two RCTs,[3,16] one nonrandomized clinical trial,[17] and nine cohort studies.[18–26]

Both RCTs were evaluated as high quality (Figure 2), the CCT had a global ideal score being 19 ($>$16) (Supplementary Table 4), and all cohort studies were considered of high quality because of the scores ranging from 6 to 9, with an average of 7.30 (Supplementary Table 5).

Study characteristics and patients' baseline characteristics

Patient characteristics are shown in Supplementary Table 6. The common demographic and baseline characteristics, such as mean age (with an average age of 82 years), body mass index, and the percentages of women, diabetes mellitus, and hypertension were similar between the NOACs and VKAs/APT groups. Coronary artery disease (CAD), previous hemorrhagic or ischemic stroke, previous venous or arterial thromboembolism, permanent pacemaker, and chronic obstructive pulmonary disease (COPD), which may have an important impact on the procedure and prognosis of TAVR; the CHA2DS2-VASc and HAS-BLED

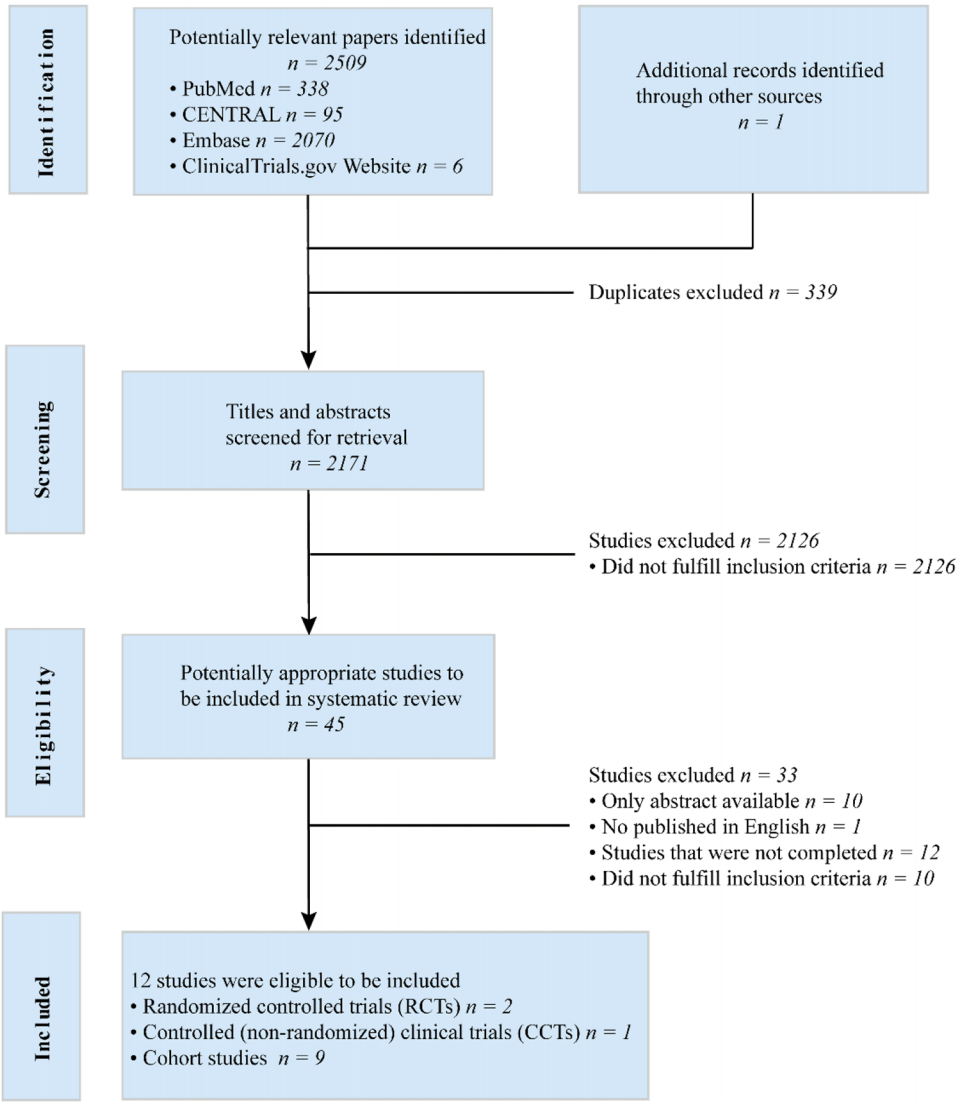

Figure 1. Flow chart for selection of eligible studies.

scores that can affect the selection of antithrombotic therapy and the study outcomes; the glomerular filtration rate (GFR) and the percentage of chronic renal failure, which reflect kidney function and are related to the choice of NOACs dose,[10] were similar between the two groups. A total of 6943 post-TAVR patients (5299 in 10 studies had indications for OAC; 1644 in two studies did not have indications for OAC) were included in this study. Indeed, GALILEO-4D was a sub-study of the GALILEO trial. After reading protocols and supplementary appendices of the two RCTs, the patients included in the GALILEO were categorized into two: those who participated in the GALILEO-4D and those who did not. Data extraction was performed in two parts. The detailed data of outcomes in the studies are shown in Supplementary Table 7.

NOACs therapy versus *standard care (VKAs/APT in patients with/without indications for OAC)*

The primary outcome (all-cause mortality). The Mantel–Haenszel random-effects model was used to pool the data of 4006 patients with indications for OAC (1459 who received NOACs *versus* 2547 who received VKAs) and 1644 patients without indications for OAC (826 who received NOACs *versus* 818 who received APT) from 10 eligible

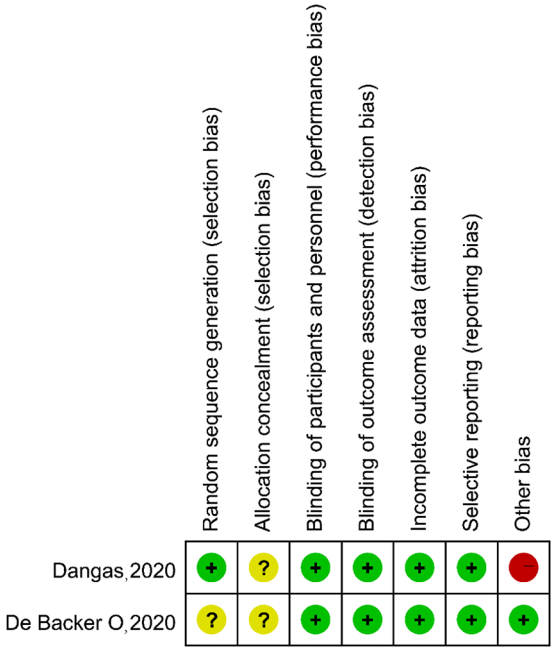

Figure 2. Risk of bias summary and quality evaluation of two randomized controlled trials.

studies. As shown in Figure 3, no significant differences were observed between NOACs and VKAs [RR= 0.85; 95% CI, (0.61, 1.18); $p = 0.32$]; however, NOACs were associated with a higher risk of all-cause mortality than APT [RR = 1.66; 95% CI, (1.12, 2.45); $p = 0.01$).

Subgroup analysis was performed because of the significantly high heterogeneity ($I^2 = 68\%$, $p = 0.002$) in studies with indications for OAC, and this study demonstrated that NOACs were associated with a lower risk of all-cause mortality than that in VKAs after more than 1 year of follow-up [RR = 0.64; 95% CI, (0.42, 0.96); $p = 0.03$; Figure 4].

Cumulative analyses were supplemented with O'Brien–Fleming sequential monitoring boundaries due to the significantly high heterogeneity in the subgroup with a follow-up period of no more than 12 months ($I^2 = 58\%$, $p = 0.05$). As shown in Figure 5, the *Z*-curve and O'Brien–Fleming futility boundaries intersect at the last point, which indicates that NOACs and VKAs were associated with a similar all-cause mortality if the follow-up period was no more than 1 year, and this conclusion was stable. In the future, clinical trials with a follow-up period of more than 1 year should be conducted.

A contour-enhanced funnel plot was completed to inspect possible publication bias, and significant publication bias was further explored using Egger's test. As a result, no significant publication bias was observed ($p = 0.2949$, Figure 6).

The secondary outcomes

The efficacy outcomes. For the efficacy outcomes including all stroke, valve thrombosis, and a composite endpoint, the Mantel–Haenszel random-effects model was utilized to pool the data from nine, four, and seven studies. As shown in Figure 7, no significant differences exist in all efficacy outcomes between NOACs and VKAs in patients with indications for OAC. In patients without indications for OAC, no significant differences exist in all stroke and a composite endpoint between NOACs and APT; however, NOACs exhibited better outcomes than APT in preventing valve thrombosis [RR = 0.19; 95% CI, (0.04, 0.83); $p = 0.03$].

Cumulative analyses were supplemented with O'Brien–Fleming sequential monitoring boundaries due to the significantly high heterogeneity in a composite endpoint (with indications for OAC; $I^2 = 66\%$, $p = 0.02$). As shown in Figure 8, the results may be false negative, and more clinical trials are needed.

The safety outcome (major/life-threatening bleeding). The Mantel–Haenszel random-effects model was utilized to analyze the data of 4005 patients with indications for OAC (1459 who received NOACs *versus* 2546 who received VKAs) and 1644 patients without indications for OAC (826 who received NOACs *versus* 818 who received APT) from 10 eligible studies. No significant differences were observed between the NOACs therapy and standard care groups (Figure 9).

Discussion

This study indicated that all-cause mortality after the use of NOACs was lower than VKAs in post-TAVR patients with indications for OAC and after more than 1 year of follow-up, whereas it was higher than APT in those without indications for OAC. No significant differences were noted between NOACs and standard care in all stroke, a composite endpoint, and major/life-threatening

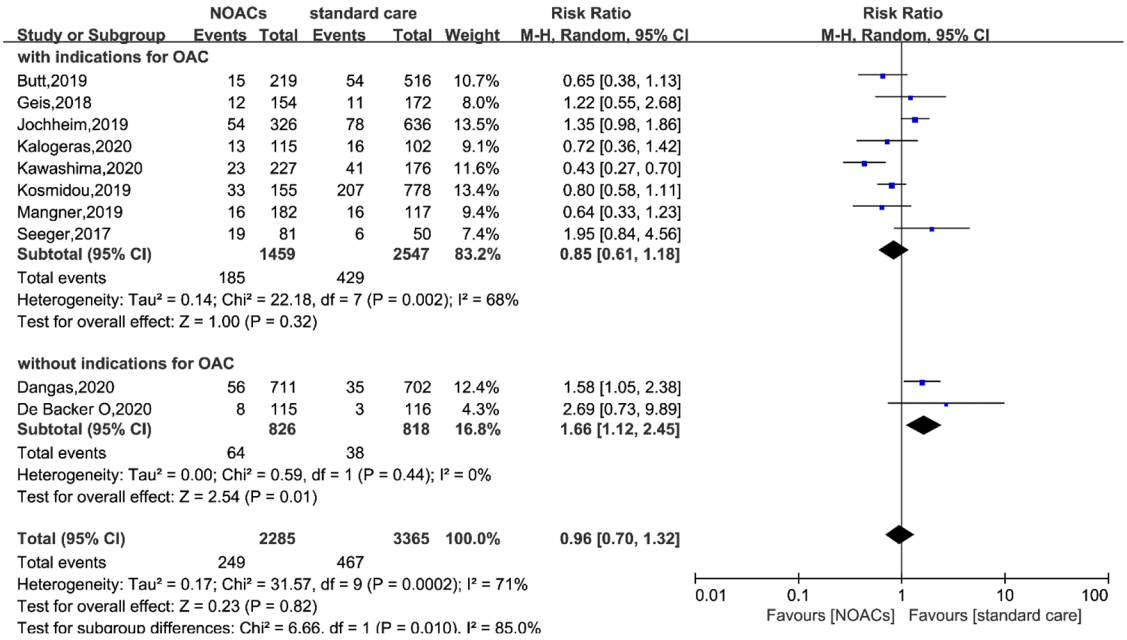

Figure 3. Results of all-cause mortality.
CI, confidence intervals; NOACs, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation.

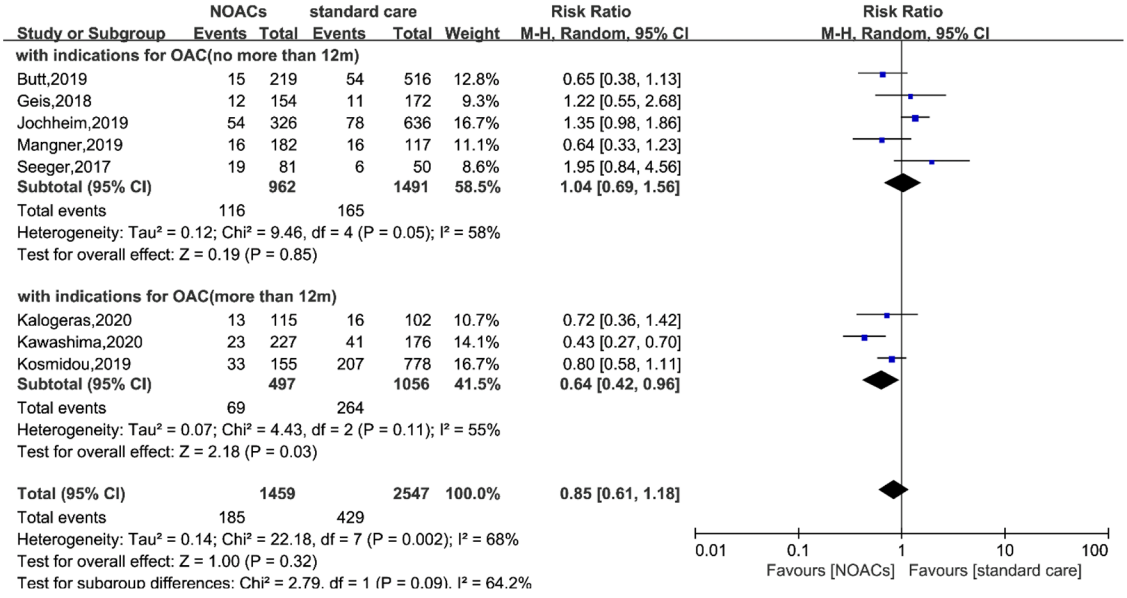

Figure 4. Subgroup analysis of all-cause mortality according to follow-up time.
CI, confidence intervals; NOACs, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation.

bleeding. As for valve thrombosis, an equal effect was observed between NOACs and VKAs, whereas NOACs possessed a better protective effect than that in APT.

Patients being considered for TAVR are adults with calcific aortic valve stenosis (CAVS) rather than those with congenital AS, rheumatic valve disease, or isolated aortic regurgitation.[1] CAVS is becoming a growing economic and health burden due to its bleak prognosis in symptomatic patients.[27,28] No pharmacotherapy has a remarkable effect on holding or delaying the disease, and the precise and specific molecular mechanism of

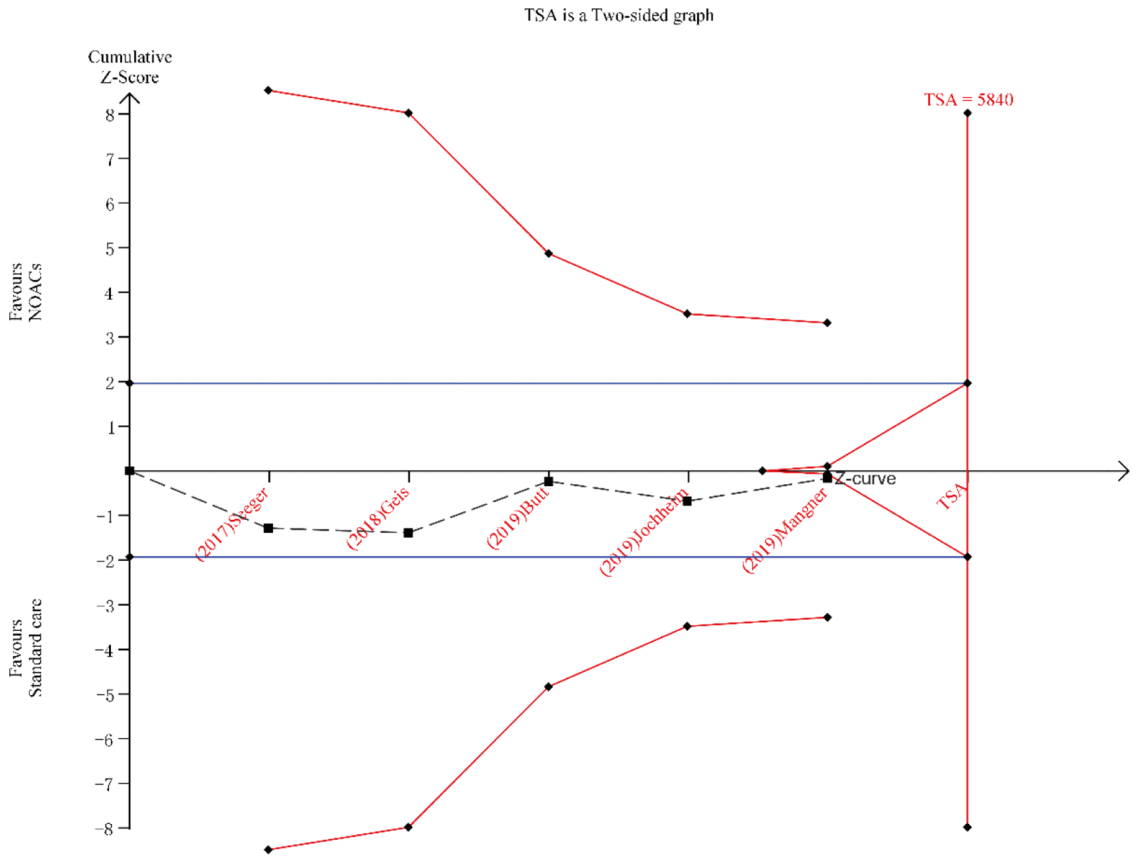

Figure 5. Cumulative analyses with O'Brien–Fleming sequential monitoring boundaries in all-cause mortality (follow-up time no more than 12 m).
TSA, Trial Sequential Analysis.

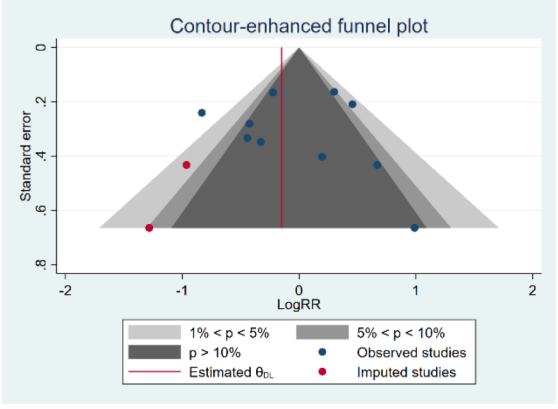

Figure 6. Contour-enhanced funnel plot that showed imputed studies.
RR, risk ratio.

the pathophysiology underlying CAVS remains insufficient, although growing pharmacological treatment targets have been uncovered, such as the vitamin K-dependent matrix Gla-protein (MGP), which is an effective inhibitor of vascular calcification,[29] and the presence of macrophages.[30] Therefore, aortic valve replacement seems to be the only available treatment option, and TAVR has been widely used. First, stroke was the most dreadful ischemic/embolic cerebrovascular complication after TAVR, which accounts for up to 7% of patients within the first year.[31] The need for antithrombotic therapy has been emphasized because of the stable stroke rate in the past decade.[32] A high thromboembolic burden, such as preexisting/new-onset AF and mechanical movement of debris falling during TAVR, increases the incidence of stroke during or after the procedure.[33,34] Second, several observational studies have suggested that valve thrombosis may be related to an increased risk of cerebrovascular events and reduced long-term durability of transcatheter heart valves.[16,35–37] The pathogenesis of valve thrombosis after TAVR is mainly due to stagnant blood flow, and implantation of the prosthetic aortic valve affects the blood flow.

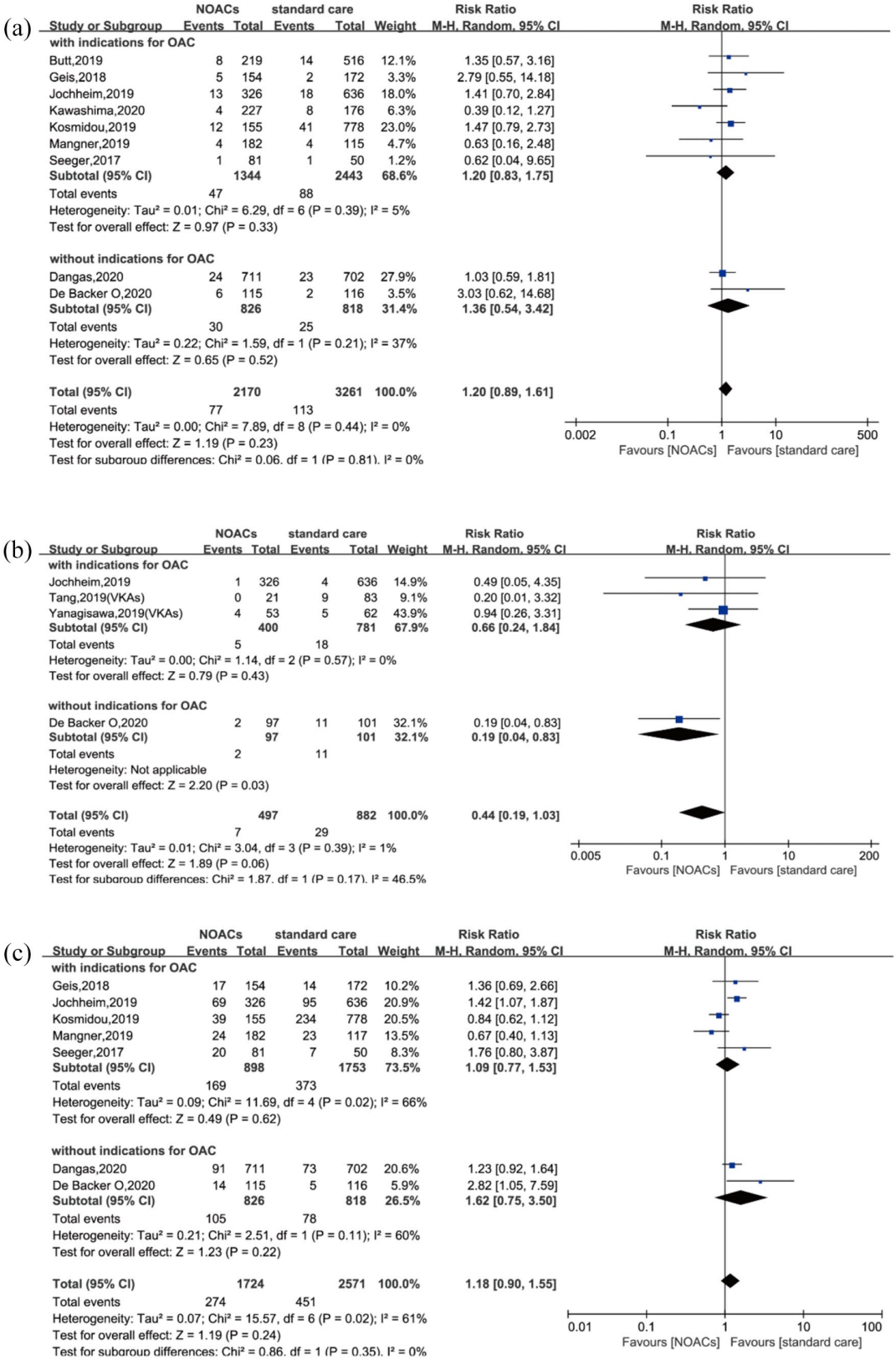

Figure 7. Results of the efficacy outcomes: (a) all stroke, (b) valve thrombosis, and (c) a composite endpoint. CI, confidence intervals; NOACs, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation.

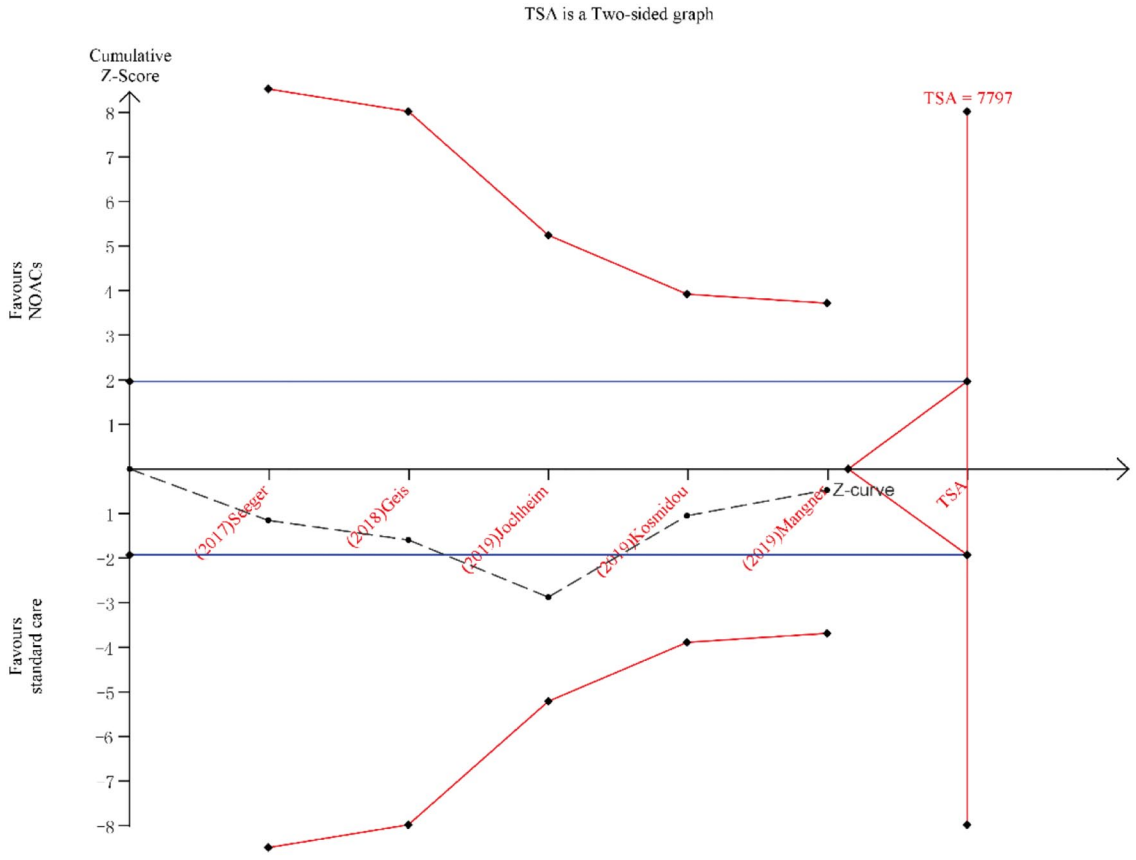

Figure 8. Cumulative analyses with O'Brien–Fleming sequential monitoring boundaries in a composite endpoint (with indications for OAC)
TSA, Trial Sequential Analysis.

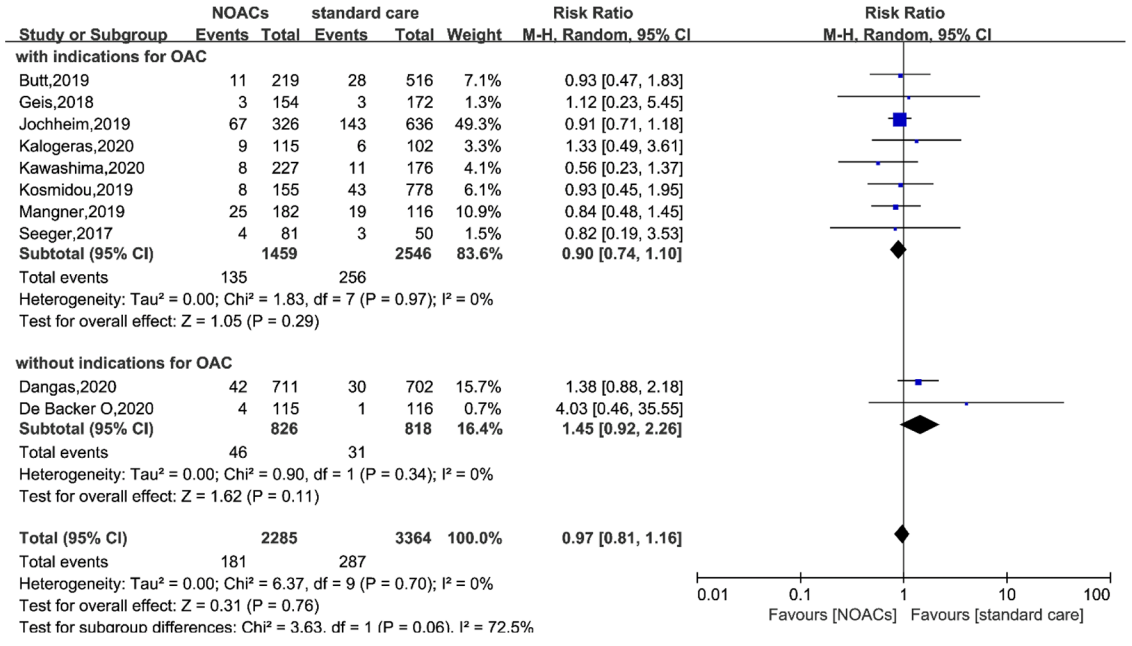

Figure 9. Results of the safety outcome.
CI, confidence intervals; NOACs, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation.

Moreno *et al.*[38] found that supra-annular transcatheter aortic heart valves were associated with a lower risk of valve thrombosis than intra-annular devices. Therefore, recommendations related to antithrombotic therapy could be different according to the type of valve implanted in the future, especially in patients without indications for OAC (e.g. oral anticoagulation may be added after intra-annular devices implantation). Third, the risk of major/life-threatening bleeding is obviously connected to a poor prognosis.[39] Consistent with the patients' baseline characteristics in this study, it is well known that CAVS is thought to be a degenerative disease, and the vast majority of post-TAVR patients are elderly.[40] The balance between thrombogenesis and bleeding is more complex because of a variety of underlying diseases and medication restrictions in the elderly. All of these demonstrated a remarkable essentiality of optimal antithrombotic therapy for post-TAVR patients, especially for those with indications for OAC.

It is worth noting that although VKAs are widely used to prevent thromboembolic events in post-TAVR patients with indications for OAC, calcification cannot be ignored as a side effect.[28] Vitamin K is one of the most essential elements of the body. It is not only involved in blood coagulation but is also associated with various vitamin K-dependent proteins related to anticancer effects, inflammation, bone metabolism, and vascular calcification. For instance, in blood vessels, the formation of hydroxyapatite, the apoptosis of vascular smooth muscle cells (VSMCs), and the transdifferentiation of VSMCs to osteoblasts can be reduced by vitamin K2.[41–44] The adverse reaction of VKAs, wherein the use of VKAs demonstrated more vascular/valvular calcification, was confirmed in animal models and humans.[45–48] Many practical inconveniences, such as multiple interactions between food and drug, narrow therapeutic window, and the need for regular monitoring, hinder the use of VKAs, especially in multimorbid patients and the elderly.[22] All of the above may be reasons for the lower all-cause mortality of NOACs compared with warfarin after long-term follow-up. Conversely, the control of bleeding, which has been insufficient in NOACs, has made great progress in recent years. Methods included dose adjustment of the agents in patients with renal dysfunction, avoiding the concomitant use of other antithrombotic agents if feasible, the use of nonspecific hemostatic agents, and the use of specific reversing agents, which were significant steps in minimizing bleeding risks with NOACs.[10,49,50] Furthermore, based on the noninferiority of NOACs, the latest guideline clearly stated that NOACs are an effective alternative to VKA.[5] This study showed that NOACs were more favorable than VKAs in patients with indications for OAC when there were no contraindications.

Consistent with current American guidelines, this study suggested that NOACs are contraindicated in those without indications for OAC despite the advantage of preventing valve thrombosis. However, NOACs or VKAs may be used to resolve the reduced leaflet motion ($\geqslant$50% reduction).[35]

No significant heterogeneity was observed in this study except for all-cause mortality (with indications for OAC and no more than 12 months of follow-up) and a composite endpoint (with indications for OAC). A subgroup analysis of the latter was conducted (Figure 10), but significant heterogeneity still existed. The Baujat plot was used to explore the source of heterogeneity (Figure 11), A study by Butt *et al.* and Jochheim *et al.* provided the highest contribution to the overall heterogeneity of the former and the latter, respectively. Therefore, data were pooled again after excluding the study by Butt *et al.* and Jochheim *et al.* respectively, as shown in Figure 12, the results were steady, and the heterogeneity was not high.

Given the extremely short follow-up time (3 days), data were pooled again after excluding the study by Yanagisawa *et al.*, with steady results (Figure 13).

Sensitivity analysis and cumulative analyses of all-cause mortality (with indications for OAC and more than 12 months of follow-up) were performed, indicating that recent studies tended to report a lower all-cause mortality of NOACs than that in VKAs after more than 1 year of follow-up (Figures 14). However, this may be a false-positive result (Figures 15). The use of NOACs has become increasingly standardized and reasonable with the updating of research and guidelines, especially the dose adjustments of NOACs in patients with chronic kidney disease.[10] The latest study by Kawashima *et al.* excluded patients with estimated GFRs $<$ 30 mL/min/1.73 m^2 who were not eligible for NOACs and reduced the doses of

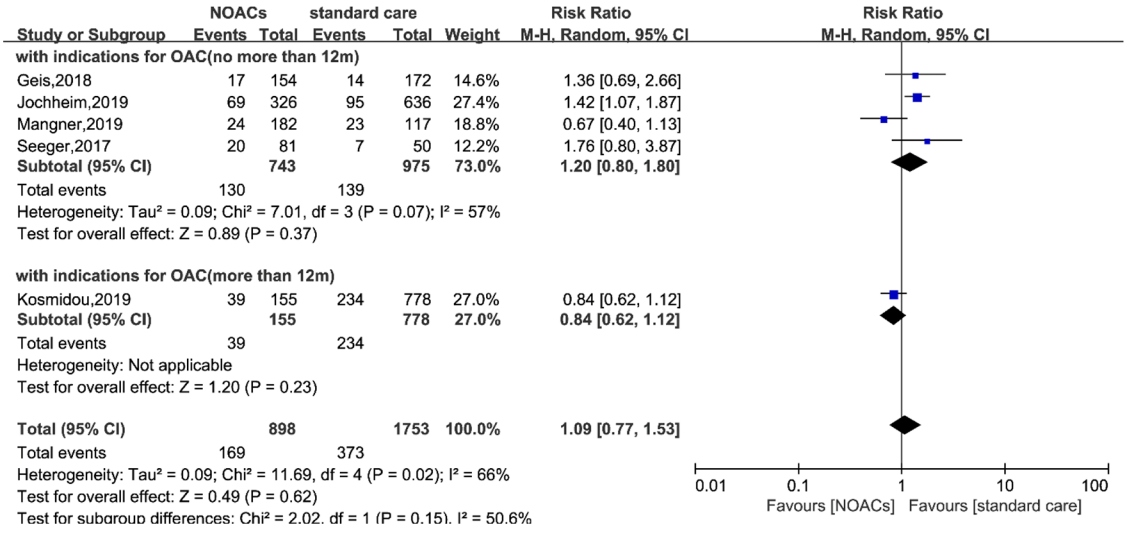

Figure 10. Subgroup analysis of a composite endpoint according to follow-up time.
CI, confidence intervals; NOACs, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation.

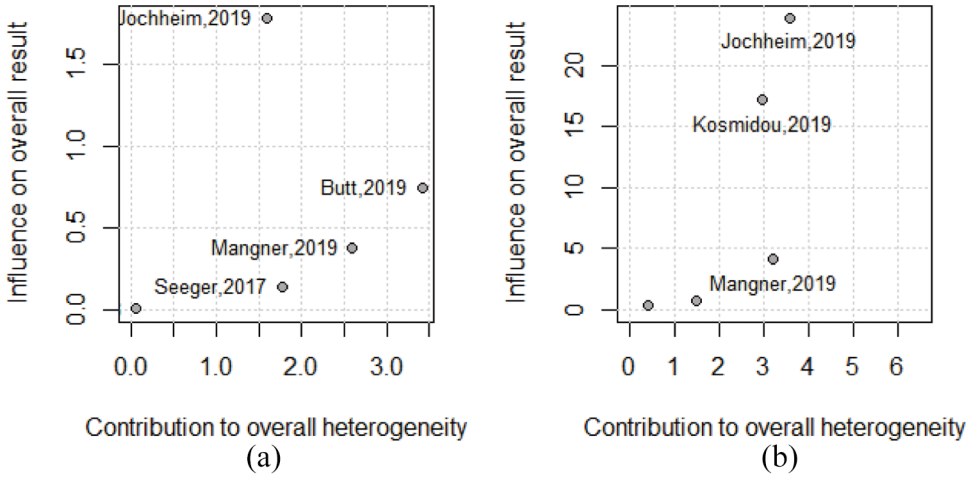

Figure 11. Baujat plot. (a) The study of Butt *et al.* provided the highest contribution to heterogeneity of all-cause mortality (with indications for OAC and no more than 12 m follow-up). (b) The study of Jochheim *et al.* provided the highest contribution to heterogeneity of a composite endpoint (with indications for OAC).

rivaroxaban according to creatinine clearance, whereas the study by Kalogeras *et al.* and Kosmidou *et al.* did not specialize the renal function of the included patients. All the above may be the source of nonsignificant heterogeneity and the reason why recent studies tend to report a lower all-cause mortality of NOACs. The upcoming clinical trials may show more information.

Upcoming clinical trials, such as the Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS) trial, may provide further information. The ATLANTIS study was a multicenter, randomized (1:1), phase IIIb, prospective, open-label, superiority study comparing standard of care (SOC group, 751 patients) and an apixaban-based strategy (anti-Xa group, 749 patients) after successful TAVR with 1-year follow-up (ClinicalTrials.gov NCT 02664649).[51] Randomization was stratified according to indications for OAC. In the experimental arm, patients received apixaban or a reduced dose according to the drug label or when apixaban was combined with antiplatelet therapy.

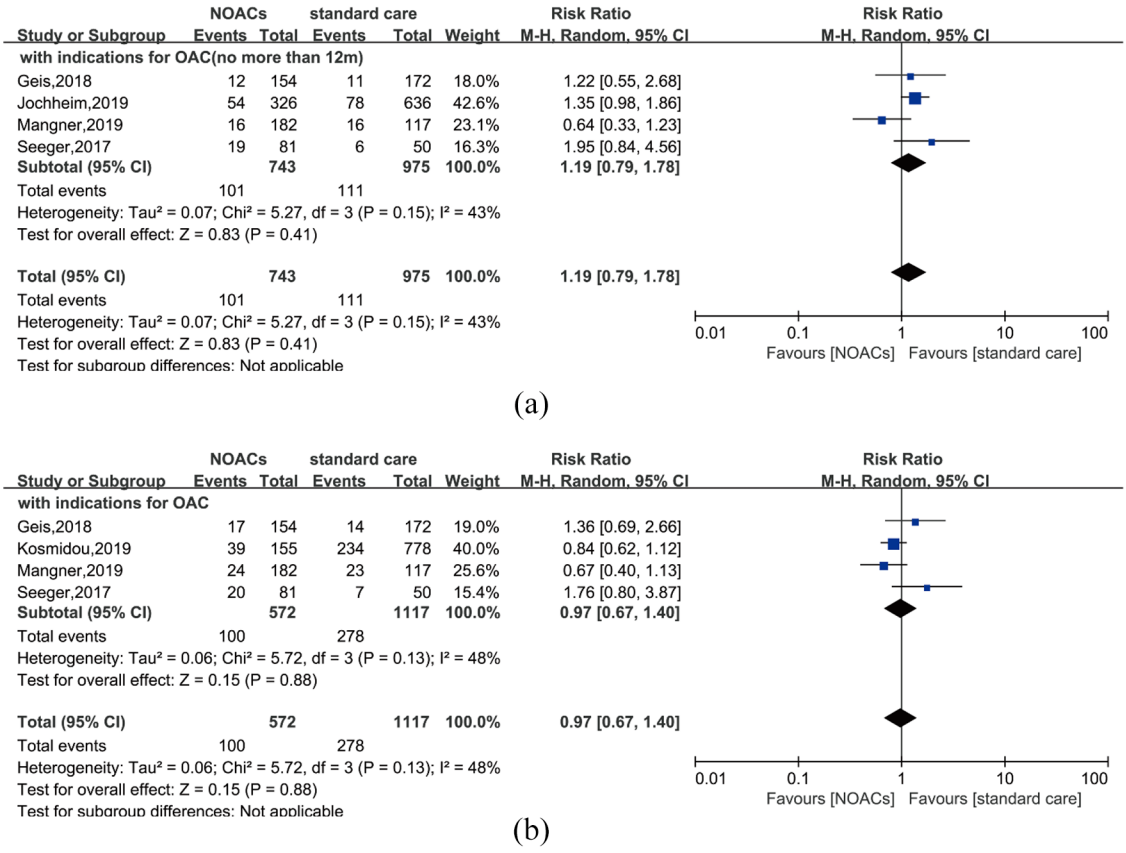

Figure 12. (a) Analysis of all-cause mortality (with indications for OAC and no more than 12 m follow-up) after excluded the study of Butt *et al.*; (b) analysis of a composite endpoint (with indications for OAC) after excluded the study of Jochheim *et al.*
CI, confidence intervals; NOACs, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation.

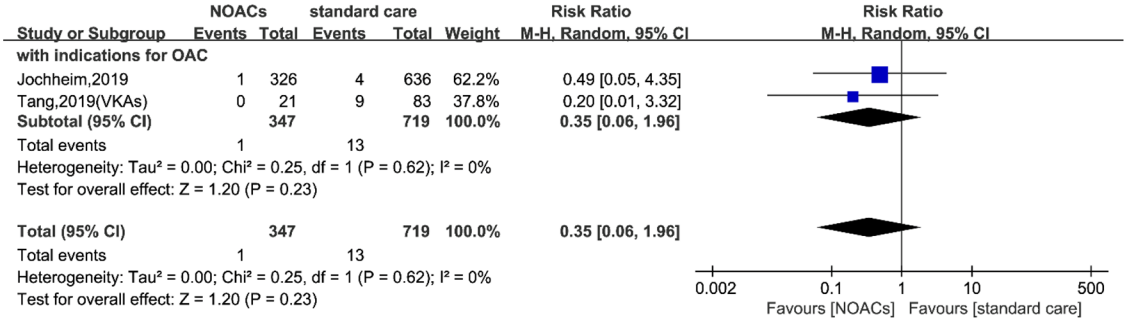

Figure 13. Analysis of the valve thrombosis after excluded the study of Yanagisawa *et al.*
CI, confidence intervals; NOACs, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation.

In the control arm, patients received VKA therapy or combined with antiplatelet therapy if there was an indication for OAC or antiplatelet therapy alone (single or dual) if there was no indication for OAC. The main results were presented at the 2021 annual meeting of the American College of Cardiology. In patients with indications for OAC, no significant differences were found between apixaban and VKAs in the primary and secondary outcomes. However, in patients without indications for OAC, apixaban was associated with a higher incidence of combined endpoint consisting of all-cause mortality, all stroke/TIA, and systemic embolism [apixaban 9.5% *versus* APT 6.3%,

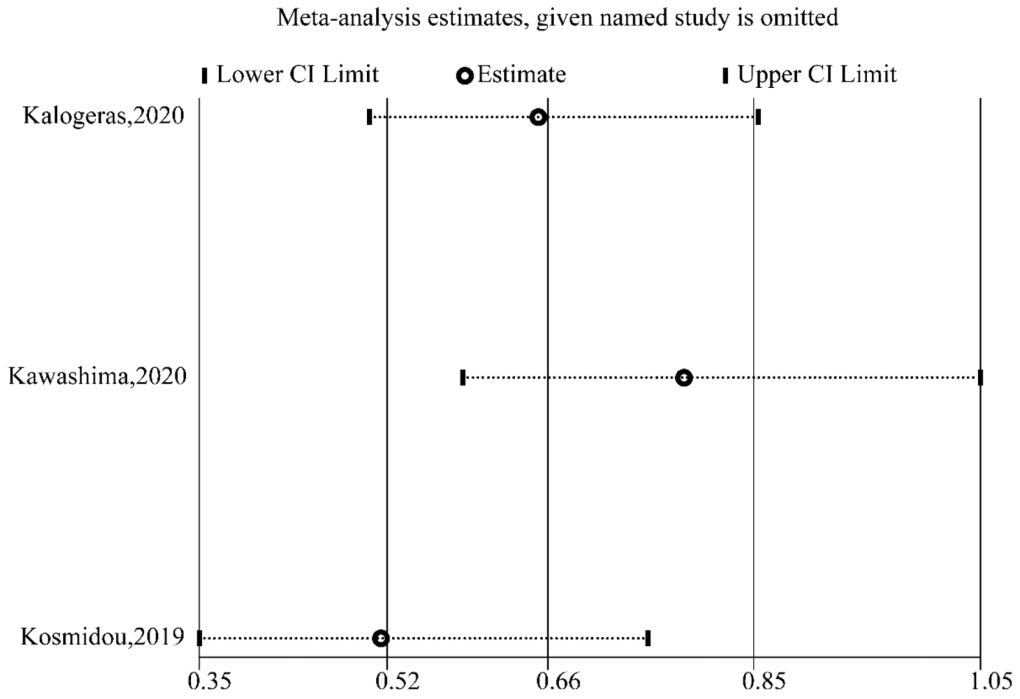

Figure 14. Sensitivity analysis of all-cause mortality (with indications for OAC and more than 12 m follow-up).
CI, confidence intervals.

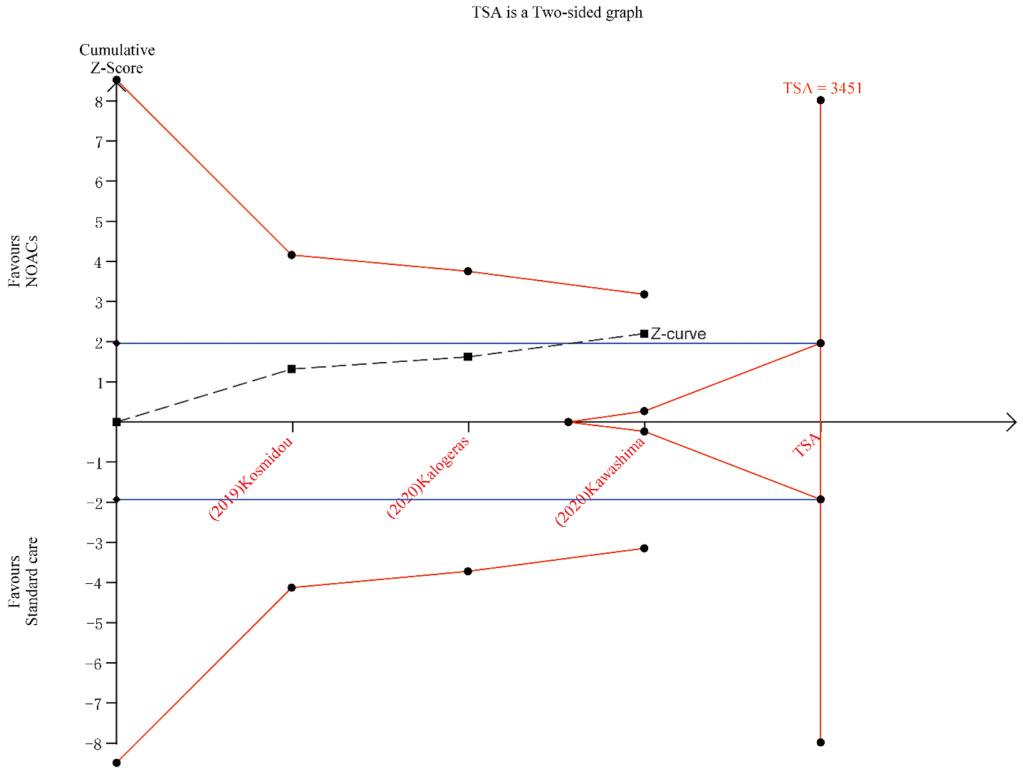

Figure 15. Cumulative analyses with O'Brien–Fleming sequential monitoring boundaries in all-cause mortality (with follow-up time more than 12 m).
TSA, Trial Sequential Analysis.

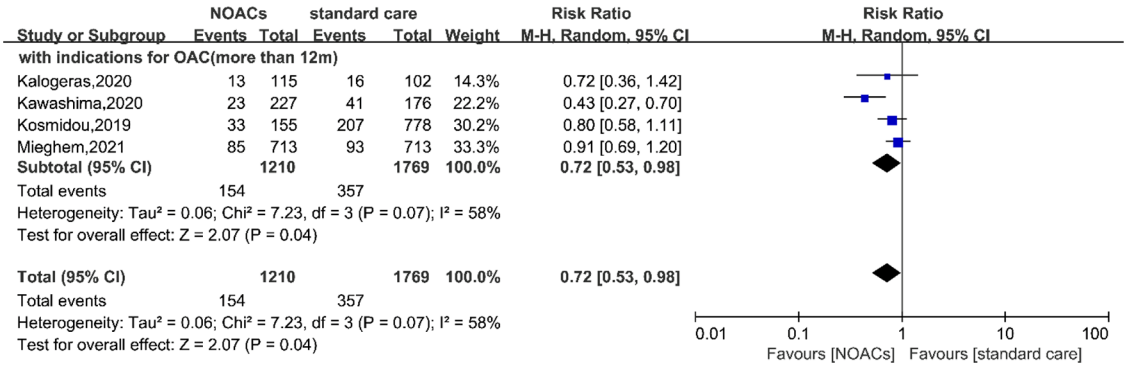

Figure 16. Analysis of all-cause mortality (more than 1-year follow-up) for post-TAVR patients with indications for OAC after adding the study of ENVISAGE-TAVI AF.

HR = 1.56, 95% CI, (1.01, 2.43)]. The risk of death was higher in the apixaban group than that in the APT group (apixaban 5.9% *versus* APT 3.4%, HR = 1.86, 95% CI, (1.04, 3.34)), which was mainly due to the significantly increased incidence of noncardiovascular death in the apixaban group [apixaban 2.66% *versus* APT 0.96%, HR = 2.99, 95% CI, (1.07, 8.35)]. As for its substudy, ATLANTIS 4D-CT, which focused on the prevention of valve thrombosis, no significant difference was observed between apixaban and VKAs in patients with indications for OAC [apixaban 9.5% *versus* VKAs 5.5%, OR = 1.80, 95% CI, (0.62, 5.25), $p = 0.28$], whereas apixaban was better than APT in patients without indications for OAC [apixaban 8.7% *versus* APT 15.9%; OR = 0.51; 95% CI, (0.30, 0.86); $p = 0.01$]. Professor Jean Philippe Collet, who was one of the core members of this clinical trial, pointed out that the apixaban-based antithrombotic strategy did not show clinical benefits superior to the standard of care in post-TAVR patients with or without indications for OAC, apixaban was comparable to warfarin or antiplatelet therapy in terms of safety outcome (bleeding), and apixaban was associated with a decreased incidence of valve thrombosis compared to APT in those without indications for OAC according to the results of the ATLANTIS study and its substudy ATLANTIS 4D-CT. It should be noted that the use of apixaban significantly increased the risk of noncardiovascular death compared with APT in post-TAVT patients without indications for OAC. The aforementioned results are consistent with those of this study.

Moreover, the results of the ENVISAGE-TAVI AF (Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients with Atrial Fibrillation) study, which was a multicenter, prospective, randomized, open-label, adjudicator-masked trial comparing edoxaban with VKAs in patients with prevalent or incident AF as an indication for OAC after successful TAVR with an 18-month follow-up, have been reported.[52] They concluded that edoxaban was noninferior to VKAs for the incidence of net adverse clinical events, with a higher incidence of major bleeding with edoxaban than that with VKAs. This study was not added to the nine cohort studies because of the heterogeneity caused by the difference between cohort studies and RCTs. However, data of all-cause mortality (with indications for OAC and more than 12 months of follow-up, Figure 16) were recombined after including this RCT, and the results indicated that all-cause mortality after the use of NOACs was lower than VKAs in post-TAVR patients with indications for OAC and for more than 1 year of follow-up [RR = 0.72; 95% CI, (0.53, 0.98); $p = 0.04$], and the heterogeneity became significant [$I^2 = 58\%$, $p = 0.07$). Finally, more RCTs with more than 1 year of follow-up that compare NOACs with VKAs in post-TAVR patients with indications for OAC are needed.

Limitations

The databases were searched comprehensively and simultaneously to evaluate the efficacy and safety of antithrombotic therapy with NOACs in post-TAVR patients with or without indications for OAC. However, there are still some limitations to this study. First, only two studies were included in the subgroup without indications for OAC. However, there have been some clinical

trials on the way to completion, such as REDOX TAVI (NCT04171726) and ADAPT-TAVR (NCT03284827), which would enrich further studies. Second, none of the studies included in the subgroup with indications for OAC were RCTs. Therefore, an ongoing RCTs, called AVATAR (NCT02735902), is expected to be published to update the present study. Third, there were inconsistencies in the doses and duration of NOACs since some of the studies were anticoagulation therapy alone, whereas the other studies were anticoagulation plus double/single antiplatelet drug therapy. All of these may be confounding factors and therefore influence the outcomes. Fourth, all included studies with indications for OAC focused on AF; therefore, more RCTs and studies focused on the other indications for OAC rather than AF are expected to clarify the optimal antithrombotic regimen after TAVR in patients with different conditions. Finally, most of the included studies focused on the use of rivaroxaban; therefore, further studies are needed to explore the details of different NOACs.

Conclusion

Based on the currently available studies, NOACs as antithrombotic therapy might be a better choice in patients with indications for OAC due to its superiority in reducing all-cause mortality (more than 1 year of follow-up), noninferiority in the other aspects, and the limitations of VKAs, and the standard of care with APT is a better antithrombotic therapy in patients lacking indications for OAC. In the future, RCTs are expected to verify this conclusion and determine the optimal antithrombotic therapy.

Author's Note

This study has been posted on pre-print servers: https://doi.org/10.21203/rs.3.rs-404977/v1 (doi: 10.21203/rs.3.rs-404977/v1). However, the manuscript we submitted has some revisions in format.

Author contributions

All authors contributed to the conceptualization. Q.A., S.S., and Q.Z. involved in data curation. Formal analysis was done by Q.A., Y.T., L.G., and G.X. Funding acquisition was done by Q.Z. Investigation was done by all authors. Q.A., L.G., and X.X. contributed to the Methodology. Project administration was done by Q.A., S.S., and Q.Z. Resources were managed by Q.Z. and D.X. Software management was done by Q.A., G.X., Y.B., and Q.Z. Supervision was carried out by Q.A., X.X., D.X., and Q.Z. All authors involved in validation. Visualization was carried out by Q.A., S.S., Y.T., and G.X. Q.A., S.S., Y. T., L.G., and G.X. contributed to writing—original draft. Q.A., Y.B., Q.Z., X.X., D.X., and Q.Z. contributed to Writing—review and editing. All authors read and approved the final manuscript to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplemental material

Supplemental material for this article is available online.

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