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Antithrombotic Strategies After Bioprosthetic Aortic Valve Replacement: A Systematic Review

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Abstract

Background.—The optimal antithrombotic regimen after bioprosthetic aortic valve replacement (bAVR) is unclear. We conducted a systematic review of various anti-coagulation strategies following surgical or transcatheter bAVR (TAVR).

Methods.—We searched Medline, PubMed, Embase, Evidence-Based Medicine Reviews, and gray literature through June 2017 for controlled clinical trials and cohort studies that directly compared different antithrombotic strategies in nonpregnant adults who had undergone bAVR. We assessed risk of bias and graded the strength of the evidence using established methods.

Results.—Of 4,554 titles reviewed, 6 clinical trials and 13 cohort studies met inclusion criteria. We found moderate-strength evidence that mortality, thromboembolic events, and bleeding rates are similar between aspirin and warfarin after surgical bAVR. Observational data suggest lower mortality and thromboembolic events with aspirin combined with warfarin compared with aspirin alone after surgical bAVR, but the effect size is small and the combination is associated with a substantial increase in bleeding risk. We found insufficient evidence for all other treatment comparisons in surgical bAVR. In TAVR patients, we found moderate-strength evidence that mortality, stroke, and major cardiac events are similar between dual antiplatelet therapy and aspirin alone, though a nonsignificantly lower rate of bleeding occurred with aspirin alone.

Conclusions.—Treatment with warfarin or aspirin leads to similar outcomes after surgical bAVR. Combining aspirin with warfarin may lead to a small decrease in thromboembolism and mortality, but is accompanied by increased bleeding. For TAVR patients, aspirin is equivalent to dual antiplatelet therapy for reducing thromboembolism and mortality, with a possible decrease in bleeding.

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The number of bioprosthetic aortic valve replacements (bAVRs) has increased substantially over the last 2 decades and now represents the majority of aortic valves implanted [1–3]. The main advantage of bioprosthetic over mechanical valves is the avoidance of long-term anticoagulation; however, the optimal antithrombotic regimen and duration is unclear, and both guideline recommendations and practice patterns vary significantly [4–9].

While both the American College of Chest Physicians (ACCP) [6] and the American College of Cardiology/American Heart Association (ACC/AHA) [7] support aspirin (acetylsalicylic acid [ASA]) use after bAVR, recommendations differ slightly. The ACCP recommends low-dose (81 mg) aspirin use for 3 months after bAVR, provided there is no indication for anticoagulation with warfarin. By contrast, recommendations by the ACC/AHA are slightly more complex; depending on the patient's bleeding risk profile, surgical AVR patients may be treated with either aspirin (75 to 100 mg) or warfarin (target international normalized ratio [INR] 2.5) for 3 to 6 months. Many patients who undergo transcatheter AVR (TAVR) are treated with dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) for 3 to 6 months after implantation [10,11], though guideline recommendations again vary [9, 12].

This systematic review aims to broadly summarize the comparative benefits and harms for various anticoagulation strategies following surgical or transcatheter implantation of a bioprosthetic aortic valve.

Material and Methods

Topic Development

The research plan was developed in consultation with internal partners, investigators, and stakeholders. A protocol describing the review plan was posted to a publicly accessible website [13] before the study was initiated.

Search Strategy

We searched Medline, PubMed, Embase, Evidence-Based Medicine Reviews (eg, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment, Cochrane Controlled Register of Trials), and gray literature sources. We searched all available years of publication from database inception (1946 for Ovid Medline) through January 2017, with a search for new or in-process citations in June 2017 (Appendix A). We reviewed the bibliographies of relevant articles and contacted experts to identify additional studies. To identify ongoing or unpublished studies, we searched [ClinicalTrials.gov](https://clinicaltrials.gov) and Agency for Healthcare Research and Quality Registry of Patient Registries.

Study Selection

We included studies that directly compared different antithrombotic strategies, against each other or against placebo, in nonpregnant adults who had undergone bioprosthetic aortic valve repair or bAVR. Eligible study designs included controlled clinical trials and cohort studies that controlled for important confounders. We excluded studies that did not

separately analyze patients with aortic procedures from mitral or other valve procedures. We included studies that reported clinical out-comes (mortality, thromboembolic events, major bleeding events, or other benefits or harms) and excluded studies that only reported outcomes detected by imaging techniques. The criteria for patient population, intervention, comparator, outcome, timing parameters, and study designs that apply to each key question are specified in Appendix B. Appendix C contains the detailed criteria we used for determining study eligibility.

Eight investigators (AL, DK, JCC, JNP, KK, LDH, MF, NN) examined titles and abstracts for potential relevance to the key questions using Abstrackr, an online tool for screening citations for systematic reviews [14]. We dualreviewed 10% of all abstracts to ensure reliability between reviewers. Working in pairs (JNP/KK, DK/LDH, NN/MF, JCC/AL), we independently reviewed the full text of all potentially relevant articles for inclusion. Disagreements were resolved through consensus using a third reviewer.

Data Abstraction

From each study, we abstracted information on study design, objectives, setting, population characteristics, subject inclusion and exclusion criteria, number of subjects, duration of follow-up, study and comparator interventions including dosage and duration of treatment, concomitant procedures, health outcomes, and harms.

Quality Assessment

Five reviewers (JCC, JNP, LDH, MF, NN) independently assessed the risk of bias, and these assessments were independently confirmed by a second reviewer (AL, DK, JCC, KK, MF) (Appendix D). Each trial was given an overall summary assessment of low, high, or unclear risk of bias using a tool developed by the Cochrane Collaboration [15]. For observational studies, we considered potential sources of bias, adapted existing assessment tools, and described the key methodologic flaws of each study [16,17]. Disagreements were resolved through team discussion among the reviewers to reach consensus.

Data Synthesis

We qualitatively synthesized the evidence on the benefits and harms. For trials with comparable interventions and outcome measures, we combined the findings in a random-effects meta-analysis [18] using RevMan 5.3 software [19].

Rating the Body of Evidence

We assessed the overall strength of evidence for individual outcomes as high, moderate, low, or insufficient using a method that considers study limitations, directness, consistency, precision, and reporting bias [20].

Results

After reviewing 4,554 titles and abstracts, we included 22 primary studies reported in 21 publications (Fig 1). The descriptive characteristics of included studies are provided in

Appendix E. Table 1 summarizes the findings and the strength of evidence overall for each antithrombotic comparison.

Surgical bAVR

We identified 4 randomized controlled trials (RCTs) and 11 cohort studies that compared antithrombotic strategies after surgical bAVR (Appendix E). Overall, the trials are limited by small sample size and limited power, and many of the observational studies had substantial methodologic flaws. Nevertheless, the results across trials and observational studies—including 1 large, well-done observational study—were consistent in showing no difference in outcomes between warfarin and aspirin.

Figure 2 shows forest plots combining data from 2 trials that reported 90-day outcomes for aspirin versus warfarin [21, 22]. There were no statistically significant differences with regard to mortality (odds ratio [OR], 1.23; 95% CI, 0.36 to 4.15), thromboembolic events (TEs) (OR, 1.28; 95% CI, 0.33 to 4.87), or major bleeding complications (OR, 2.05; 95% CI, 0.49 to 8.51) at 90 days.

Among observational studies the best data come from a large (N = 25,656) multicenter registry of patients throughout the United States undergoing bAVR (Appendix E) [5]. Among this cohort, there was no significant difference in 3-month incidence of death (4.0% versus 3.0%; relative risk [RR], 1.01; 95% CI, 0.80 to 1.27), embolic events (1.0% versus 1.0%; RR, 0.95; 95% CI, 0.61 to 1.47), or bleeding events (1.4% versus 1.0%; RR, 1.23; 95% CI, 0.85 to 1.79). On subgroup analysis, the lack of difference for benefits and harms between treatment groups was consistent for patients with and without specific thromboembolic risk factors including atrial fibrillation, reduced left ventricular ejection fraction, and prior stroke or thromboembolism.

This study also showed that warfarin plus aspirin was associated with a small reduction in 3-month mortality (RR, 0.80; 95% CI, 0.66 to 0.96; number needed to treat = 153) and TEs (RR, 0.52; 95% CI, 0.35–0.76; number needed to treat = 212), but these benefits were accompanied by a substantial increase in bleeding risk (RR, 2.80; 95% CI, 2.18–3.60; number needed to harm = 55). On subgroup analysis, among patients with 1 or more thromboembolic risk factors, the combination of warfarin plus aspirin reduced TEs more than aspirin alone, but was not associated with reduced mortality and was associated with a higher risk of bleeding.

Three cohort studies compared warfarin with no treatment (Appendix E). One found worse long-term survival with warfarin [23]. Another study found elevated risk of TEs associated with warfarin after 4.2 years [24]. Only 1 study provided data on bleeding risk, and reported no difference between treatment groups [25]. The strength of evidence for these findings is insufficient given the paucity of data, insufficient detail about dose or duration of treatment, and other methodologic limitations.

Three cohort studies compared aspirin with no treatment (Appendix E) [24–26]. No differences by treatment were found in the risk of TEs [24–26], mortality [25], or

hemorrhage [25]. The overall strength of evidence for these findings is insufficient, given the paucity of available data and methodologic weaknesses of studies.

Transcatheter AVR

We found 3 RCTs, 5 cohort studies, and 1 meta-analysis assessing various antiplatelet and anticoagulation strategies in patients who have undergone TAVR (Appendix E).

Three RCTs and 1 cohort study each demonstrated no significant difference in mortality or incidence of stroke between single antiplatelet therapy (SAPT) with aspirin when compared with DAPT using aspirin and clopidogrel over short (30 days) [27,28], intermediate (3 to 6 months) [27–29], and longer-term (1 year) [30] follow-up (Appendix E). These studies excluded patients with recent percutaneous coronary intervention or an indication for anticoagulation including atrial fibrillation.

Figures 3 and 4 show forest plots of 3 trials that compared ASA versus DAPT after TAVR [27–29]. A meta-analysis combining the 3 trials indicated no statistically significant differences in mortality and TEs at either 30 days or 3 to 6 months post-TAVR and no difference in major bleeding at 30 days. The 2 trials that provided data on major bleeding events at 3 to 6 months [28, 29] suggested a lower bleeding risk with ASA compared with DAPT; however, the difference did not reach statistical significance (OR, 0.43; 95% CI, 0.17 to 1.08) (Fig 4).

A small cohort study found no significant difference between SAPT compared with DAPT over 1 year of follow-up in terms of mortality (7% versus 7%; $p > 0.05$) or stroke (10% versus 10%; $p > 0.05$) among TAVR patients. Although there was a trend toward a reduction in bleeding events with SAPT (4.6% versus 18.2%; $p = 0.058$) the risk for potential bias was judged as high [30].

The 2 cohort studies that examined the role of various combinations of antiplatelet therapy with and without anticoagulation included a mix of patients on SAPT, DAPT or SAPT and DAPT in combination with an anticoagulant. There were significantly more patients with atrial fibrillation in the anticoagulant therapy groups. As such, there was a high risk of bias in the findings; insufficient evidence was available to provide clinical guidance.

One cohort study compared warfarin monotherapy to the use of warfarin plus an antiplatelet regimen for TAVR and found no significant reduction in mortality (23% versus 19%; $p > 0.05$) or stroke (5% versus 5%; $p > 0.05$) at 1 year. A decreased risk of life-threatening or major bleeding with warfarin monotherapy (14.9% versus 25.9%; $p = 0.02$) [31] was seen. The risk of bias in this cohort study is unclear, and the evidence is insufficient to determine treatment effect.

Another cohort study compared warfarin monotherapy to direct oral anticoagulant (DOAC) monotherapy [32] and found no significant difference in mortality or stroke but a significant reduction in life-threatening bleeding (3.5% versus 5.3%; $p < 0.01$) with the use of apixaban when compared with warfarin [32]. The risk of bias is high, given a substantial loss to follow-up and numerous subgroup comparisons in this study, and there is insufficient evidence to determine a treatment effect.

Antithrombotic Risk-Benefit Ratio According to Patient Subgroups

In 1 large observational study of patients with bAVR comparing warfarin alone to aspirin alone, there was no difference in benefits or harms according to thromboembolic risk factors including atrial fibrillation, reduced left ventricular ejection fraction, and prior stroke or thrombo-embolism [5]. This study found that, among patients with 1 or more thromboembolic risk factors, the combination of warfarin plus aspirin reduced TEs more than aspirin alone [5], although therapy did not reduce mortality and was associated with a higher risk of bleeding. There was insufficient evidence to determine whether treatment effects differed for patients undergoing concomitant coronary artery bypass grafting. Similarly, TAVR trials and cohort studies provided insufficient evidence to draw conclusions of comparative benefits and harms of different strategies according to thromboembolic risk profile.

Comment

We systematically reviewed the literature and found 14 studies comparing different anticoagulation strategies in patients who had undergone surgical bAVR, and 8 studies comparing strategies in patients who had undergone TAVR. Overall, there is consistent, moderate-strength evidence that aspirin and warfarin are associated with similar risks of mortality, TEs, and bleeding after surgical bAVR, but insufficient evidence to draw conclusions about the effects of no treatment compared with monotherapy with aspirin or warfarin, or the effects of other antithrombotic agents in surgical bAVR.

Data from 1 large registry study of bAVR in the United States using the Society of Thoracic Surgeons database found a small survival benefit of warfarin plus aspirin compared with aspirin alone, though the combination was associated with a substantial increase in bleeding risk. Even though the study was reasonably well conducted and was broadly representative of the target population of interest, it lacked longitudinal data on antithrombotic use and the risk of confounding by indication remains even after propensity score matching because clinical characteristics such as frailty that may have determined choice of strategy were not captured in risk-adjustment strategies. Another recently conducted, propensity-matched study of several thousand patients within the Veterans Administration found similar mortality and thromboembolic outcomes regardless of antithrombotic regimen. Specifically, patients who received warfarin plus aspirin, DAPT, or aspirin alone (the most commonly prescribed regimen within the Veterans Administration) after bAVR all showed similar survival. This study found that the combination of warfarin plus aspirin was associated with a substantially elevated bleeding risk (D. Bravata, personal communication, May 30, 2018).

Our findings support the current guideline recommendations from the ACCP, which suggest aspirin (81 mg/day) over warfarin therapy for the first 3 months after surgery for patients for whom there is no other indication for anticoagulation, such as atrial fibrillation or history of thromboembolism (Grade 2C recommendation) [6].

In TAVR patients, we found data from 3 open-label randomized trials and 2 observational studies that SAPT with aspirin was associated with similar mortality and TE risk, but lower bleeding risk than DAPT with aspirin and clopidogrel. These findings may evolve as data

from larger, in-progress trials [33] emerge but the existing data thus far suggest that at least some patients may be able to safely use aspirin alone after TAVR. Of note, this body of evidence largely excludes patients with atrial fibrillation.

The TAVR findings are novel and the clinical implications of this data should be discussed by clinicians and clinical policy groups. Our findings that SAPT and DAPT have similar clinical outcomes are at odds with prior guideline recommendations in part because newer trial data have been published [6]. However, the newer trials have small sample sizes and limited power to detect small differences in clinical outcomes. Ongoing trials of TAVR are not designed to resolve the comparative benefits and harms of SAPT versus DAPT (Appendix E) and instead focus on anticoagulation considerations [7–9, 12, 34, 35].

We found very little evidence directly examining whether the benefits and harms of different anticoagulation strategies differed according to patients' thromboembolic risk profiles. As expected, in the studies that did report subgroup information, patients with atrial fibrillation were more likely to receive warfarin therapy [5]. Unfortunately, there are no studies comparing the combination of warfarin and aspirin to warfarin alone, which would have been a clinically relevant comparison for patients with chronic atrial fibrillation. It is possible that some patients with substantially elevated thrombo-embolic risk who are not at high risk of bleeding might benefit from the combination of warfarin and aspirin after surgical bAVR. We also found no good evidence examining the relative benefits and harms of different strategies in patients who had concomitant procedures such as coronary artery bypass grafting [6–9, 36, 37].

Limitations

Our investigation is limited by several factors. First, for most comparisons other than SAPT to DAPT after TAVR, there are too few studies to draw conclusions. Second, much of the evidence comes from observational studies with substantial variation in the methodologic rigor even after exclusion of studies that did not adjust for confounding factors. As anticoagulation was typically left to the surgeon's discretion in bAVR studies, it is very likely that patient groups receiving different anticoagulation treatments differed in substantive ways that may not have been adequately captured in adjusted analyses. Third, warfarin studies are difficult to interpret because the balance of benefits and harms of the medication depends in part on the duration that the medication is in a therapeutic range and many studies did not report this data. Studies that did report this found that INR was outside the therapeutic range for a majority of time. This likely reflects real-world practice, but leaves open the possibility that the lack of superiority of warfarin may be due to this issue and that more robust warfarin management might yield different results.

Ongoing and Future Research

Event rates in most of the included studies were fairly low, and it is possible that the lack of difference reflects lack of power to detect a difference rather than true similarity in effect. Among 3 large, noncomparative cohort studies in surgical bAVR (N range, 461 to 1,260), the mean rate of 5-year TEs was 4% (range 3.4% to 5.9%) [38–40]. Across 6 large cohort studies (N range, 461 to 1,594), the mean 5-year bleeding rate was 3.8% (range, 1.4% to

6.2%) [38–43]. To detect small differences in TE rates, trials would need to enroll many more patients than they have thus far. For instance, assuming baseline event rates of 4% over 5 years, a trial would need to have 6,226 subjects per arm to detect a 1% difference in TEs, and 1,586 subjects per arm to detect a 2% difference.

Recent studies have examined the association between anticoagulation strategies and imaging findings such as reduced leaflet motion [44], but the impact of these findings on clinical outcomes including stroke and transient ischemic attack remains to be determined.

It would be interesting to conduct further research in patients at high risk of thromboembolism, such as those with preexisting atrial fibrillation, as well as other comparisons of antithrombotic strategies, such as warfarin versus warfarin plus aspirin. The potential role of DOACs after surgical bAVR also remains largely unexplored.

Large ongoing trials examining various anticoagulation strategies after TAVR are underway (Appendix E), although most do not focus on SAPT versus DAPT.

Conclusion

We found that aspirin is a reasonable antithrombotic strategy in many bAVR patients based on moderate-strength evidence that aspirin is associated with similar effects on mortality, TEs, and bleeding rates as warfarin after bAVR. Observational data suggest that, although the combination of warfarin plus aspirin may be associated with lower mortality and TEs compared with aspirin alone after surgical bAVR, the effect size is small and the combination is associated with a substantial increase in bleeding risk. Future studies of surgical bAVR should focus on subgroups at high thromboembolic risk, and should also examine the effectiveness of the increasingly used DOAC agents. Use of aspirin alone after TAVR is associated with similar short-term effects on mortality and stroke and possibly lower bleeding rates compared with use of DAPT, though larger trials are needed to exclude the possibility of small differences in comparative effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig 1.

Literature flow diagram. (bAVR = bioprosthetic aortic valve replacement; CDSR = Cochrane Database of Systematic Reviews; Cochrane CENTRAL = Cochrane Controlled Register of Trials; DARE = Database of Abstracts of Reviews of Effects; EBM Reviews = Evidence-Based Medicine Reviews; HTA = Health Technology Assessment; RCT = randomized controlled trial; TAVR = transcatheter aortic valve replacement.)

Fig 2.

Mortality, thromboembolic events, and major bleeding complications at 90 days in trials that compared warfarin with acetylsalicylic acid (ASA) after surgical bioprosthetic aortic valve replacement. (CI = confidence interval; M-H = Mantel-Haenszel.)

Fig 3.

Mortality, thromboembolic events, and major bleeding complications at 30 days in trials that compared acetylsalicylic acid (ASA) versus dual antiplatelet therapy (DAPT) after transcatheter aortic valve replacement. (CI = confidence interval; M-H = Mantel-Haenszel.)

Fig 4.

Mortality, thromboembolic events, and major bleeding complications at 3 to 6 months in trials that compared acetylsalicylic acid (ASA) versus dual antiplatelet therapy (DAPT) after transcatheter aortic valve replacement. (CI = confidence interval; M-H = Mantel-Haenszel.)

Table 1.

Summary of the Evidence on Antithrombotic Strategies After bAVR and TAVR

Treatment Comparison	Studies per Outcome ^a	Findings on Mortality, TEs, and Major Hemorrhagic Complications	Strength of Evidence ^b	Comments
Surgical bAVR				
Warfarin versus ASA				
• Mortality	3 RCTs [21, 22, 45] (n = 355) 5 cohorts [5, 25, 45–47] (n = 17,331)	No difference. Best evidence from 2 studies, at 3 months: ■ 1 low-ROB RCT [22] (n = 236): 3.8% versus 2.9%, $p = 0.721$ ■ 1 large cohort study [5] (n = 15,456): 4.0% versus 3.0%, $p > 0.05$	Moderate	Small RCTs, likely underpowered, but results are consistent with 1 large, well-conducted cohort study.
• TEs	3 RCTs [21, 22, 45] (n = 355) 8 cohorts [5, 24, 25, 45–49] (n = 18,506)	No difference. Best evidence from 2 studies, at 3 months: ■ 1 low-ROB RCT [22] (n = 236): 3.8% versus 2.9%, $p = 0.721$ ■ 1 large cohort study [5] (n = 15,456): 1.0% versus 1.0%, $p > 0.05$	Moderate	
• Major bleeding	3 RCTs [21, 22, 45] (n = 355) 7 cohorts [5, 25, 45–49] (n = 18,212)	No difference. Best evidence from 2 studies, at 3 months: ■ 1 low-ROB RCT [22] (n = 236): 2.9% versus 1.9%, $p = 0.683$ ■ 1 large cohort study [5] (n = 15,456): 1.0% versus 1.4%, $p > 0.05$	Moderate	
Warfarin + ASA versus ASA				
• Mortality	1 RCT [22] (n = 119) 2 cohorts [5, 50] (n = 18,485)	Best evidence from 1 large cohort [5] RR, 0.80 (95% CI, 0.66–0.96), NNT 153	Low	Findings are based mostly on 1 large, well-conducted cohort study, in which absolute benefits were small relative to risk of harm. Other cohort studies and 1 RCT showed no difference.
• TEs	1 RCT [22] (n = 119) 4 cohorts [5, 22, 26, 50] (n = 19,551)	Best evidence from 1 large cohort [5] RR, 0.52 (95% CI, 0.35–0.76), NNT 212	Low	
• Major bleeding	1 RCT [22] (n = 135) 1 cohort [5] (n = 18,429)	Best evidence from 1 large cohort [5] RR, 2.80 (95% CI, 2.18–3.60), NNH 55	Low	
Warfarin + ASA versus warfarin				
0 studies				
Warfarin versus no treatment				
• Mortality	2 cohorts [23, 25] (n = 210)	Short-term: no differences at 3 months [25] Long-term: poorer survival with warfarin: 67.9% versus 76.1% at 8 years ($p = 0.03$) [23]	Insufficient	No evidence currently available.
• TEs	2 cohorts [24, 25] (n = 347)	Elevated TE risk with warfarin in 1 study with 4.2 years follow-up [24]. Adjusted RR, 3.0 (95% CI, 1.5–6.3), $p = 0.0028$; not specified whether the referent group consisted of patients treated with ASA, no treatment, or a group combining patients treated with ASA and patients with no treatment.	Insufficient	Evidence from smaller retrospective studies. INR generally not reported
• Major bleeding	1 cohort [25] (n = 88)	No difference by treatment group in long-term freedom from hemorrhage.	Insufficient	
ASA versus no treatment				

Treatment Comparison	Studies per Outcome ^a	Findings on Mortality, TEs, and Major Hemorrhagic Complications	Strength of Evidence ^b	Comments
• Mortality	1 cohort [25] (n = 360)	No difference.	Insufficient	ASA dose and duration were reported in only 1 study [24].
• TEs	3 cohorts [24–26] (n = 1983)	No difference.	Insufficient	
• Major bleeding	1 cohort [25] (n = 360)	No difference.	Insufficient	
TAVR				
ASA versus DAPT				
• Mortality	3 RCTs [27–29] (n = 421) 1 cohort [30] (n = 144)	No difference. Combined estimate at 3–6 months from meta-analysis of all 3 trials, ASA versus DAPT: 0.86 (95% CI, 0.38–1.95)	Moderate	Consistent findings of no difference among 3 low-ROB trials. Sample sizes limit power to detect small differences in treatment effect.
• TEs	3 RCTs [27–29] (n = 421) 1 cohort [30] (n = 144)	No difference. Combined estimate at 3–6 months from meta-analysis of 2 trials [28, 29] ASA versus DAPT: 0.46 (95% CI, 0.13–1.62)	Moderate	
• Major bleeding	3 RCTs [27–29] (n = 421) 1 cohort [30] (n = 144)	Marginally significant increased risk with DAPT versus ASA in 1 trial [29] (n = 222): 10.9% versus 3.6%, $p = 0.038$ Combined estimate at 3–6 months from meta-analysis of 2 trials [28, 29] ASA versus DAPT: 0.43 (95% CI, 0.17–1.08)	Moderate	
APT versus APT + OAC				
• Mortality	2 cohorts [51, 52] (n = 806)	No difference.	Insufficient	Treatment arms contain a mix of antithrombotic regimens.
• TE	2 cohorts [51, 52] (n = 806)	No difference.	Insufficient	
• Major bleeding	2 cohorts [51, 52] (n = 806)	No difference at 1 year for DAPT (n = 315) versus OAC (n = 199, includes 188 warfarin, 7 rivaroxaban, and 4 dabigatran) [52] More bleeding complications at 30 days with DAPT (ASA + clopidogrel) versus SAPT (adding/maintaining ASA or maintaining clopidogrel), propensity score matched (n = 182) [51]: 30.8% versus 9.9%, $p = 0.002$.	Insufficient	
Warfarin monotherapy versus warfarin + APT				
• Mortality	1 cohort [31] (n = 621)	No difference.	Insufficient	Evidence is from 1 study.
• TEs	1 cohort [31] (n = 621)	No difference.	Insufficient	
• Major bleeding	1 cohort [31] (n = 621)	Increased risk of hemorrhage with warfarin + APT versus warfarin monotherapy: Adjusted HR for VARC-2 major or life-threatening bleeding, median 13 months follow-up: 1.85 (95% CI, 1.05–3.28), $p = 0.04$	Insufficient	
Warfarin versus DOAC (apixaban):				
• Mortality	1 cohort [32] (n = 272)	No difference.	Insufficient	Evidence is from 1 study.
• TEs	1 cohort [32] (n = 272)	No difference.	Insufficient	
• Major bleeding	1 cohort [32] (n = 272)	No difference.	Insufficient	

^aThe n values indicate combined participants.

^bThe overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows [20]: high = further research is very unlikely to change our confidence on the estimate of effect; moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and insufficient = any estimate of effect is very uncertain.

APT = antiplatelet therapy; ASA = acetylsalicylic acid; bAVR = bioprosthetic aortic valve replacement; CI = confidence interval; DAPT = dual antiplatelet therapy; DO AC = direct oral anticoagulant; HR = hazard ratio; INR = international normalized ratio; NNH = number needed to harm; NNT = number needed to treat; OAC = oral anticoagulant; OR = odds ratio; RCT = randomized controlled trial; ROB = risk of bias; RR = relative risk; SAPT = single antiplatelet therapy; TAVR = transcatheter aortic valve replacement; TE = thromboembolic event; VARC-2 = Valve Academic Research Consortium-2.