



# Comparing Antithrombotic Strategies after Bioprosthetic Aortic Valve Replacement: A Systematic Review

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## PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for 4 ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

Develop clinical policies informed by evidence;

Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and

Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at [Nicole.Floyd@va.gov](mailto:Nicole.Floyd@va.gov).

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## TABLE OF CONTENTS

<b>Executive Summary</b> .....	1
Introduction.....	1
Methods.....	1
Results.....	1
Summary and Discussion.....	3
Current Practice and Outcomes in VA.....	4
Limitations .....	4
Ongoing and Future Research.....	4
Conclusions.....	5
Table. Summary of the Evidence on Antithrombotic Strategies after bAVR and TAVR.....	6
Abbreviations Table.....	9

## EVIDENCE REPORT

Introduction.....	11
Methods.....	11
Topic Development.....	11
Search Strategy .....	12
Study Selection .....	12
Data Abstraction .....	14
Quality Assessment.....	14
Data Synthesis.....	14
Rating the Body of Evidence .....	14
Peer Review .....	15
Results.....	16
Literature Flow.....	16
Key Questions 1 and 2: What are the comparative benefits and harms of antithrombotic strategies for patients who have had BAVR? .....	17
Warfarin vs ASA.....	24
Warfarin Combined with ASA vs ASA Monotherapy .....	31
Warfarin vs No Treatment .....	36
Aspirin vs No Treatment.....	39
Other Comparison: Triflusal vs Acenocoumarol.....	41
Key Question 3: What are the comparative benefits and harms of antithrombotic strategies for patients who have TAVR? .....	42

Summary of Findings.....	42
Detailed Results .....	42
KQ3A. Do the benefits/harms differ according to thromboembolic risk profile? .....	45
KQ3B. Do the benefits/harms differ according to concomitant procedure (eg, PTCA with stent?) .....	46
Summary and Discussion.....	59
Limitations .....	61
Ongoing and Future Research.....	61
Conclusions.....	63
References.....	67

## TABLES

Table 1. PICOTS and Key Questions .....	13
Table 2. Descriptive Characteristics of Studies that Compare Antithrombotic Treatment Strategies after Surgical bAVR.....	18
Table 3. Findings of Studies that Compared Warfarin with ASA after Surgical bAVR.....	26
Table 4. Findings of Studies that Compared Warfarin Combined with ASA vs ASA Monotherapy after Surgical bAVR.....	34
Table 5. Findings of Cohort Studies that Compared Warfarin with No Treatment after Surgical bAVR .....	38
Table 6. Findings of Cohort Studies that Compared ASA with No Treatment after Surgical bAVR .....	40
Table 7. Descriptive Characteristics of Studies that Compared Antithrombotic Strategies after TAVR.....	47
Table 8. Findings of TAVR Studies by Treatment Comparison .....	52
Table 9. Ongoing Clinical Trials Comparing Antithrombotic Strategies after bAVR/TAVR .	62
Table 10. Summary of the Evidence on Antithrombotic Strategies after bAVR and TAVR...	64

## FIGURES

Figure 1. Literature Flow Diagram .....	16
Figure 2. Mortality at 90 Days in Trials that Compared Warfarin with ASA after Surgical bAVR.....	30
Figure 3. TE Events at 90 Days in Trials that Compared Warfarin with ASA after Surgical bAVR.....	30
Figure 4. Major Bleeding Complications at 90 days in Trials that Compared Warfarin with ASA after Surgical bAVR .....	30

Figure 5. Risk of Mortality at 30 Days in Trials that Compared ASA vs DAPT after TAVR ..... 57

Figure 6. Risk of Mortality at 3-6 Months in Trials that Compared ASA vs DAPT after TAVR ..... 57

Figure 7. Risk of TE Events (Includes Major Stroke and MI) at 30 Days in Trials that Compared ASA vs DAPT after TAVR..... 57

Figure 8. Risk of TE Events (Includes Major Stroke and MI) at 3-6 Months in Trials that Compared ASA vs DAPT after TAVR ..... 58

Figure 9. Risk of Major or Life-threatening Bleeding Events at 30 Days in Trials that Compared ASA vs DAPT after TAVR..... 58

Figure 10. Risk of Major or Life-threatening Bleeding Events at 3-6 Months in Trials that Compared ASA vs DAPT after TAVR ..... 58

**Appendix A.** Search Strategies ..... 72

**Appendix B.** Study Selection ..... 78

**Appendix C.** Quality Assessment Criteria and Tables ..... 81

**Appendix D.** Peer Reviewer Comments ..... 89



# EVIDENCE REPORT

## INTRODUCTION

The use of bioprosthetic aortic valve replacement (bAVR) has become a common solution for the treatment of valvular heart disease.<sup>23</sup> Bioprosthetic valves have a low long-term thromboembolic risk and therefore do not require lifelong anticoagulation. The choice of bioprosthetic valve, when compared to mechanical valves, may be appealing in older patients and those with higher risk of complications from anticoagulation.<sup>24</sup> However, in the first 3 months following implantation, there is – at least theoretically – an increased risk of thromboembolic events while endothelialization of the cloth sewing ring is occurring.<sup>25-27</sup>

Thromboembolic stroke rates after bAVR have been reported to range from less than 1 percent per year to greater than 3 percent per year, with lower rates of thromboembolism generally being seen in patients in sinus rhythm.<sup>25,26,28</sup> While most patients are treated with anticoagulant and/or antiplatelet therapy for a period of time after surgery, the optimal antithrombotic regimen and duration after placement of a bioprosthetic valve in the aortic position is unclear, and both guideline recommendations and practice patterns vary significantly.<sup>5,25,29-32</sup>

In recent years, transcatheter aortic valve replacement (TAVR) continues to be increasingly used to address severe aortic stenosis. Many patients are treated with dual antiplatelet therapy (aspirin and clopidogrel) for 6 months after implantation, largely based on the initial protocol in the PARTNER trial,<sup>33,34</sup> though guideline recommendations again vary.

In addition, the role for direct oral anticoagulants (DOACs) in the setting of bioprosthetic aortic valves remains unclear. Several large randomized trials of DOACs for stroke prevention in atrial fibrillation have included patients with pre-existing bioprosthetic valves,<sup>35</sup> but the question of whether the DOACs are safe and effective as a primary anticoagulation strategy immediately post-bAVR remains undefined.

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, and to determine whether effects differed according to thromboembolic risk profile or concomitant procedure.

## METHODS

### TOPIC DEVELOPMENT

The research questions for this systematic review were developed after a topic refinement process that included a preliminary review of published peer-reviewed literature and consultation with internal partners, investigators, and stakeholders. The Key Questions were as follows:

**KQ1:** What are the comparative benefits of antithrombotic strategies for patients who have had bioprosthetic aortic valve replacement (bAVR)?

**KQ1A:** Do the benefits differ according to thromboembolic risk profile?

**KQ1B:** Do the benefits differ according to concomitant procedure (*eg*, coronary artery bypass graft [CABG])?

**KQ2:** What are the comparative harms of antithrombotic strategies for patients who have had bAVR?

**KQ2A:** Do the harms differ according to thromboembolic risk profile?

**KQ2B:** Do the harms differ according to concomitant procedure (*eg*, CABG])?

**KQ3:** What are the comparative benefits and harms of antithrombotic strategies for patients who have had transcatheter aortic valve replacement (TAVR)?

**KQ3A:** Do the benefits or harms differ according to thromboembolic risk profile?

**KQ3B:** Do the benefits or harms differ according to concomitant procedure (*eg*, percutaneous transluminal coronary angioplasty [PTCA] with stent)?

A protocol describing the review plan was posted to the PROSPERO register of systematic reviews (registration number [CRD42017057064](https://www.crd.york.ac.uk/PROSPERO/record/CRD42017057064)) before the study was initiated.<sup>36</sup>

## SEARCH STRATEGY

Search strategies were developed in consultation with a research librarian. To identify relevant articles, we searched MEDLINE®, PubMed, EMBASE, EMB Reviews (CDSR, DARE, HTA, Cochrane CENTRAL, etc.), and grey literature sources. We searched all available years of publication from database inception (1946 for Ovid MEDLINE®) through January 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 and AHRQ Registry of Patient Registries.

## STUDY SELECTION

The criteria for patient population, intervention, comparator, outcome, timing parameters, and study designs (PICOTS) that apply to each key question are specified in Table 1.

We included studies that directly compared different antithrombotic strategies, against each other or placebo, in non-pregnant adults who had undergone bioprosthetic aortic valve repair or replacement. 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 from mitral or other valve procedures. We included studies that reported clinical outcomes (mortality, thromboembolic events, major bleeding events, or other benefits/harms) and excluded studies that only reported outcomes detected by imaging techniques. Appendix B contains the detailed criteria we used for determining study eligibility.

**Table 1. PICOTS and Key Questions**

Key Question (KQ)	<p>KQ1: What are the comparative benefits of antithrombotic strategies for patients who have had bAVR?</p> <p>KQ1A: Do the benefits differ according to thromboembolic risk profile?</p> <p>KQ1B: Do the benefits differ according to concomitant procedure (eg, CABG)?</p>	<p>KQ2: What are the comparative harms of antithrombotic strategies for patients who have had bAVR?</p> <p>KQ2A: Do the harms differ according to thromboembolic risk profile?</p> <p>KQ2B: Do the harms differ according to concomitant procedure (eg, CABG)?</p>	<p>KQ3: What are the comparative benefits and harms of antithrombotic strategies for patients who have had TAVR?</p> <p>KQ3A: Do the benefits or harms differ according to thromboembolic risk profile?</p> <p>KQ3B: Do the benefits or harms differ according to concomitant procedure (eg, PTCA with stent)?</p>
Population	<p>Adult patients who have had bAVR. Exclude: bAVRs no longer used in practice; patients with valve replacements in positions other than the aorta (eg, mitral valve, Ross procedure); pregnant women.</p>		<p>Adult patients who have had TAVR with stenting of aortic valves. Exclude: pregnant women</p>
Intervention/Comparators	<p>Agents:</p> <ul style="list-style-type: none"> <li>• Warfarin</li> <li>• Warfarin plus ASA or other antiplatelet agents</li> <li>• ASA or other antiplatelet agents</li> <li>• Dual antiplatelet therapy</li> <li>• Direct oral anticoagulants (DOACs)</li> <li>• No therapy</li> </ul> <p>Duration of antithrombotic therapy:</p> <ul style="list-style-type: none"> <li>• &lt; 90 days</li> <li>• ≥ 90 days</li> </ul>		
Outcomes	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Thromboembolic events</li> <li>• Stroke</li> <li>• Myocardial infarction</li> <li>• Heart failure</li> <li>• Readmission rates</li> <li>• Need for valve reoperation (eg, valve thrombosis)</li> <li>• Length of stay</li> <li>• Need for change in antithrombotic strategy</li> </ul>	<ul style="list-style-type: none"> <li>• Major bleeding events <ul style="list-style-type: none"> <li>- GI bleeds</li> <li>- Intracranial hemorrhage</li> <li>- Other (eg, retroperitoneal)</li> </ul> </li> <li>• Other/minor bleeding</li> <li>• Readmission rates</li> <li>• Pericardial or pleural effusion*</li> </ul> <p>*We will prioritize effusions requiring intervention.</p>	<p>Benefits and harms listed under KQs 1 and 2.</p>
Timing	<ul style="list-style-type: none"> <li>• Perioperative, defined as in-hospital or within 30 days.</li> <li>• Long-term, defined as &gt;30 days to 1-year or longer.</li> </ul> <p>Both timeframes are of interest for each outcome.</p>		
Study design	<ul style="list-style-type: none"> <li>• Randomized controlled trials</li> <li>• Non-randomized controlled trials</li> <li>• Cohort studies (retrospective or prospective) or case-control studies that adequately control for important confounders</li> </ul>		

**Abbreviations:** ASA = aspirin (acetylsalicylic acid); bAVR = bioprosthetic aortic valve replacement; CABG = coronary artery bypass graft; GI = gastrointestinal; KQ = key question; PTCA = percutaneous transluminal coronary angioplasty; TAVR = transcatheter aortic valve replacement.



One of 9 investigators examined titles and abstracts for potential relevance to the key questions using Abstractkr.<sup>37</sup> We dual-reviewed 10 percent of all abstracts in order to ensure reliability between reviewers. Two investigators independently reviewed the full text of all potentially relevant articles for inclusion. Disagreements were resolved through consensus using a third reviewer.

## DATA ABSTRACTION

Data from published reports were abstracted into a customized database by one reviewer and confirmed by a second reviewer. From each study, we abstracted the following where available: study design, objectives, setting, population characteristics, subject inclusion and exclusion criteria, number of subjects, duration of follow-up, the study and comparator interventions including dosage and duration of treatment, concomitant procedures, health outcomes, and harms.

## QUALITY ASSESSMENT

Two reviewers independently assessed the risk of bias of each study (Appendix C). Disagreements were resolved through discussion. To assess the risk of bias of trials we used a tool developed by the Cochrane Collaboration.<sup>38</sup> Each trial was given an overall summary assessment of low, high, or unclear risk of bias. To assess the risk of bias of observational studies we considered potential sources of bias most relevant to this evidence base, adapted existing assessment tools, and described the key methodologic flaws of each study.<sup>39,40</sup>

## DATA SYNTHESIS

We qualitatively synthesized the evidence on the benefits and harms. We combined trials with comparable interventions and outcomes in meta-analysis using systematic review software developed by the Cochrane Collaboration.

## RATING THE BODY OF EVIDENCE

We assessed the overall strength of evidence for outcomes using a method developed for the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers (EPCs).<sup>41</sup> The AHRQ EPC method considers study limitations, directness, consistency, precision, and reporting bias to classify the strength of evidence for individual outcomes independently for randomized controlled trials (RCTs) and observational studies, with supplemental domains of dose-response association, plausible confounding that would decrease the observed effect, and strength of association, as well as separate guidance for applicability.<sup>42</sup> Ratings were based on the following criteria:

**High** = Very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies, the findings are stable, and another study would not change the conclusions.

**Moderate** = Moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies and the findings are likely to be stable, but some doubt remains.

Low = Limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). Additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

Insufficient = No evidence, unable to estimate an effect, or no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

## **PEER REVIEW**

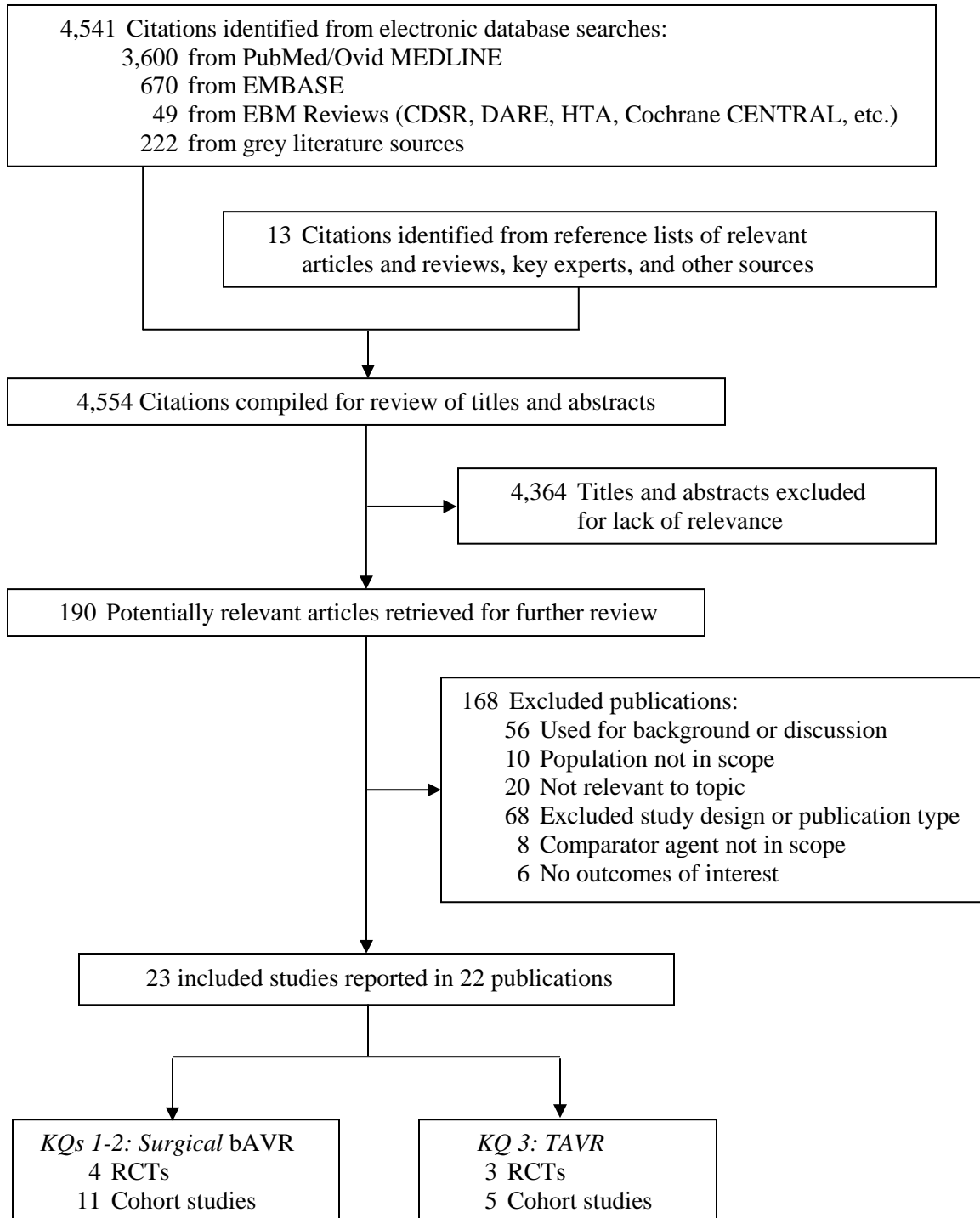
A draft version of this report was reviewed by technical experts and key stakeholders. Reviewer comments and our responses are provided in Appendix D.

## RESULTS

### LITERATURE FLOW

We included 23 primary studies reported in 22 publications after reviewing 4,554 titles and abstracts (Figure 1).

**Figure 1. Literature Flow Diagram**

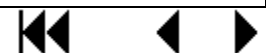


**KEY QUESTIONS 1 AND 2: What are the comparative benefits and harms of antithrombotic strategies for patients who have had BAVR?**

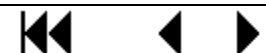
We identified 11 cohort studies and 4 RCTs that address KQs 1 and 2. Table 2 shows the descriptive characteristics of all included studies. Following Table 2, the findings are presented according to the antithrombotic treatments being compared.

**Table 2. Descriptive Characteristics of Studies that Compare Antithrombotic Treatment Strategies after Surgical bAVR**

Study design & setting Years bAVR performed Total sample size Mean follow-up	Treatment arms	Patient characteristics (T1 vs T2)	Patients with atrial fibrillation	CABG or other concomitant procedures	Notes on risk of bias assessment
<i>Randomized controlled trials (N=4)</i>					
Aramendi, 2005 <sup>14</sup> RCT, open-label pilot Multicenter, Spain 2000-2003 N=200 6 m follow-up	Triflusal Acenocoumarol)	Triflusal vs Acenocoumarol: AVR%: 94.8 vs 92.7 (Mitral%: 4.1 vs 6.3) Age: 73.4±6.8 vs 71.5±9.5 Male %: 50 vs 50 DM %: 17 vs 21 HTN %: 56 vs 53 CHF %: 84 vs 82 (majority NYHA 2-3) CABG %: N/A Smoker %: N/A	Afib %: 9.3 vs 9.4 Primary end-point reported afib patients ("The incidence of primary end-point among those patients who were on atrial fibrillation pre-operatively was low: 1/9 (11%) vs 1/9 (11%).")	No/NR	Low ROB. Post-randomization exclusions: 3.5% of randomized patients were excluded because they did not receive medication. Otherwise no notable methodological limitations.
Colli, 2007 <sup>1</sup> RCT, pilot study Hospital Clinic, Barcelona, Spain 2003-2004 N=75 3 m follow-up	War ASA	Age: 69.5±3.3 vs 70.7±3.7 Male %: 97.1 vs 74.3; P = .0072 DM %: 38.2 vs 25.7 HTN %: 55.9 vs 51.4 CHF %: 82.4 vs 71.4 (nyha 3-4) LVEF %: 52.5±10.2 vs 53.6±11.6 Aortic stenosis %: 67.7 vs 77.1 Aortic insufficiency %: 14.7 vs 8.6 EuroSCORE: 6.7±2.4 vs 6.5±1.7 Smoker %: NR	"De novo" postoperative permanent afib (>48 hours) excluded from final statistical analysis but "considered for the follow up" (6 patients [8%])  Transient afib (<48 hours) was included	None	Unclear ROB. The sample size was underpowered to demonstrate statistical differences between the 2 groups. Randomization method not reported, and groups were not balanced: "The 2 groups were similar except for the male:female ratio, which differed due to the method of randomization applied."
di Marco, 2007 <sup>2</sup> RCT, Single center, Italy April-Oct 2005 N=250 3 m follow-up	War ASA	<b>APMES vs ACMES</b> Age 75+/-5 vs 75+/-5 Male % 64 vs 52 Smoking history 32 vs 48 Hypertension 80 vs 92 Diabetes 16 vs 32 Dyslipidemia 40 vs 76 P = .01 Peripheral artery disease 12 vs 12 Prior cerebrovascular event 16 vs 12 Atrial fibrillation 8 vs 28 P = .15	Patients with a history of afib now in sinus were included, but "all patients affected by comorbidities requiring chronic antithrombotic therapy and who were receiving preoperative warfarin were excluded from the study"	Associated procedures were performed in 34% of group 1 patients versus 42% of group 2 patients (P = .44), mainly CABG	Unclear ROB. Method of randomization and allocation concealment not described. Authors note in discussion: "the randomization methods (especially in group 1) might imply some bias".



Study design & setting Years bAVR performed Total sample size Mean follow-up	Treatment arms	Patient characteristics (T1 vs T2)	Patients with atrial fibrillation	CABG or other concomitant procedures	Notes on risk of bias assessment
		Coronary artery disease >75% 16 vs 20 P = .66 <75% 8 vs 24 P = .11 LVEF% 56+/-11 vs 57+/-12			
Rafiq, 2017 <sup>3</sup> RCT, open-label Single site, Denmark 2005-2012 N=370 3 months	BAVR only: War ASA  BAVR + CABG: War + ASA ASA	Age: 73.1±6.4 vs 72.7±7.2 Male %: 71.3 vs 68.8 DM %:20.4 vs 20.5 HTN %:57.5 vs 62.1 LVEF mean: 51.4±12.5 vs 52.6±10.5 Hx MI (CAD): 13.2 vs 10.6	Excluded	CABG: N=135 (36.5%): N = 56, ASA N = 63, War + ASA	Low ROB except for lack of blinding (open-label trial).
<b>Cohort studies (N=11)</b>					
Al-Atassi, 2012 <sup>11</sup> Cohort, prospective Single site, Canada Years of procedure NR N=56 12 m follow-up	War + ASA ASA	Age: 72±9 vs 71±10 Male %: 75 vs 68 DM %: 32 vs 25 HTN %: 75 vs 61 CHF %: 50 vs 64	Excluded	% CABG patients; War + ASA: 43% ASA only: 43%	No notable methodological flaws.
Blair, 1994 <sup>4</sup> Cohort, retrospective Single site, US 1975-1990 N=378 10y follow-up	War ASA None	Age: NR Sex: NR  CAD: NR PAD: NR	Afib included: 71% War, 33% ASA, 34% No Tx	CABG 23% isolated AVR and/or MVR 60% CABG 23%	Representativeness of cohort is unclear: excluded 13% of operated patients who died before discharge. Insufficient detail on dose and/or duration of treatment, completeness of survey outcome assessment, and adjustment for potential confounders.
Brennan, 2012 <sup>5</sup> Cohort, retrospective Multicenter, US 2004-2006 N=25,656 3 m follow-up	War ASA War + ASA	ASA vs War vs Both: Age: 76.4±6.2 vs 77.0±6.0 vs 76.6±5.8 (P < .0001) Male %: 59.5 vs 58.6 vs 62.9 (P < .0001) DM %: 22.1 vs 20.7 vs 23.6 (P = .03)	Included ASA vs War vs Both, %: 32.9 vs 58.2 vs 58.0 (P < .0001)	% of CABG pts, ASA vs War vs Both: 55.2 vs 44.6 vs 60.9 (P < .0001)	Insufficient detail on treatment dosages. Death and embolic events were relatively rare in the first 3 months after surgery.



Study design & setting Years bAVR performed Total sample size Mean follow-up	Treatment arms	Patient characteristics (T1 vs T2)	Patients with atrial fibrillation	CABG or other concomitant procedures	Notes on risk of bias assessment
		EF<30% (%): 4.5 vs 4.3 vs 5.4 (P = .01) CHF %: 34.1 vs 38.5 vs 34.9 (P < .0001)  RF for thromboembolism in 13,458 patients (52.5%), afib (41.1%), Thromboembolism (13.6%), low ef (4.8%)		More patients with afib pre-discharge were put on warfarin or warfarin + ASA ASA only 32.9% Warfarin only 58.2% ASA + Warfarin 58.0%  Also true of prior thromboembolism	
Colli, 2013 <sup>6</sup> Cohort, prospective Multicenter, multinational 2006-2009 N=1118 6 m follow-up	War ASA	Age: 74.6±7.0 vs 74.8±7.0 Male %: 57 vs 57 DM %: 23.4 vs 19.3 HTN %: 66.0 vs 62.9 CHF %: 59.4 vs 63.4 CABG %: N/A Smoker %: 20.6 vs 26.8, P = .0416 CAD 37.4 vs 23.1, P < .0001 HLD 33.3 vs 44.0, P = .0003 MI 6.0 vs 2.9, P = .0167 Cr > 200 umol/L 4.2 vs 1.3, P = .0037 EuroSCORE 6.9 +/- 2.6 vs 6.7 +/- 2.2, P = .5953	Excluded	Isolated AVR was performed in 840 patients, and 489 underwent concomitant AVR and CABG surgery	Insufficient detail on dose and/or duration of treatment. Treatment groups differed at baseline; proportionally more CAD, CKD, and peripheral vascular disease in War group. Differential follow-up: 78% in War vs 89% in ASA.
di Marco, 2007 <sup>2</sup> Cohort, prospective Single center, Italy 2002-2005 N=250 24±14 m follow-up	War ASA	<b>Group 1 (ASA) vs Group 2 (AC)</b> Age 75+/-6 vs 75+/-5 Male%: 53 vs 52 Hypertension% 52 vs 46 Diabetes% 22 vs 22 Dyslipidemia 30 vs 23 Peripheral artery disease 21 vs 14 Coronary artery disease 26 vs 26 Prior stroke 6 vs 11 Atrial fibrillation 6 vs 8	Patients with a history of afib now in sinus were included, but "all patients affected by comorbidities requiring chronic antithrombotic therapy and who were receiving preoperative warfarin were excluded from the study"	Associated procedures were performed in 34% of group 1 patients versus 42% of group 2 patients (P = .44), mainly CABG	Insufficient detail on dose and/or duration of treatment. Unclear whether analysis sufficiently adjusted for potential confounders. Used mixed outcome assessment methods; unclear if complete and consistent.
Gherli, 2004 #552 <sup>7</sup> Cohort, prospective Single center, Italy 2001-2002	War ASA	Age: 70.0±8 vs 72.9±7.1 P = .007 Male %: 38.3 vs 40.8 DM %: 15 vs 12 HTN %: 48.9 vs 51.4	Excluded	Majority of patients underwent isolated BAVR (59% in the ASA group and 53% in the warfarin group; P	Insufficient detail on dose and/or duration of treatment. Outcomes not assessed independently; study

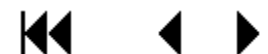


Study design & setting Years bAVR performed Total sample size Mean follow-up	Treatment arms	Patient characteristics (T1 vs T2)	Patients with atrial fibrillation	CABG or other concomitant procedures	Notes on risk of bias assessment
N=249 3 m follow-up		CHF %: 74.5 vs 79.6 CABG %: N/A Smoker %: N/A EuroSCORE 6.1 vs 6.9 P = .015		NS)  AVR 1 SVG 16 (11.4) 9 (8.4) AVR 2 SVG 2 (1.4) 5 (4.6) AVR LIMA 1 SVG 9 (6.4) 13 (12.0) AVR LIMA 2 SVG 8 (5.7) 4 (3.7) AVR LIMA 13 (9.2) 7 (6.5) AVR AAR 3 (2.1) 5 (4.6) Bentall procedure 3 (2.1) 8 (7.4) AVR MV repair 3 (2.1) 0 (0.0)	investigator performed clinical exams.
Jamieson, 2007 <sup>12</sup> Cohort, retrospective Multisite, Canada 1994-2000 N=1,372 30 days follow-up	ASA War + ASA None	Age: 72.6 Male %: 64.3 DM %: 11.0 HTN %: N/A CHF %: N/A Pre-operative ejection fraction <35 %: 4.2% CABG %: 4.5% for previous CABG	Included Among patients with prior atrial fibrillation: AC or AC + AP 37.2% AP 45.3% No therapy 17.5%	CABG 58.7%	Insufficient detail on dose and/or duration of treatment. Completeness of follow-up not specified.
Lee, 2017 <sup>9</sup> Cohort, retrospective Single site, Korea 1994-2014 N=479 3 m follow-up	War ASA	After Propensity Score matching: War 86 vs ASA 86 Age: 70.98±4.72 vs 71.62±6.12 (P = .444) Male n(%): 45(52.3%) vs 43((50%) (P = .760) HTN n(%): 37(43%) vs 38 (44.2%) (P = .878) Stroke n (%): 3 (3.5%) vs 8 (9.3%) (P = .119) CKD n (%): 1 (1.2%) vs 2 (2.3%) (P > .999) CAD n(%): 7 (8.1%) vs 7 (8.1%) (P > .999)	Hx of Afib was included and was AF n(%): 12(3.8%) vs 1 (0.6%) (P = .037) predominantly in the War group	CABG n(%): 10 (3.2%) vs 56 (33.5%) (P < .001)  After Propensity Score matching:  CABG n(%): 7 (8.1%) vs 7 (8.1%) (P > .999)	Outcomes not assessed independently: study investigators treated patients and examined patients for outcomes.





Study design & setting Years bAVR performed Total sample size Mean follow-up	Treatment arms	Patient characteristics (T1 vs T2)	Patients with atrial fibrillation	CABG or other concomitant procedures	Notes on risk of bias assessment
		AF n(%): 1 (1.2%) vs 1 (1.2%) (P > .999) Preop LVEF %: 58.8±12.3 vs 57.4±12.18 (P = .453) LVEF <30 n(%): 6 (7.0%) vs 4 (54.7%) (P = .746)			
Lytle, 1988 <sup>13</sup> Cohort, retrospective Single site, US 1967-1986 N=125 10 y follow-up	War No Tx	Age % <50: 4.4. 51-59: 30.3. 60-69: 49.0. >69: 16.3 Male % 84.3 Hx of MI % 19.0	Afib NR	100% CABG	Method used to ascertain treatment is unclear. Insufficient detail on dose and/or duration of treatment.
Mistiaen, 2004 <sup>8</sup> Cohort, retrospective Belgium, # sites NR 1986-2001 N=500 4.2 y follow-up	War ASA No treatment	Age: 73 Male: 271, 54% DM: 47 EF: 65% Prev CABG: 35	Afib included	CABG, N=348 (69.6%) Procedure on the ascending aorta (n= 27) mitral annuloplasty (n=13)	Inadequate description of cohort formation; dose and/or duration of treatment; and completeness of survey outcome ascertainment.
van der Wall, 2016 <sup>10</sup> Cohort, retrospective 3 hospitals, Netherlands 2008-2014 N=402 1 y follow-up	War Acenocoumarol ASA	Male n (%): 226(56.2) Logistic Euroscore, mean±SD: 7.3±5.1 missing n: 19 prior stroke: 29(7.2) prior MI: 37(9.2) prior embolism: 42(10.4) LVEF n(%): LVEF >40%: 355(88.3) <> LVEF 20-40%: 32(8.0) <> LVEF <20%:14(3.2) <> LVEF Missing: 1(0.2) preop AF n(%): 51(12.7) Missing AF data n(%): 31(7.7) prev CABG: 14(3.5) prev PCI: 44(10.9) smoking: 75(18.7) preop ASA: 178(44.3) preop War: 59(14.7)	Hx of AF included n(%): 51(12.7) Missing AF data n(%): 31(7.7)	CABG n(%):169(42) missing n: 2 prev PCI: 44(10.9)	Analyzes effect of duration of treatment with War vs ASA as a continuous variable (number of days). No notable methodological flaws.



<b>Study design &amp; setting</b> <b>Years bAVR performed</b> <b>Total sample size</b> <b>Mean follow-up</b>	<b>Treatment arms</b>	<b>Patient characteristics (T1 vs T2)</b>	<b>Patients with atrial fibrillation</b>	<b>CABG or other concomitant procedures</b>	<b>Notes on risk of bias assessment</b>
		prev thoracotomy: 25(6.2) Missing: 31(7.7)			

**Abbreviations:** ACMEs = Anticoagulant microembolic signal; Adj = Adjusted; AF = Atrial fibrillation; APMEs = Antiplatelet microembolic signal; ASA = Aspirin (acetylsalicylic acid); BAVR = Bioprosthetic aortic valve replacement; CABG = Coronary artery bypass grafting; CAD = Coronary artery disease; CHF = Chronic heart failure; CKD = Chronic kidney disease; DM = Diabetes mellitus; DVT = Deep vein thrombosis; GI = Gastrointestinal; HTN = Hypertension; Hx = History (of); INR = International Normalized Ratio; LIMA = Left internal mammary artery (graft); LOS = Length of stay; LVEF = Left ventricular ejection fraction; MEs = Microembolic signal; MOF = Multi-organ failure; NR = Not reported; OR = Odds ratio; PCI = Percutaneous coronary intervention; PSM = Propensity score matching; ROB = Risk of bias; RR = Relative risk; SVG = Saphenous vein graft; TE = Thromboembolism; TIA = Transient ischemic attack; Tx = Treatment; War = Warfarin.

## Warfarin vs ASA

### Summary of Findings

*KQs 1 & 2: What are the comparative benefits and harms of antithrombotic strategies for patients who have had bAVR/TAVR?*

Three RCTs and 8 observational studies evaluated the benefits and harms of a vitamin K antagonist compared with aspirin after bAVR (Table 3). 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 one large, well-done observational study – were consistent in showing no difference in outcomes between warfarin and aspirin (moderate-strength evidence).

#### *A. Do the benefits/harms differ according to thromboembolic risk profile?*

In one large observational trial<sup>5</sup> 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 thromboembolism.

#### *B. Do the benefits/harms differ according to concomitant procedure (eg, CABG)?*

No evidence is available.

### Detailed Results

The largest trial enrolled 236 patients aged 60 years or older and in sinus rhythm referred for first-time bAVR with a stented porcine valve.<sup>3</sup> Patients were randomized to receive either warfarin (goal INR range 2.0-3.0) or aspirin 150 mg once daily for 3 months postoperatively. Difficulty in the management of anticoagulation therapy was demonstrated by the fact that only 27.1% of patients achieved an INR in therapeutic range for more than 75% of the time and 12.7% of patients had at least one INR measurement equal to or above 4.5. After 3 months of follow-up there was no significant difference in 90-day mortality (3.8% vs 2.9%,  $P = .72$ ), thromboembolic events (3.8% vs 2.9%,  $P = .72$ ), or major bleeding events (2.9% vs 2.9%,  $P = .68$ ) between groups. There was no significant difference in other harms reported including re-operation for bleeding, drainage of pericardial effusion, or total length of stay. Even though this is the largest trial to compare warfarin to aspirin, it had an unclear risk of bias due to lack of blinding and was underpowered to detect important differences in outcomes.

Two small pilot RCTs ( $n=69$  and  $n=50$ ,  $n=119$  total) similarly did not show a significant difference in mortality (5.9% vs 5.7%,  $P = .99$ ), postoperative cerebral ischemia (2.9% vs 2.9%,  $P = .99$ ), major bleeding (8.8% vs 2.9%,  $P = .36$ ), or total postoperative stay ( $9\pm 4d$  vs  $9\pm 3d$ ,  $P = .96$ ).<sup>1,2</sup> However, both trials have an either high or unclear risk of bias and given the small sample sizes are not adequately powered to detect differences between groups.

Figures 2-4 show forest plots combining data from 2 trials that reported 90-day outcomes.<sup>1,3</sup> There were no statistically significant differences between warfarin and aspirin in mortality (OR 1.23, 95% CI 0.36 to 4.15), thromboembolic events (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.<sup>5</sup> Among this cohort there was no significant difference in 3-month incidence of death (4.0% vs 3.0%, RR 1.01, 95% CI 0.80-1.27), embolic events (1.0% vs 1.0%, RR 0.95, 95% CI 0.61–1.47), or bleeding events (1.4% vs 1.0%, RR 1.23, 95% CI 0.85–1.79) between patients who received warfarin (N=2,999) versus aspirin (N=12,457). 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 (LVEF), and prior stroke or thromboembolism.

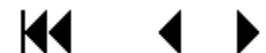
Five other observational studies which had lower numbers of patients and were of lower overall quality similarly found no significant difference in mortality, thromboembolism, or bleeding in patients treated with warfarin versus aspirin.<sup>2,4,6,7,9</sup>

One cohort study showed an increased risk of thromboembolism among patients treated with warfarin (RR 3.0, 95% CI 1.5-6.3, P = .0028) but was determined to be low quality given its high risk of selection and ascertainment bias.<sup>8</sup> Another cohort study found an increased risk of bleeding events for patients treated with warfarin versus aspirin (RR 8.41, 95% CI 3.58–19.79, P < .001) but no significant difference in thromboembolic events (RR 1.2, 95% CI 0.47–3.02, P = .7).<sup>10</sup>

Finally, a relatively large (n=4075 enrolled, n=3194 followed) retrospective cohort study from Denmark examined the association of duration of warfarin therapy after bAVR with risk of mortality, thromboembolic complications, and bleeding. While the authors concluded that discontinuation of warfarin treatment within 6 months after bioprosthetic AVR surgery was associated with increased cardiovascular death, this study was not included in our analysis because groups were compared only on the basis of warfarin versus no warfarin treatment without consideration of aspirin or other antithrombotic therapy.<sup>43</sup>

**Table 3. Findings of Studies that Compared Warfarin with ASA after Surgical bAVR**

Study design Combined N in War vs ASA Tx arms Mean follow-up time	N per Tx group Dose and duration of treatment	Mortality	Thromboembolic events	Major hemorrhagic complications	Other benefits/harms
<i>Randomized controlled trials (N=3)</i>					
Colli, 2007 <sup>1</sup> RCT, pilot study N=69 3 m follow-up	Warfarin = 34 ASA = 35  (i) Warfarin (goal INR range 2-3) for the first 3 months, followed by ASA (100 mg/day); or (ii) ASA alone (100 mg/day)	Perioperative (30-day) death: Warfarin: 1 (2.9%) ASA: 1 (2.9%) P = .99  Death at follow-up: Warfarin: 2 (5.9%) ASA: 2 (5.7%) P = .99	Postoperative cerebral ischemia, 24 hours to 3 months: Warfarin: 1 (2.9%) ASA: 1 (2.9%) P = .99  >3 months: Warfarin: 0 (0%) ASA: 1 (2.9%) P = .99	Warfarin: 3 (8.8%) ASA: 1 (2.9%) P = .36	NR
di Marco, 2007 <sup>2</sup> RCT N=50 3 m follow-up	ASA = 25 warfarin = 25  ASA 100 mg/d Warfarin (target INR 2-3; 100 patients)  Duration: first 3 months postop	NR	Warfarin group, n = 0; ASA group, n = 0	Warfarin group, n = 0; ASA group, n = 2 (8%) P > .05	Intensive care unit stay (d) 1 +/-1 1 +/-1 Mechanical ventilation length (h) 9+/-3 10+/-5 .90 Total postoperative stay (d) 9+/-4 9+/-3 .96
Rafiq, 2017 <sup>3</sup> RCT, open-label N=236 3 m follow-up	BAVR only: War = 117 ASA = 119  Dosage: (War INR 2.0–3.0 + ASA 75mg/d) vs ASA 150mg/d 3 months postop  Percentage of time in which INR was in therapeutic range (2.0 to 3.0) Above 75%, n 36 (27.1%) 50%–75%, n 58 (43.6%)	BAVR only subgroup: 4 (3.8%) warfarin vs 3 (2.9%) aspirin; P = .721	MI (n(%)) 0 (0%) vs 1 (1%) P = .495 DVT (n(%)) 0 vs 0 P = 1.000 TIA/Stroke (n(%)) 3 (2.9%) vs 2 (1.9%) P = .683 Total thromboembolic events: 4 (3.8%) vs 3 (2.9%); P = .721	GI-bleeding n(%) 3 (2.9%) vs 1 (1.0%) P = .369 Cerebral hemorrhage 0 (0%) vs 1 (1.9%) P = 1.00 Severe hematuria: 0 vs 0; P = 1.00  Total bleeding events: 3 (2.9%) vs 2 (1.9%) P = .683.  Warfarin was associated with major bleeding in a multivariate analysis: OR (95% CI) 5.18 (1.06 to 25.43) P = .043	Re-admission to hospital: 16 (15.4%) 15 (14.2%) P = .959 Perioperative events: Re-exploration for bleeding within 24 h 4 (3.8%) 2 (1.9%) P = .434 Drainage of Pericardial effusion after 24 h 1 (1.0%) 2 (1.9%) P = 1.000 Cardioversion 19 (18.3%) 16 (15.2%) P = .703 Dialysis 4 (3.8%) 3 (2.9%) P = 1.000 MOF 2 (1.9%) 1 (1.0%) P =



Study design Combined N in War vs ASA Tx arms Mean follow-up time	N per Tx group Dose and duration of treatment	Mortality	Thromboembolic events	Major hemorrhagic complications	Other benefits/harms
	25%–49%, n 33 (24.7%) Below 25%, n 6 (4.5%) At least one measurement of INR ≥ 4.5 17 (12.7%)				.615 LOS (days) (median(range)) 8.5[4–80] 7.5(5–149) P = .328
<b>Cohort studies (N=8)</b>					
Blair, 1994 <sup>4</sup> Cohort N = 308 7 ±4 y follow-up	War = 18 ASA = 290 No Tx = 70  Dosage: Warfarin goal INR 1.4-1.7 in the earlier years of the study; 1.2-1.4 ASA dose NR. Duration NR	"Survival did not differ significantly between the 3 treatment groups (P = .7)."	Mean linearized rate per patient-year: Warfarin: 2.9 ± 1.6% ASA: 0.8 ± 0.2% No Tx: 1.5 ± 0.6% P = .07  Freedom from TE at 10 years: War: 80±11% ASA: 93±2% No Tx: 88±5% P = .08	Rate of hemorrhage in the first 90 days (16.7% vs 3.4%, P = .14 by Cox model)  Treatment group was not associated with risk of hemorrhage in univariate Cox model (P = .11)	NR
Brennan, 2012 <sup>5</sup> Cohort N=15,456 3 m	ASA = 12457 Warfarin = 2999 ASA + warfarin = 5972  Dosage not specified. Duration 3 months	Warfarin: 4.0% ASA: 3.0% RR 1.01, 95% CI 0.80-1.27	Warfarin 1.0% ASA 1.0% RR 0.95, 95% CI 0.61–1.47	Warfarin 1.4% ASA 1.0% RR 1.23, 95% CI 0.85–1.79	NR
Colli, 2013 <sup>6</sup> Cohort N=1118 6 m	War = 500 ASA = 618  Dosage: ASA 100-325 mg daily INR target of 2.5 (therapeutic range 2 to 3) achieved in only 43% of the sample throughout the entire study period. Duration: 6 months	ASA group, n = 13 (2.1%); War group, n = 13 (2.6%) p = 0.69	Cerebral thromboembolism 12 (2.4%) War vs 9 (1.5%) ASA, P = .2737 P = .80 PSM  Systemic thromboembolism 2 (0.4%) War vs 1 (0.2%) ASA, P = .5896 P = .99 PSM  AVR + CABG: cerebral TE 8 (4.3%) vs 2	ASA group, n = 8 (1.3%); War group, n = 18 (3.6%) P = .0153 P = .14 PSM	Repeat operation 6 (1.2%) War vs 1 (0.2%) ASA, P = .0496  Non-structural valve dysfunction 4 (0.8%) War vs 1 (0.2%) ASA, P = .1792



Study design Combined N in War vs ASA Tx arms Mean follow-up time	N per Tx group Dose and duration of treatment	Mortality	Thromboembolic events	Major hemorrhagic complications	Other benefits/harms
			(0.9%), P = .0499 systemic TE 0 vs 1 (0.5%), P = .99 no PSM reported		
di Marco, 2007 <sup>2</sup> Cohort N=200 24±14 m	ASA = 100 Warfarin = 100  ASA 100 mg/d Warfarin (target INR 2-3; 100 patients)  Duration: first 3 months postop	Warfarin group, n = 0; ASA group, n = 0 at 30 days	Warfarin group, n = 0; ASA group, n = 0	Warfarin group, n = 2 (1.6%); ASA group, n = 2 (1.6%) P > .05	APMES vs ACMES Intensive care unit stay (d) 1 +/-1 1 +/-1 Mechanical ventilation length (h) 9+/-3 10+/-5; P = .90 Total postoperative stay (d) 9+/-4 9+/-3; P = .96
Gherli, 2004 <sup>7</sup> Cohort N=249 3 m	ASA = 141 Warfarin = 108  ASA 100 mg/d Warfarin goal INR 2-3	Warfarin group, n= 7 (6.4%); ASA group, n = 4 (2.8%) p = 0.299	Warfarin group, n = 8 (7.4%); ASA group, n = 4 (2.8%) p = 0.319	Warfarin group, n = 4 (3.7%); ASA group, n = 3 (2.1%) P = .473	Mean intensive care unit stay for patients treated with ASA and with warfarin differed (2.1 1.4 and 2.8 2.2 days, respectively; P = .003)
Lee, 2017 <sup>9</sup> Cohort N=479 3 months	ASA = 167 War = 312  INR target range 1.5-2.5 ASA 100 mg/daily Duration 3 months	Warfarin group, n = 0 ASA group, n = 0	Thromboembolic event (cerebral infarction) during 90 days n(%): 1(1.%) vs 0(0%) (P > .999)	Bleeding (upper GI bleeds) during 90 days n(%): 2(2/3%) vs 1(1.2%) (P < .999)	
Mistiaen, 2004 <sup>8</sup> Cohort N=294 4.2 y	War = 74 ASA = 220 No Tx = 185  Dose and duration: Warfarin: Target INR not reported; duration 3 months, continued further in pts with AF or other indications. ASA: 160 mg/d for 3 months	NR	With afib: 4/44 warfarin 9% 1/35 ASA 2% 3/26 none 11.5%  No afib: 7/30 warfarin 23% 12/185 ASA 6.4% 10/159 none 6.3%  Adjusted for history of stroke; hospital thromboebolism; and HTN:	NR	



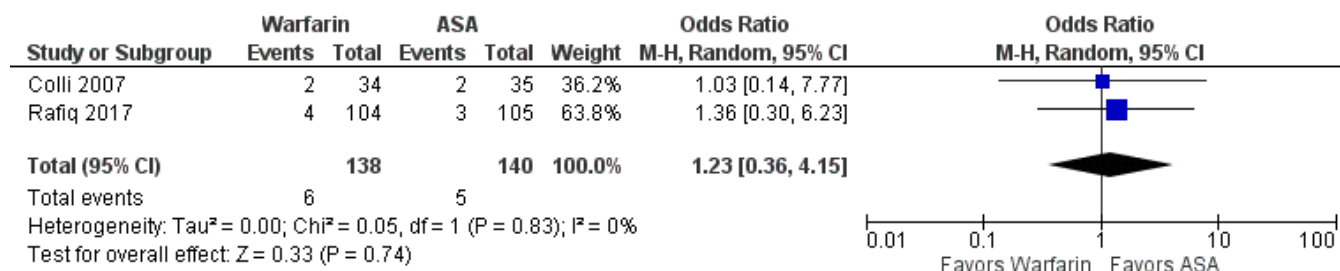
Study design Combined N in War vs ASA Tx arms Mean follow-up time	N per Tx group Dose and duration of treatment	Mortality	Thromboembolic events	Major hemorrhagic complications	Other benefits/harms
			RR (95%CI), War vs ASA: 3.0 (1.5-6.3), P = .0028		
<p>van der Wall, 2016<sup>10</sup> Cohort, retrospective N=402 1 year follow-up</p>	<p>Before policy change (War) = 163 After policy change (ASA) = 239</p> <p>Nadroparin was started on the first postoperative day followed by acenocoumarol (INR target range 2.5-3.5), or ASA.</p> <p>Anticoagulation with acenocoumarol was maintained for 3 postoperative months, then discontinued at the discretion of the referring cardiologist and most often replaced by aspirin. BAVR+CABG pts received ASA only.</p> <p>After July 1 2011: ASA 100 mg/d was started on the first postoperative day and continued lifelong in patients in sinus rhythm (could be changed to War as needed for afib/TE risk factors).</p>	NR	<p>Risk of TE events 1 year after BAVR was not significantly associated with current acenocoumarol use (Adj RR 1.2 0.47 to 3.02, P = .7).</p> <p>Risk of TE was increased with prior acenocoumarol use: Adj RR (95% CI): 3.1 (1.37 to 7.4), P = .007</p>	<p>Risk of bleeding events 1 year after BAVR was significantly increased for past and current use of acenocoumarol: RR (95% CI) for bleeding events, adjusted for sex, age, Hx MI, Hx PCI, smoking, HTN, dyslip, prior use of acenocoumarol, and concomitant CABG, associated with acenocoumarol use at 1 year: 8.41 (3.58 to 19.79), P &lt; .001. Prior acenocoumarol use also had higher risk of bleeding: Adj RR 2.46 (95% CI 1.32to4.56) P = .004</p> <p>Adj RR (95% CI) for 'major' bleedings associated with acenocoumarol: 14.60 (1.95 to 109.37)</p>	NR

**Abbreviations:** ACMES = Anticoagulant microembolic signal; Adj = Adjusted; AF = Atrial fibrillation; APMES = Antiplatelet microembolic signal; ASA = Aspirin (acetylsalicylic acid); BAVR = Bioprosthetic aortic valve replacement; CABG = Coronary artery bypass grafting; DVT = Deep vein thrombosis; GI = Gastrointestinal; HTN = Hypertension; Hx = History (of); INR = International Normalized Ratio; LOS = Length of stay; MES = Microembolic signal; MOF = Multi-organ failure; NR = Not reported; OR = Odds ratio; PCI = Percutaneous coronary intervention; PSM = Propensity score matching; RR = Relative risk; TE = Thromboembolism; TIA = Transient ischemic attack; Tx = Treatment; War = Warfarin.

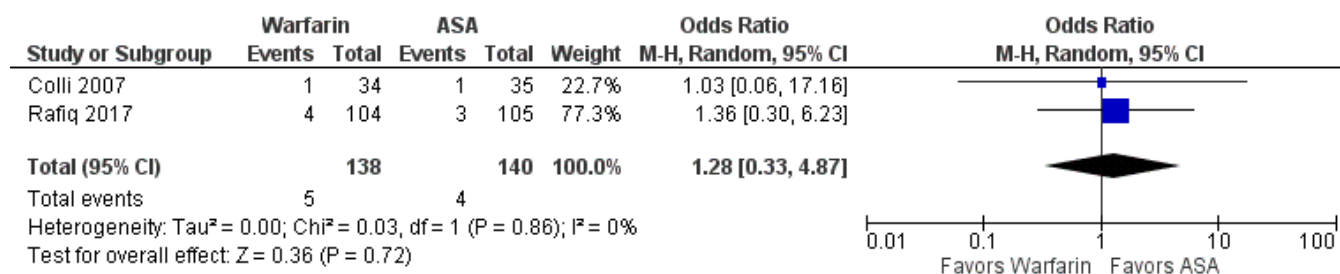




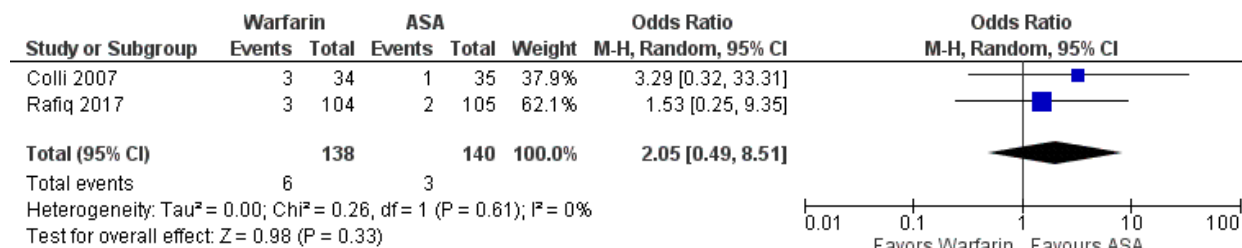
**Figure 2. Mortality at 90 Days in Trials that Compared Warfarin with ASA after Surgical bAVR**



**Figure 3. TE Events at 90 Days in Trials that Compared Warfarin with ASA after Surgical bAVR**



**Figure 4. Major Bleeding Complications at 90 days in Trials that Compared Warfarin with ASA after Surgical bAVR**



## Warfarin Combined with ASA vs ASA Monotherapy

### Summary of Findings

*KQs 1 & 2: What are the comparative benefits and harms of antithrombotic strategies for patients who have had BAVR?*

One RCT and 3 observational studies evaluated the benefits and harms of warfarin plus ASA compared with ASA alone following bioprosthetic aortic valve replacement. Overall, there is limited evidence from one large, well-done cohort study showing that warfarin plus aspirin was associated with a reduction in mortality and thromboembolic events (low-strength evidence). However, the effect size was small and there was a substantial increase in bleeding risk. The other studies do not substantively add to the body of evidence due to methodologic flaws and small sample size.

#### *A. Do the benefits/harms differ according to thromboembolic risk profile?*

Data from one large observational study suggests that among patients with one or more thromboembolic risk factors (atrial fibrillation, prior thromboembolism, depressed ejection fraction) the combination of warfarin plus aspirin reduced thromboembolic events more than aspirin alone. However the combination was not associated with reduced mortality and was associated with a higher risk of bleeding.

#### *B. Do the benefits/harms differ according to concomitant procedure (eg, CABG)?*

There is insufficient evidence to suggest that benefits or harms of different anticoagulation strategies differed according concomitant procedure.

### Detailed Results

Three cohort studies<sup>5,11,12</sup> and one RCT<sup>3</sup> compared warfarin and ASA in combination with ASA alone (Table 4).

Jamieson et al included patients with atrial fibrillation and found more patients with atrial fibrillation were on anticoagulation (37%) than in the total study population (11%)<sup>12</sup> The authors do not differentiate between preoperative and postoperative atrial fibrillation. However, atrial fibrillation was not an independent risk factor for thromboembolism plus reversible ischemic neurologic events (RIND). Rather, only CABG and preoperative stroke were predictive of thromboembolism, but anticoagulation did not offer significant protection. Brennan et al included atrial fibrillation as a risk factor for thromboembolism along with prior thromboembolism and depressed ejection fraction (<30%).<sup>5</sup> Among patients with these risk factors, warfarin plus aspirin offered protection against thromboembolism (RR 0.61, 95% CI 0.40-0.94) but not against death (RR 0.86, 95% CI 0.69-1.07). Patients with risk factors had a significantly increased risk of bleeding when given warfarin plus aspirin compared to aspirin alone (RR 2.17, 95% CI 1.60-2.94). Atrial fibrillation was the most common risk factor among the 52.5% of patients with a risk factor. Warfarin was more commonly used in patients with concomitant atrial fibrillation, but less than half of the patients with atrial fibrillation were discharged on warfarin plus ASA. The authors note that patients with a pre-operative indication for warfarin were excluded, but it was unclear to what extent this exclusion extended to patients

with pre-operative atrial fibrillation. Propensity scoring included pre-discharge atrial fibrillation without further differentiation of pre- versus post-operative atrial fibrillation.

The single RCT comparing this anticoagulation strategy was a single-center, open-label prospective trial, and stratified patients by type of surgical procedure – either isolated bAVR or bAVR and concomitant CABG.<sup>3</sup> Patients in the bAVR plus CABG group were randomized to warfarin plus 75 mg of ASA daily or ASA alone at 150 mg daily. The warfarin plus ASA group included 72 patients, while the ASA-only group included 63 patients. Notably, patients with pre-existing atrial fibrillation or prior TIA or stroke were excluded from the trial. Patients who developed post-operative atrial fibrillation lasting >48 hours were started on warfarin, but included in an intention to treat manner. Difficulties with anticoagulation were noted, with only 27.1% of patients being in goal range more than 75% of the time. No significant difference was seen in the benefits or harms between the groups at 3 months, in either thromboembolic events or major bleeding events.

The largest cohort study (N=8,971) comes from a multi-center registry of patients throughout the United States undergoing bAVR, with or without CABG.<sup>5</sup> Patients with atrial fibrillation or pre-operative stroke were included. Outcomes assessed at 3 months included death or readmission for embolic and bleeding events. The anticoagulation strategy was ASA only in 49% of patients, warfarin only in 12% of patients and warfarin plus aspirin in 23% of patients. Seven percent of patients had no anticoagulation, and 8 percent of patients had dual antiplatelet therapy. Dosage of aspirin and time in goal range for INR were not reported. Combined treatment with warfarin plus aspirin was associated with a 0.6% absolute and 20% relative risk reduction for 3-month mortality (adjusted RR: 0.80, 95% CI 0.66 to 0.96; NNT 153) compared to the use of aspirin alone. The mortality effect only became evident after propensity adjustment and it is unclear whether the benefits of the combination of aspirin and warfarin over aspirin was primarily driven by patients with atrial fibrillation.<sup>25</sup> The incidence of embolic events was low (0.9%), but the events were frequently neurologic in nature. Adding warfarin to ASA was associated with a 0.4% absolute reduction of embolic events overall (P = .006). After risk adjustment, the adjusted RR was 0.52 (95% CI: 0.35 to 0.76; NNT 212). Patients older than 75 years old had the most benefit. Bleeding events requiring hospital stay at 3 months were low (1.6%) and the majority were GI bleeds (77.5%). After risk adjustment, patients treated with warfarin plus ASA had an increased risk of bleeding (RR 2.80, 95% CI: 2.18 to 3.60, NNH 55).

A small prospective cohort study by Al-Atassi compared warfarin plus 81 mg of ASA daily versus 325 mg of ASA daily following bAVR with or without CABG.<sup>11</sup> After 3 months, patients in the warfarin plus ASA group were switched to ASA only, at a dose of 325 mg daily. Follow-up was completed for 12 months from surgical date. Patients with pre-existing atrial fibrillation or TIA or stroke were excluded. In addition, patients who developed post-operative atrial fibrillation were excluded from the study. Anticoagulation regiment was chosen a priori by the surgeon, independent of surgical findings, in concordance with their routine practices. The primary outcomes of the study were transcranial Doppler evidence of thromboembolism and assessment of platelet function, outcomes that would be outside the scope of this review. However, there was no mortality, stroke, or transient ischemic attacks at one year in either treatment group. Bleeding events were not reported. The trial was small, with 28 patients in each arm, and no patients were lost to follow up. The authors reported no additional benefit to warfarin and ASA above ASA alone.

Jamieson et al performed a retrospective cohort trial of 1,372 patients undergoing bAVR with or without CABG.<sup>12</sup> The mean age of the patients in the study was 72.6 years old and patients with atrial fibrillation or prior stroke were included. Patients were given warfarin with a target INR of 2.5-3.5 either alone or plus ASA between 81 and 325 mg daily (AC or AC + AP group) or ASA 81 to 325 mg daily alone (AP group) or no anticoagulation. Patients were followed for 3 months. Most patients were discharged from the hospital on antiplatelet therapy alone (66.5%) with only 11.2% being discharged with warfarin (either alone or in combination with ASA). Notably, 22.3% of patients were on no antithrombotic therapy at all at the time of discharge. In patients with atrial fibrillation, a slightly higher percentage (37.2%) were managed with warfarin (alone or with ASA). However, atrial fibrillation was not found to be predictive of thromboembolism in the multi-variate analysis. Overall, there were no significant differences in thromboembolic events between groups with different anticoagulant strategies. Even without anticoagulation of any type, rates of thromboembolic events were 3.6%, compared with 2.2% with antiplatelet alone and 3.9% with anticoagulant or anticoagulant plus ASA ( $P = .264$ ). Major bleeding was not reported as an outcome. The authors concluded that there did not appear to be an indication for routine antithrombotic management, but suggested possible use in patients with concomitant CABG or pre-operative stroke, as these were identified by multi-variate analysis to be the strongest predictors of thromboembolism or RIND.

All included studies addressing warfarin combined with ASA versus ASA monotherapy included patients undergoing CABG. The overall rates of CABG varied from 36.5% to 58.7%. In the largest study, more patients undergoing AVR plus CABG received ASA plus warfarin (60.9% vs 44% for warfarin only vs 55.2% for ASA only;  $P < .0001$ ).<sup>5</sup> However, outcomes of interest were not stratified according to surgical procedure. In one study [Jamieson] concomitant CABG was a risk factor for thromboembolism plus reversible ischemic neurologic deficit (RIND) (OR 3.19, 95% CI 1.16 to 8.76,  $P = .025$ ), however neither anticoagulant nor antiplatelet therapies gave significant protection.<sup>12</sup> Other included studies either had no difference in outcome among patients who had CABG, or did not stratify outcomes based on surgical procedure.

**Table 4. Findings of Studies that Compared Warfarin Combined with ASA vs ASA Monotherapy after Surgical bAVR**

Study N in Tx comparison Mean follow-up	N per treatment group Dose and duration of treatment	Mortality	Thromboembolic events	Major hemorrhagic complications	Other benefits/harms
<b>Randomized controlled trial (N=1)</b>					
Rafiq, 2017 <sup>3</sup> RCT N=119 3 months	CABG subgroup: WAR + ASA = 72 ASA = 63  Dosage: (War INR 2.0–3.0 + ASA 75mg/d) vs ASA 150mg/d 3 months postop  Percentage of time in which INR was in therapeutic range (2.0 to 3.0) Above 75%, n 36 (27.1%) 50%–75%, n 58 (43.6%) 25%–49%, n 33 (24.7%) Below 25%, n 6 (4.5%) At least one measurement of INR ≥ 4.5 17 (12.7%)	90-day mortality, N (%):  BAVR + CABG subgroup: (War+ASA) vs ASA: 4 (6.3%) vs 3 (5.4%), P = .800	TE events at 3 months, N (%):  BAVR + CABG subgroup: (War+ASA) vs ASA: 7 (11.1) vs 9 (16.1), P = .592  TE events include MI, DVT, and TIA/stroke.  Most thromboembolic events occurred during index hospitalization.	Total bleeding events at 3 months, N (%):  BAVR + CABG subgroup, (War+ASA) vs ASA: 6 (9.5) vs 1 (1.8), P = .117  Adjusted OR (95% CI): War: 5.18 (1.06-25.43), P = .043 ASA: 2.14 (0.42–10.79), P = .358	Re-admission to hospital: 25 (15.0%) vs 21 (13%); P = .825 Paravalvular leak (n): Grade 1 : 12 vs 15 Grade 2: 2 vs 2 P = .636 Ejection fraction: 53.9 ± 8.4 vs 54.7 ± 8.1 ; P = .515  Perioperative events: Re-exploration for bleeding within 24 h 6 (3.6%) vs 6 (3.75) P = 1.000 Drainage of Pericardial effusion after 24 h 1 (0.6%) vs 3 (1.9%) P = .340 Cardioversion 24 (14.3%) vs 23 (14.2%) P = .990 Dialysis 9 (5.4%) vs 4 (2.5%) P = .259 MOF 4 (2.4%) vs 2 (1.2%) P = .685 LOS (days) (median(range)) 8 [4–80] vs 9 (5–149) P = .352
<b>Cohort studies (N=3)</b>					
Al-Atassi, 2012 <sup>11</sup> Cohort N=56 12 months	War+ASA = 28 ASA = 28 Dosage: (War INR 2.0–3.0 + 81 mg/d ASA) vs 325 mg/d ASA for 3 months postop. After 3 months: all pts 325 mg/day ASA.	0% vs 0%	0% vs 0% No stroke or TIA in either group.	NR	NR
Brennan, 2012 <sup>5</sup> Cohort	War+ASA = 5972 ASA = 12457	% Mortality at 3 months, ASA vs War vs Both:	% Embolism at 3 months, ASA vs War vs Both:	% Bleeding at 3 months, ASA vs War vs Both:	Almost all embolic events were stroke (71%).



Study N in Tx comparison Mean follow-up	N per treatment group Dose and duration of treatment	Mortality	Thromboembolic events	Major hemorrhagic complications	Other benefits/harms
N=18,429 3 months	War = 2999  Dosage not specified. Duration 3 months	3.0 vs 4.0 vs 3.1  Adjusted RR (95% CI): War vs ASA: 1.01 (0.80–1.27)  Both vs ASA: 0.80 (0.66–0.96), NNT 153	1.0 vs 1.0 vs 0.6  Adjusted RR (95% CI): War vs ASA: 0.95 (0.61–1.47) Both vs ASA: 0.52 (0.35-0.76), NNT 212  Effect most prominent in subgroup > or = 75 RR 0.44 (0.27-0.72)	1.0 vs 1.4 vs 2.8  Adjusted RR (95% CI): War vs ASA: 1.23 (0.85–1.79)  Both vs ASA: 2.80 (2.18–3.60), NNH = 55	Almost all bleeding was GI (77%), no difference in hemorrhagic stroke across groups
Jamieson, 2007 <sup>12</sup> Cohort N=1066 30 days	AC or AC+AP = 154 AP = 912 No Tx = 306  Dosage: ASA 81-325mg/d War target INR 2.5-3.5 90 days	NA	Major TE, N (%): AP: 20 (2.2) AC or AC+AP: 6 (3.9) None: 11 (3.6) P = .264	NR	NR

**Abbreviations:** AC = Anticoagulation; AP/APT = Antiplatelet therapy; ASA = Aspirin (acetylsalicylic acid); CABG = Coronary artery bypass grafting; DVT = Deep vein thrombosis; INR = International Normalized Ratio; LOS = Length of stay; MI = Myocardial infarction; N = Number; NNT = Number needed to treat; OR = Odds ratio; P = P-value; RCT = Randomized controlled trial; RR = Relative risk; TE = Thromboembolism; TIA = Transient ischemic attack; Tx = Treatment; War = Warfarin.



## Warfarin vs No Treatment

### Summary of Findings

*KQs 1 & 2: What are the comparative benefits and harms of antithrombotic strategies for patients who have had bAVR?*

Three cohort studies compared warfarin with no treatment. One found poorer long-term survival with warfarin.<sup>13</sup> Another study found elevated risk of TE associated with warfarin after 4.2 years.<sup>8</sup> Only one study provided data on bleeding risk, and reported no difference between treatment groups.<sup>4</sup> The strength of evidence for these findings is insufficient given the paucity of data, insufficient detail about dose and/or duration of treatment, and other methodologic limitations.

*A. Do the benefits/harms differ according to thromboembolic risk profile?*

In a subgroup of patients with AF (N=105), there was no significant difference in TE events comparing warfarin and no treatment in one study.<sup>8</sup>

*B. Do the benefits/harms differ according to concomitant procedure (eg, CABG)?*

No evidence is available.

### Detailed Results

*KQs 1 & 2: What are the comparative benefits and harms of antithrombotic strategies for patients who have had bAVR?*

Three cohort studies compared warfarin with no treatment (Table 5). Two studies included small samples of patients who received warfarin: 18 in one study<sup>4</sup> and 24 in another.<sup>13</sup> A third study included 74 patients treated with warfarin.<sup>8</sup> Information on target INR and/or duration of treatment was lacking in each study.

Two of the studies provided information about mortality. One study reported no difference in 3-month mortality between the treatment groups.<sup>4</sup> Another study found poorer long-term survival with warfarin compared with no treatment (67.9% vs 76.1% survival at 8 years,  $P = .03$ ).<sup>13</sup>

TE risk did not significantly differ between warfarin and no treatment in one small study (N=18 patients on warfarin).<sup>4</sup> A larger study with 74 patients on warfarin found significantly elevated risk of TE with warfarin after 4.2 years of follow-up (RR 3.0, 95% CI 1.5 to 6.3,  $P = .0028$ ).<sup>8</sup> The risk estimate was adjusted for stroke, hospital thromboembolism, and hypertension, although it is 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.

Only one study provided data on bleeding risk, and reported no difference between treatment groups.<sup>4</sup>

*A. Do the benefits/harms differ according to thromboembolic risk profile?*

One study reported TE events in a subgroup of patients with postoperative chronic atrial fibrillation (N=105).<sup>8</sup> TE events did not significantly differ between groups who received

warfarin versus no treatment: 4/44 (9.09%) versus 3/26 (11.5%),  $P > .05$ . Warfarin treatment continued beyond 3 months in patients with atrial fibrillation.

*B. Do the benefits/harms differ according to concomitant procedure (eg, CABG)?*

No evidence is available.



**Table 5. Findings of Cohort Studies that Compared Warfarin with No Treatment after Surgical bAVR**

Study N in Tx comparison Mean follow-up	N per treatment group Dose and duration of treatment	Mortality	Thromboembolic events N (%); OR (95% CI)	Major Hemorrhagic Complications	Other benefits/ harms
Blair, 1994 <sup>4</sup> N=88 7±4 y follow-up	War = 18 No Tx = 70  Warfarin goal INR 1.4-1.7 --> 1.2-1.4 Duration NR	"Survival did not differ significantly between the 3 treatment groups (P = .7)"	Mean linearized rate per patient-year: Warfarin: 2.9 ± 1.6% No Tx: 1.5 ± 0.6% P = .07 for overall comparison of 3 groups including ASA  % Freedom from TE at 10 years: War: 80±11% No Tx: 88±5% P = .08 for overall comparison of 3 groups including ASA	No difference between treatment groups in long-term freedom from hemorrhage (P = .14).  Treatment group not associated with risk of hemorrhage in univariate Cox model (P = .11)	NR
Lytle, 1988 <sup>13</sup> N=122 10 y follow-up	War = 24 No Tx = 98  Dosage: NR Duration: NR	Survival at 8 yrs: War: 67.9% No Tx: 76.1% P = .03	NR. Reported findings include mechanical valve patients, who make up the 57.5% of the sample.	NR. Reported findings include mechanical valve patients, who make up the 57.5% of the sample.	NR
Mistiaen, 2004 <sup>8</sup> N=259 4.2 y follow-up	War = 74 No Tx = 185  Dose and duration: Warfarin: Target INR not specified. 3 months, continued further in pts with AF or other indications.	All-cause mortality NR.	Adjusted for history of stroke; hospital thromboembolism; and HTN: RR (95% CI) for War: 3.0 (1.5-6.3), P = .0028 Not specified if referent group is ASA, No Tx, or ASA + No Tx groups combined.  TE events in 105 pts with postop chronic AF: War: 4/44 (9.09%) No Tx: 3/26 (11.5%) P =not significant	NR	NR

**Abbreviations:** ASA = Aspirin (acetylsalicylic acid); NR = Not reported; P = P-value; Tx = Treatment; War = warfarin; Y = Years.

## Aspirin vs No Treatment

### Summary of Findings

*KQs 1 & 2: What are the comparative benefits and harms of antithrombotic strategies for patients who have had bAVR?*

Three cohort studies compared aspirin with no treatment. No differences by treatment were found in the risk of TE events,<sup>4,8,12</sup> mortality,<sup>4</sup> or hemorrhage.<sup>4</sup> The overall strength of evidence for these findings is insufficient given the paucity of available data and methodologic weaknesses of studies.

*A. Do the benefits/harms differ according to thromboembolic risk profile?*

In a subgroup of patients with AF (N=105), TE events did not significantly between groups who received ASA vs no treatment in one study.<sup>8</sup>

*B. Do the benefits/harms differ according to concomitant procedure (eg, CABG)?*

No evidence is available.

### Detailed Results

*KQs 1 & 2: What are the comparative benefits and harms of antithrombotic strategies for patients who have had bAVR?*

Three cohort studies compared aspirin with no treatment (Table 6).<sup>4,8,12</sup> These studies had fairly large samples of patients in the ASA arm, numbering 220,<sup>8</sup> 290,<sup>4</sup> and 912.<sup>12</sup> ASA dose and duration were reported in only study.<sup>8</sup>

All 3 studies provided data on TE events, and reported no differences by treatment group up to 10 years of follow-up.

One study provided information about mortality and bleeding risk, and found no differences between treatment groups.<sup>4</sup>

*A. Do the benefits/harms differ according to thromboembolic risk profile?*

One study reported TE events in a subgroup of patients with postoperative chronic atrial fibrillation (N=105).<sup>8</sup> TE events did not significantly differ between groups who received ASA versus no treatment: 1/35 (2.86%) versus 3/26 (11.5%),  $P > .05$ .

*B. Do the benefits/harms differ according to concomitant procedure (eg, CABG)?*

No evidence is available.

**Table 6. Findings of Cohort Studies that Compared ASA with No Treatment after Surgical bAVR**

Study N in Tx comparison Mean follow-up	N per treatment group Dose and duration of treatment	Mortality	Thromboembolic events N (%); OR (95% CI)	Major Hemorrhagic Complications	Other benefits/ harms
Blair, 1994 <sup>4</sup> N=360 7±4 y follow-up	ASA = 290 No Tx = 70  ASA dose and duration NR.	"Survival did not differ significantly between the 3 treatment groups (P = .7)"	Mean linearized rate per patient-year: ASA: 0.8 ± 0.2% No Tx: 1.5 ± 0.6% P = .07 for overall comparison of 3 groups including War  Freedom from TE at 10 years: ASA: 93±2% No Tx: 88±5% P = .08 for overall comparison of 3 groups including War	No difference between treatment groups in long-term freedom from hemorrhage (P = .14).  Treatment group not associated with risk of hemorrhage in univariate Cox model (P = .11)	NR
Jamieson, 2007 <sup>12</sup> N=1218 30 d follow-up	ASA = 912 No Tx = 306 ASA dosage was based on antithrombotic therapy during the study era (81-325 mg/d). Actual ASA dose NR. Duration: NR Findings for a 3 <sup>rd</sup> treatment arm, consisting of pts who received either warfarin alone or (warfarin+ASA) are not included here.	NR	At 30 days, TE Major + RIND: No Tx: 9/306 (2.9%) ASA: 5/912 (1.6%) P = .301  Adjusted OR (95% CI) for TE Major + RIND (n=26): ASA vs No Tx: 0.54 (0.23-1.36), P = .175	NR	NR
Mistiaen, 2004 <sup>8</sup> N=405 4.2 y follow-up	ASA = 220 No Tx = 185  ASA dose: 160 mg/d Duration: 3 months	All-cause mortality NR.	Mean follow-up 4.2 years; fatal TE events: ASA: 2/220 (0.9%) No Tx: 8/206 (3.9%) P = .091 TE events in 105 pts with postop chronic AF: ASA: 1/35 (2.86%) No Rx: 3/26 (11.5%) P = NR	NR	NR

**Abbreviations:** ASA = Aspirin (acetylsalicylic acid); NR = Not reported; P = P-value; RIND = Reversible ischemic neurologic deficit; TE = Thromboembolism; Tx = Treatment; War = warfarin; Y = Years

## Other Comparison: Triflusal vs Acenocoumarol

### Summary of Findings

*KQs 1 & 2: What are the comparative benefits and harms of antithrombotic strategies for patients who have had bAVR?*

One RCT (N=200) with low risk of bias compared 3 months of treatment with triflusal versus acenocoumarol. The study found no significant difference in mortality at 30 days, or in thromboembolic events at 3 months. Risk of bleeding events was significantly higher with acenocoumarol versus triflusal. The study investigators suggest that triflusal presents a safer profile with avoidance of repeated blood tests and dosage adjustments required for acenocoumarol. Because evidence for this treatment comparison comes from a single study, the overall strength of evidence was graded insufficient. Neither medication is currently used in the US, therefore applicability of these findings to practice in the US is limited.

*A. Do the benefits/harms differ according to thromboembolic risk profile?*

Nine percent of included patients had AF at baseline. The study author states that triflusal was useful in preventing thromboembolism among patients with atrial fibrillation similarly to patients in sinus rhythm, but no data were provided.

*B. Do the benefits/harms differ according to concomitant procedure (eg, CABG)?*

No evidence was available to address this KQ.

### Detailed Results

Antithrombotic strategies other than warfarin and antiplatelet agents were examined in only one study: a randomized open-label pilot trial comparing 3 months of treatment with either triflusal (600 mg/d) or acenocoumarol (target INR 2.0–3.0).<sup>14</sup> The randomized sample (N=200) included 10 patients with isolated mitral and 2 patients with double valve replacement. Nine percent of the total sample had AF at baseline.

The trial found no differences between treatment groups in mortality after 30 days (8% vs 3.2%,  $P = 0.14$ ), or in thromboembolic events after 3 months (6% vs 3%,  $P = .50$ ). The risk of bleeding events after 3 months was higher with acenocoumarol compared with triflusal (10% vs 3%) and the difference was marginally significant ( $P = .048$ ).<sup>14</sup>

Other than post-randomization exclusion of 3.5% of enrolled patients, this trial had a low risk of bias. The overall strength of evidence for this treatment comparison is insufficient, however, because no other studies are currently available. Furthermore, the medications in this study are not currently used in the US, and applicability of these findings to practice in the US is limited.

## KEY QUESTION 3: What are the comparative benefits and harms of antithrombotic strategies for patients who have TAVR?

### Summary of Findings

In 3 small, open-label, randomized controlled trials and one cohort study of patients without atrial fibrillation undergoing TAVR, the strategy of adding a second antiplatelet agent to aspirin for 3 to 6 months after TAVR had similar effects as aspirin alone on mortality, stroke and major cardiac events (moderate-strength evidence), though use of aspirin alone was associated with a non-significantly lower rate of bleeding (low-strength evidence).

#### *A. Do the benefits/harms differ according to thromboembolic risk profile?*

Patients with atrial fibrillation were largely excluded from the majority of available trials. The cohort trials including patients with atrial fibrillation provide insufficient evidence for assessment of the risk profile comparing different management strategies.

#### *B. Do the benefits/harms differ according to concomitant procedure (eg, CABG)?*

No evidence was found to address this key question.

### Detailed Results

We found 3 randomized controlled trials, 5 cohort studies, and 1 meta-analysis assessing various antiplatelet and anticoagulation strategies in patients who have undergone TAVR (Tables 7 and 8).

#### *Single Antiplatelet Therapy (SAPT) versus Dual Antiplatelet Therapy (DAPT)*

Three randomized controlled trials (RCT) and 1 cohort study have each separately demonstrated no significant difference in mortality or incidence of stroke between single antiplatelet therapy (SAPT) with aspirin when compared with dual antiplatelet therapy (DAPT) with aspirin and clopidogrel over short (30 days),<sup>16,17</sup> intermediate (3-6 month),<sup>15-17</sup> and longer term (1 year)<sup>18</sup> follow-up (Table 7). These studies excluded patients with recent percutaneous coronary intervention and/or an indication for anticoagulation including atrial fibrillation.

All 3 RCTS were open-label and provided short- (30 days) and intermediate- (3-6 month) term follow-up.

Ussia et al performed an open label, single-center RCT in France comparing SAPT (low dose aspirin, n = 39) to DAPT (low dose aspirin combined with 3 months of clopidogrel post-procedure, n = 40) in patients undergoing TAVR with the 3<sup>rd</sup> general CoreValve Revalving System (Medtronic, Minneapolis, Minnesota).<sup>17</sup> Results were reported at 30 days and 6 months. There was no significant difference in all-cause mortality between SAPT and DAPT at 30 days (10% vs 10%, P > .05) and 6 months (13% vs 10%, P > .05). Major stroke was also similar between SAPT and DAPT at 30 days (5% vs 3%, P > .05) and was unchanged at 6 months (5% vs 3%, P > .05). Similarly, there was no differences in life-threatening bleeding (5% vs 5%, P > .05) or major bleeding (3% vs 5%, P > .05) at 30 days; no additional events accrued over the 6-month follow-up and bleeding results remained unchanged (non-significant). Finally, the

composite endpoint of major adverse cardiac and cardiovascular events (MACCE) as defined by the Valve Academic Research Consortium (VARC), including all-cause death, nonfatal myocardial infarction, nonfatal stroke, and major or life-threatening bleeding complications, were similar between the SAPT and DAPT groups at both 30 days (15% vs 13%,  $P = .71$ ) and 6 months (15% vs 18%,  $P = .85$ ).

Another open-label, single-center RCT (SAT-TAVR, Single Antiplatelet Therapy for TAVR), this time performed in Italy, compared SAPT (low dose aspirin,  $n = 60$ ) to DAPT (low dose aspirin with the addition of clopidogrel or ticlopidine for 6 months post-procedure,  $n = 60$ ) in patients undergoing TAVR with the Sapien XT-Novaflex (Edwards Lifesciences, Irvine, California). At 30 days there was no significant difference in cardiovascular death (3.3% versus 1.7%,  $P > .05$ ), major stroke (1.7% vs 1.7%,  $P > .05$ ), or life-threatening/disabling bleeding (5.0% vs 6.7%,  $P > .05$ ).<sup>16</sup> Following patients for 6 months Stabile et al reported similar risk of all-cause mortality (5.0% vs 5.0%,  $P > .05$ ) and major stroke (1.7% vs 1.7%,  $P > .05$ ); bleeding events were not reported at 6 months.<sup>16</sup>

Rodes-Cabau et al performed the most recent open-label RCT (ARTE – Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation – Randomized Clinical Trial) comparing SAPT (low-dose aspirin,  $n = 111$ ) to DAPT (low dose aspirin combined with clopidogrel for 6 months post-procedure,  $n = 111$ ).<sup>15</sup> This study included 9 centers in Canada, Europe, and South America and included patients eligible for TAVR; most patients (92%) received the SAPIEN XT. The ARTE study was terminated early due to low enrollment. This trial did not find any significant difference in SAPT versus DAPT in terms of all-cause mortality at 30 days (2.7% vs 5.4%,  $P > .05$ ) or 90 days (3.6% vs 6.3%,  $P > .05$ ). Additionally, there was no significant difference in disabling stroke at 30 days (0.9% vs 0.9%,  $P > .05$ ) and findings were unchanged at 90 days (0.9% vs 0.9%,  $P > .05$ ).<sup>15</sup> There was, however, a lower incidence of major bleeding seen in the SAPT arm compared to those in the DAPT arm at 30 days (3.6% vs 10.8%,  $P = .038$ ) which carried through to 90 days (3.6% vs 10.8%,  $P = .038$ ; no additional events occurred).<sup>15</sup> Overall, a non-significant trend toward lower incidence of a combined endpoint of death, myocardial infarction, stroke/TIA, or life-threatening/major bleeding event as defined by the VARC was seen at 3 months in the ARTE trial.

Figures 5-10 show forest plots of 3 trials that compared ASA versus DAPT after TAVR.<sup>15-17</sup> Meta-analyses combining the 3 trials indicate there were no statistically significant differences in mortality and thromboembolic events at both 30 days and 3-6 months post-TAVR, and no difference in major bleeding at 30 days. Two trials provided data on major bleeding events at 3-6 months.<sup>15,17</sup> The combined estimate from these 2 trials suggests a lower bleeding risk with ASA compared with DAPT, although the difference did not reach statistical significance (OR 0.43, 95% CI 0.17 to 1.08; Figure 10).

A small retrospective cohort study of propensity score-matched patients undergoing TAVR at a single center in Japan found no significant difference between SAPT (low-dose aspirin,  $n = 44$ ) when compared with DAPT (low dose aspirin combined with clopidogrel for 6 months post procedure,  $n = 44$ ) over 1 year of follow-up in terms of mortality (7% vs 7%,  $P > .05$ ) and stroke (10% vs 10%,  $P > .05$ ).<sup>18</sup> There was a trend toward a reduction in bleeding events (defined as intracranial bleeding, cardiac tamponade, gastrointestinal bleeding, hemorrhagic pleural effusion, and access-site related bleeding) seen in the SAPT patients when compared to the DAPT patients

(4.6% vs 18.2%,  $P = .058$ ).<sup>18</sup> This cohort adds little to the above RCTs and the risk for potential bias is high.

### *Antiplatelet Therapy versus Antiplatelet and Anticoagulant Therapy*

Two cohort studies and a meta-analysis examined the role of various combinations of antiplatelet therapy with and without anticoagulant.

A retrospective analysis of DAPT (low-dose aspirin combined with clopidogrel for 3-6 months,  $n = 315$ ) versus OAC/clopidogrel (OAC combined with clopidogrel x 3-6 months,  $n = 199$ ) in patients undergoing TAVR at a single center in Germany was performed. There were significantly more patients with atrial fibrillation in the OAC/clopidogrel group than in the DAPT group (69.2% vs 10.5%,  $p < 0.01$ ).<sup>19</sup> This study demonstrated no significant difference in terms of mortality at 30 days (3.5% vs 3.5%,  $P > .05$ ), 6 months (7.9% vs 12.0%,  $P > .05$ ), or 1 year (12% vs 18%,  $P > .05$ ) and no significant difference in stroke at 30 days (3.8% vs 3.5%,  $P > .05$ ) or 6 months (4.4% vs 4.0%,  $P > .05$ ).<sup>20</sup> Similarly, there was no difference in life-threatening (7.3% vs 9.6%,  $P > .05$ ) or major bleeding (16.8% vs 15.1%,  $P > .05$ ) at 30 days or major bleeding (17.5% vs 16.5%,  $P > .05$ ) at 6 months (Holy); life-threatening bleeding at 6 months was not reported. Interestingly, this trial did find a reduction in the incidence of valve thrombosis at 1 year with the use of OAC when compared to DAPT (respectively 0 vs 2.5%;  $P = .02$ ). Adjusted logistic regression analysis confirmed that OAC reduced the risk of valve thrombosis independent of age, sex, BMI, AF, and whether staged PCI was performed (OR 0.53; 95% CI 0.23-0.76).<sup>20</sup> Although this finding is interesting, the evidence at this point is insufficient and further trials are likely to have an impact on the estimate of treatment effect.

A cohort study utilizing propensity score-matched patients from a prospective registry in France was performed to assess 2 different strategies of antiplatelet therapy, which varied depending on baseline treatment.<sup>19</sup> Strategy A ( $n = 91$ ) utilized SAPT or, if warfarin was indicated, SAPT + warfarin. Strategy B ( $n = 91$ ) utilized DAPT or, if warfarin was indicated, DAPT + warfarin. If patients were taking warfarin the duration of the additional antiplatelet therapy was reduced to 1 month post-procedure (from 3 to 6 months). Thirty percent of patients in the original cohort had atrial fibrillation; propensity score matching was performed, but the number of patients in this more restricted cohort was not reported. No significant difference in mortality (8.8% vs 7.7%,  $P > .05$ ) or stroke (0 vs 1.1%,  $P > .05$ ) was seen in either strategy at 30 days. The utilization of a more aggressive strategy was found to increase the risk of bleeding complications including life-threatening bleeding (3.3% vs 14.3%,  $p = 0.021$ ) and major bleeding (2.2% vs 12.1%,  $P = .022$ ) in short term follow-up. The less aggressive SAPT strategy compared to the more aggressive DAPT strategy also resulted in fewer transfusions (7.7% vs 25.3%,  $P = .005$ ). The inclusion of patients with atrial fibrillation introduced a population on triple therapy including aspirin, clopidogrel, and warfarin. Triple therapy is known to have an increased risk of bleeding in populations of patients with mechanical heart valves or atrial fibrillation receiving percutaneous coronary interventions.<sup>44</sup> This increased the risk of bias toward the SAPT arm in favor of a reduction in bleeding as was seen by this cohort analysis. Overall, there is a high risk of bias in these findings as utilization of the strategies varied based on assignment by participating registry site and due to the inclusion of patients with atrial fibrillation.

A meta-analysis of 2 randomized controlled trials<sup>16,17</sup> and 2 cohort studies<sup>19,45</sup> evaluated the issue of DAPT versus SAPT. This meta-analysis provided data on the 30-day follow-up from these studies and found no significant difference between DAPT and SAPT in terms of all-cause mortality, cardiovascular mortality, or stroke. The results were largely driven by the non-randomized cohort studies; in particular, the Durand cohort was weighted 39% in terms of the results. The decision to include the Durand cohort in this meta-analysis introduced a population of atrial fibrillation patients who were taking warfarin and who would have been excluded from the RCTs. The meta-analysis also included a cohort study<sup>45</sup> which was excluded from this review as there was no adjustment for risk factors and the patients were not propensity-matched. Overall, there is evidence that DAPT and SAPT are similar in terms of mortality (7.3% vs 6.4%, risk ratio 1.18, 95% CI 0.66 to 2.11) and stroke benefit over 30 days (2.4% vs 1.4%, risk ratio 1.42, 95% CI 0.43 to 4.71). This meta-analysis demonstrated an increased risk of life-threatening or major bleeding with DAPT when compared to SAPT (19% vs 7.0%, risk ratio 2.38, 95% CI 1.332 to 4.30). Overall, for a combined end-point of stroke, MI, all-cause mortality, and major bleeding at 30 days the results favored SAPT when compared to DAPT suggesting a risk ratio of 1.66 (95% CI 1.04 to 2.66) in patients treated with DAPT. Further studies could alter these findings as this meta-analysis was subject to significant bias.

### **KQ3A. Do the benefits/harms differ according to thromboembolic risk profile?**

Coronary artery disease (CAD) and atrial fibrillation (AF) are frequent co-morbid conditions in patients with aortic stenosis (AS). Patients who have had a recent percutaneous coronary intervention (PCI) are frequently indicated for dual antiplatelet therapy regardless of any valvular intervention. Patients with atrial fibrillation are frequently indicated for oral anticoagulation (OAC). The randomized controlled trials excluded patients who had prior indications for OAC (*ie*, atrial fibrillation with CHADS<sub>2</sub>-VASc >1) or DAPT (*ie*, recent PCI).<sup>15-17</sup> Several cohort studies included patients with atrial fibrillation but did not specify outcomes based on presence or absence of AF.

Atrial fibrillation increases the likelihood that a patient will be indicated for, and prescribed, an OAC in the peri-procedural period and will be continued on the OAC chronically.<sup>19</sup> Three cohort studies addressed antiplatelet and anticoagulation strategies in the population of TAVR with atrial fibrillation.

#### *Warfarin Monotherapy versus Combination Warfarin and Antiplatelet Therapy*

One cohort study compared warfarin monotherapy to the use of warfarin plus an antiplatelet regimen.<sup>21</sup> Another cohort study compared warfarin monotherapy to direct oral anticoagulant (DOAC) monotherapy.<sup>22</sup>

A large, prospective, multi-center, cohort study of patients with atrial fibrillation who were eligible for TAVR compared warfarin monotherapy (n = 101) to warfarin and at least one antiplatelet agent (n = 520).<sup>21</sup> There appeared to be no significant reduction in mortality (23% versus 19%, P > .05) or stroke (5% versus 5%, P > .05) at 1 year. The risk of life-threatening or major bleeding at one year was lower for patients prescribed warfarin monotherapy compared to those prescribed warfarin plus at least one antiplatelet agent (14.9% versus 25.9%, P = .02). Overall, the addition of an antiplatelet agent to warfarin in patients with atrial fibrillation undergoing TAVR does not seem to be superior to warfarin therapy alone in terms of stroke



prevention while posing a significantly greater bleeding risk. The risk of bias in this cohort study is unclear, and the evidence is insufficient to determine treatment effect.

### *Warfarin versus Direct Oral Anticoagulant*

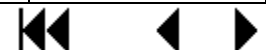
There was a single, multi-center, prospective cohort study which compared a direct oral anticoagulant, apixaban (n = 141), to a vitamin K antagonist (n = 131) in patients with atrial fibrillation.<sup>22</sup> The atrial fibrillation group was a subpopulation of the entire study, which was designed to ascertain differences in outcomes between patients in sinus rhythm with those in atrial fibrillation. This systematic review excluded the patients in sinus rhythm in this trial from analysis as the antiplatelet strategy (single vs dual) was unclear in relation to outcomes. In this cohort study the early safety endpoint including all-cause mortality, major vascular complications, stroke, bleeding complications, acute kidney injury, coronary obstruction, and valve dysfunction requiring reintervention occurred less frequently at 30 days in the patients treated with apixaban compared with warfarin (13.5% vs 30.5%,  $p < 0.01$ ).<sup>22</sup> The study found no significant difference in mortality or stroke. There was, however, a significant reduction in life-threatening bleeding (3.5% vs 5.3%,  $p < 0.01$ ) with the use of apixaban when compared to warfarin.<sup>22</sup> There were no significant differences in intracerebral bleeding (0.7% vs 0,  $P > .05$ ) or major vascular complications (3.5% vs 7.6%,  $P > .05$ ). 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.

### **KQ3B. Do the benefits/harms differ according to concomitant procedure (eg, PTCA with stent?)**

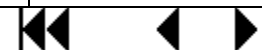
No evidence was found to address this key question.

**Table 7. Descriptive Characteristics of Studies that Compared Antithrombotic Strategies after TAVR**

Study design & setting Years TAVR performed Sample size Mean follow-up	Valves and access sites used	Treatment arms	Patient characteristics	Hx atrial fibrillation	Concomitant procedures	ROB assessment; methodological limitations (if any)
<i>ASA vs DAPT: 3 trials</i>						
Rodes-Cabau, 2017 <sup>15</sup> RCT Multisite, multinational 2012-2017 N = 222 3 m follow-up	TAVR: Edwards SAPIEN XT or SAPIEN 3 valve (Edwards Lifesciences, Irvine, California)	ASA DAPT	ASA (n = 111) vs DAPT (n = 111) Age: 79 ± 9 vs 79 ± 9 (P > .05) Male: 63.1% vs 53.2% (P > .05) DM: 36.9% vs 32.7% (P > .05) CAD: 68.5% vs 63.6% (P > .05) Prior Cardiac Surgery (CABG): 35.1% vs 38.5% (P > .05) -Staged PCI 40.1% vs 28.3% (p < 0.01) CHF (NYHA III or IV): NR CKD (EGFR <60 mL/min): 63.1% vs 63.1% (P > .05) Smoker: 2.7% vs 1.8% (P > .05) Hx Stroke/TIA: NR Hx Stroke: 11.1% vs 12.1% (P > .05) Hx TIA: NR Hx thromboembolic event: NR Hx vascular disease: NR Prior MI: 23.4% vs 18.4% (P > .05) PAD: 25.2% vs 20.0% (P > .05) Aortic Plaque/Porcelain Aorta: 16.2% vs 10.1% (P > .05)  STS-PROM score (%): 6.2 ± 4.4 vs 6.4 ± 4.6 (P > .05) HTN: 77.5% vs 79.8% (P > .05) COPD: 25.2% vs 30.0% (P > .05)	Excluded if requirement for anticoagulation.	None	Low ROB. Study prematurely ended (anticipated 300 patients) due to slow enrollment and lack of continued financial support
Stabile, 2014 <sup>16</sup> RCT Italy, # sites NR 2010-2011 N=120 6 m	TAVR: Sapien XT-Novaflex (Edwards Lifesciences, Inc.)	ASA DAPT	Age 81.1 ± 4.8 vs 80.2 ± 5.7 (P > .05) Male 40% vs 33.3% (P > .05) DM 28.3% vs 25.0% (P > .05) CAD not-reported HTN 95% vs 95% (P > .05) CHF (EF%) 51.3 ± 11.0 vs 52.4 ± 14.4 (P > .05) EF <30%: 13.0 vs 11.6 (P > .05) Euroscore: 25.1 ± 12.0 vs 23.34 ± 8.15	Afib was excluded.	No concomitant procedures were performed.	High ROB. Underpowered to assess clinical endpoints due to small sample size and 30-day endpoint for selected outcomes



Study design & setting Years TAVR performed Sample size Mean follow-up	Valves and access sites used	Treatment arms	Patient characteristics	Hx atrial fibrillation	Concomitant procedures	ROB assessment; methodological limitations (if any)
			Smoker NR H/o Stroke/TIA NR H/o thromboembolism NR H/o vasc dz NR			
Ussia, 2011 <sup>17</sup> RCT Single site 2009-2010 N = 79 6 months follow-up	TAVR 18F 3rd Generation CoreValve Revalving System 26-mm and 29-mm (Medtronic, Minneapolis, Minnesota) via Transfemoral (97%) or Trans-subclavian (3%) approach	ASA DAPT	ASA vs DAPT Age: 81 ±4 vs 80±6 (P > .05) Male: 41% vs 50% (P > .05) DM: 21% vs 33% (P > .05) Prior MI: 10% vs 18% (P > .05) Prior CABG: 10% vs 5% (P > .05) Prior PCI 23% vs 30% (P > .05) CHF: 36% vs 45% (P > .05) CKD: 13% vs 15% (P > .05) Smoker: NR Hx Stroke: 10% vs 5% (P > .05) Hx TIA: 5% vs 5% (P > .05) Hx thromboembolic event: NR Prior MI: as above PAD: 10% vs 8% (P > .05) Aortic Plaque/Porcelain Aorta: 3% vs 3% (P > .05)	ASA vs DAPT Afib: 15% vs 10% (P > .05)	None	Unclear ROB. Small sample size.
<b>ASA vs DAPT: 1 cohort study</b>						
Ichibori, 2017 <sup>18</sup> Cohort, retrospective Japan 2009-2015 N=144 1 year follow-up	TAVR SAPIEN or SAPIEN XT heart valve system (Edwards Lifesciences, Irvine, California) via transfemoral or alternative approach	ASA DAPT	ASA (n = 78) vs DAPT (n = 66) Age: 83 ±6 vs 84±6 (P > .05) Male: 45.9% vs 46.4% (P > .05) DM: 30.8% vs 33.3% (P > .05) CAD: 37.2% vs 53.0% (P > .05) Prior CABG: 12.8% vs 15.2% (P > .05) <b>Prior PCI 14.1% vs 37.8% (P = .0018)</b> <b>CHF (NYHA III or IV): 47.4% vs 66.7% (P = .028)</b> CKD (EGFR, mL/min/1.73m <sup>2</sup> ): 42.1 ±22.5 vs 45.9 ±19.5 (P > .05) Smoker: NR Hx Stroke: 28.2% vs 19.7% (P > .05) Hx TIA: NR Hx thromboembolic event: NR	NR	Incompletely reported. In the aspirin cohort there were 23 patients with indication for DAPT because of coronary stent or "other reasons" allocated to the DAPT group	Insufficient detail on how exposure and outcomes were assessed. Three authors received funding from valve manufacturer.



Study design & setting Years TAVR performed Sample size Mean follow-up	Valves and access sites used	Treatment arms	Patient characteristics	Hx atrial fibrillation	Concomitant procedures	ROB assessment; methodological limitations (if any)
			Hx vascular disease: NR Prior MI: NR PAD: NR Aortic Plaque/Porcelain Aorta: NR  ASA (n = 44) vs DAPT (n = 44) Age: 84 ±6 vs 84±5 (P > .05) Male: 31.8% vs 40.9% (P > .05) DM: 29.6% vs 31.8% (P > .05) CAD: 38.6% vs 45.5% (P > .05) Prior CABG: 9.1% vs 15.9% (P > .05) Prior PCI 25.0% vs 27.3% (P > .05) CHF (NYHA III or IV): 61.4% vs 61.4% (P > .05) CKD (EGFR, mL/min/1.73m2): 42.7 ±22.9 vs 43.9 ±19.6 (P > .05) Smoker: NR Hx Stroke: 27.3% vs 20.5% (P > .05) Hx TIA: NR Hx thromboembolic event: NR Hx vascular disease: NR Prior MI: NR PAD: NR Aortic Plaque/Porcelain Aorta: NR			
<b>Other treatment comparisons: 4 cohort studies</b>						
Abdul-Jawad Altisent, 2016 <sup>21</sup> Cohort, prospective 2007-2015 N=621 13 m follow-up 12 sites	TAVR: Sapien, Sapien XT, Sapien 3, and CoreValve were most common. Transfemoral approach was performed in 70%.	War War+SAPT War+DAPT	War (n = 101) vs MAT (n = 520) Age: 81 ± 7 vs 82 ± 7 (P = .69) Male %: 51.5 vs 45.6 (P = .28) DM %: 35.6 vs 32.3 (P = .56) CAD %: 24 vs 51.5 (p < 0.01) HTN %: NR Smoker: NR Hx Stroke/TIA %: 19.8 vs 19.6 (P = .99) Hx VTE %: NR CKD %: 63.4 vs 58.1 (P = .38); defined as EGFR <60 mL/m or stage 3) COPD %: 21.8 vs 28.1 (P = .22) LVEF %: 54.6 ± 13.6 vs 55.3 ± 14.6 (P = .68)	Atrial fibrillation in 100% of patients.	None	Insufficient detail on dose and/or duration of treatment. Outcome assessment methods not fully described.



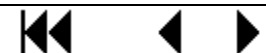
Study design & setting Years TAVR performed Sample size Mean follow-up	Valves and access sites used	Treatment arms	Patient characteristics	Hx atrial fibrillation	Concomitant procedures	ROB assessment; methodological limitations (if any)
			Euroscore mean: 17.1 ± 11.6 vs 20.8 ± 14.2 (P = .05)			
Durand, 2014 <sup>19</sup> Cohort, N= 292 3 sites, France 2010-2011 SAPIEN devices (3/3 centers) or CoreValve (2/3 centers)	TAVR: SAPIEN devices (3/3 centers) or CoreValve (2/3 centers)	Strategy A: SAPT either adding/ maintaining ASA or maintaining clopidogrel; in patients with War aspirin was added.  Strategy B: DAPT with ASA + clopidogrel; in patients with War the clopidogrel maintenance dose was excluded.	A (n = 164) vs B (n = 128) <b>Age: 82.7 ± 6.3 vs 84.6±5.8 (P = .001)</b> <b>Male: 54.9% vs 39.1% (P = .007)</b> DM: 24.4% vs 23.4% (P > .05) <b>CAD: 50.0% vs 30.5% (P = .001)</b> <b>Prior Cardiac Surgery: 18.3% vs 7.8 (P = .01)</b> Recent PCI: NR CHF (NYHA III or IV): 79.9% vs 77.4% (P > .05) *all patients had NYHA II or greater CKD (Cr >2.25 mg/dL): 7.3% vs 8.6% (P > .05) Smoker: NR Hx Stroke/TIA: 7.9% vs 9.4% (P > .05) Hx Stroke: 7.9% vs 9.4% (P > .05) Hx TIA: NR Hx thromboembolic event: NR Hx vascular disease: NR Prior MI: NR <b>PAD: 17.1% vs 7.8% (P = .020)</b> Aortic Plaque/Porcelain Aorta: 3.7% vs 6.3% (P > .05) COPD: 34.1% vs 20.3% (P = .009) HLD: 59.1% vs 43.0% (P = .006)	A (n = 164) vs B (n = 128) AF 23.0% vs 35.2% (P = .23)  Baseline AP or AC strategy <b>Aspirin: 56.1% vs 35.9% (P = .001)</b> Clopidogrel: 7.9% vs 6.3% (P > .05) War: 28.0% vs 32.8% (P > .05) <b>ASA or Clop and War: 15.9% vs 5.5% (P = .005)</b>	NR	Methodologically sound but limited applicability: follow-up was only 30 days
Holy, 2017 <sup>20</sup> Cohort, N= 514 Single site, Germany 2007-2014	Multiple access sites (trans-femoral, trans-subclavian, trans-apical, trans-aortic) using multiple devices (Balloon-expandable, Self-Expanding, Lotus) and including valve-in-valve procedures.	ASA + clopidogrel OAC/DOAC + clopidogrel	DAPT (n = 315) vs OAC (n = 199) Age: 80.4 ±7.0 vs 80.6 ±5.7 (P > .05) Male: 42.4% vs 46.0% (P > .05) DM: 25.8% vs 29.8% (P > .05) CAD: 68.5% vs 63.6% (P > .05) Prior Cardiac Surgery (CABG): 20.4% vs 15.6% (P > .05) <b>Staged PCI 40.1% vs 28.3% (p &lt; 0.01)</b> CHF (NYHA III or IV): NR CKD (EGFR <60 mL/min): NR Smoker: NR Hx Stroke/TIA: NR Hx Stroke: 11.1% vs 12.1% (P > .05)	DAPT (n = 315) vs OAC (n = 199) <b>Atrial Fibrillation 10.5% vs 69.2% (p &lt; 0.01)</b>	PCI performed in a staged fashion (usually 6 months ahead of time).	Insufficient detail on dose and/or duration of treatment; method of exposure ascertainment not described.

Study design & setting Years TAVR performed Sample size Mean follow-up	Valves and access sites used	Treatment arms	Patient characteristics	Hx atrial fibrillation	Concomitant procedures	ROB assessment; methodological limitations (if any)
			Hx TIA: NR Hx thromboembolic event: NR Hx vascular disease: NR Prior MI: NR PAD: 14.6% vs 16.2% (P > .05) Aortic Plaque/Porcelain Aorta: NR Euroscore: 18.5 vs 18.2 (P > .05) <b>BMI: 26.4 ± 4.9 vs 27.5 ± 4.8 (p &lt; 0.01)</b>			
Seeger, 2017 <sup>22</sup> Cohort N=617 12 m follow-up	TAVR SAPIEN (Edwards Lifesciences, Irvine, California) Boston Lotus (Boston Scientific, Marlborough, Massachusetts) CoreValve (Medtronic, Minneapolis, Minnesota) Evolute (Medtronic, Minneapolis, Minnesota)	War DOAC (apixaban)	Apixaban vs War Age: 82 ±5.3 vs 80.5±6.3 (P > .05) Male: 49.6% vs 51.9% (P > .05) DM: 32.6% vs 32.0% (P > .05) CAD: 66.0% vs 58.8% (P > .05) Prior MI: 17.7% vs 21.4% (<0.01) Prior CABG*: 12.8% vs 12.2% (P > .05) *h/o cardiac surgery Prior PCI: NR CHF: NR CKD: 44.7% vs 48.9% (P > .05) -Renal Replacement Therapy: 0 vs 6.1% (<0.01) Smoker: NR Hx Stroke/TIA: NR Hx Stroke: 11.3% vs 14.5% (P > .05) *includes intracranial bleeding Hx TIA: NR Hx thromboembolic event: NR Hx vascular disease: 82.9% vs 88.5% (<0.01) PAD: NR Aortic Plaque/Porcelain Aorta: NR	Study was designed to assess outcomes in patients with atrial fibrillation versus those in sinus rhythm. We excluded the sinus rhythm (n = 345) – unable to determine outcomes in relation to antiplatelet therapy. We included the atrial fibrillation (n = 272).	NR	Insufficient detail on dose and/or duration of treatment. Differential loss to follow-up among treatment groups. Outcome assessment methods varied (clinic visit vs phone contact).

**Abbreviations:** AAR = Ascending aorta replacement; AC = Anticoagulation; AF = Atrial fibrillation; AP/APT = Antiplatelet therapy; ASA = Aspirin (acetylsalicylic acid); AVR = Aortic valve replacement; CAD = Coronary artery disease; CHF = Chronic heart failure; CKD = Chronic kidney disease; COPD = Chronic Obstructive Pulmonary Disease; CV = Cardiovascular; DAPT = Dual antiplatelet therapy; DM = Diabetes mellitus; DOAC = Direct oral anticoagulant; EGFR = Estimated glomerular filtration rate; HR = Hazard ratio; HTN = Hypertension; INR = International Normalized Ratio; LIMA = left internal mammary artery (graft); LVEF = Left ventricular ejection fraction; MAT = Multiple antithrombotic therapy; MI = Myocardial infarction; MV = Mitral valve; NR = Not reported; NYHA = New York Heart Association functional classification; OAC = Oral anticoagulation; P = P-value; PAD = Peripheral artery disease; RCT = Randomized controlled trial; ROB = Risk of bias; SVG = Saphenous vein graft; TAVR = Transcatheter aortic valve replacement; TIA = Transient ischemic attack; VTE = Venous thromboembolism; War = Warfarin.

**Table 8. Findings of TAVR Studies by Treatment Comparison**

Study Sample size Follow-up time	Treatment comparison N per treatment arm	Mortality (all-cause)	Thromboembolic Include all stroke except hemorrhagic	Major Hemorrhagic	Other benefits/harms:
<i>ASA vs DAPT: 3 trials</i>					
Rodes-Cabau, 2017 <sup>15</sup> RCT N=222 3 m follow-up	ASA = 111 DAPT = 111  Dosage: Aspirin 80-100 mg daily versus Aspirin 80-100 mg daily + Clopidogrel 75 mg daily. Duration: 3 months	ASA (n = 111) vs DAPT (n = 111) At 30 days: All-cause: 2.7% vs 5.4% (P > .05) Cardiovascular: NR At 90 days: All-cause: 3.6% vs 6.3% (P > .05) Cardiovascular: NR	ASA (n = 111) vs DAPT (n = 111) At 30 days: Disabling Stroke: 0.9% vs 0.9% (P > .05) Nondisabling Stroke: 0 vs 1.8% (P > .05) TIA: 0 vs 0 At 90 days: Disabling Stroke: 0.9% vs 0.9% (P > .05) Nondisabling Stroke: 0 vs 1.8% (P > .05) TIA: 0 vs 0	ASA (n = 111) vs DAPT (n = 111) At 30 days: <b>Life-threatening/Major Bleeding: 3.6% vs 10.8% (P = .038)</b> Life-threatening bleeding: 0.9% vs 6.3% (P > .05) Major bleeding: 2.7% vs 4.5% (P > .05) Minor bleed: NR At 90 days: Life-threatening/Major Bleeding: 3.6% vs 10.8% (P = .038) Life-threatening bleeding: 0.9% vs 6.3% (P > .05) Major bleeding: 2.7% vs 4.5% (P > .05) Minor bleed: NR	Major vascular complication: 6.4% vs 9.0% (P > .05) New-onset atrial fibrillation: 10.8% vs 10.8% (P > .05)
Stabile, 2014 <sup>16</sup> RCT N=120 6 m follow-up	ASA = 60 DAPT = 60  Dosage: All patients taking aspirin (75-160 mg/day) at time of surgery DAPT group: aspirin and clopidogrel 75 mg/qd or ticlopidine 500 mg/bid  Duration: 6 m	All-cause: ASA: 5% vs 5%, P > .05  CV death: ASA, n = 2 (3.3%) DAPT, n = 1 (1.7%), P > .05	Major stroke: 1 (1.7%) vs 1 (1.7%), P > .05 Minor stroke: 1 (1.7%) vs 0 (0%), P > .05	Incidence of bleedings at 30 days: All bleedings: 6 (10%) vs 9 (15%) Lethal or disabling (all during hospital stay): 3 (5%) vs 4 (6.6%) (In the DAPT group, 1 patient had a retroperitoneal hematoma, 1 patient had hemorrhagic stroke, and 2 patients had pericardial bleeding. In the ASA group, 3 lethal or disabling bleeding episodes developed; these were 3 cases of pericardial bleeding.)	Major vascular complication: 0 (0%) vs 3 (5%) ns Minor vascular complication: 3 (5%) vs 5 (8.3%) ns Major and minor vascular complication: 3 (5%) vs 8 (13.3%), P < .05  The cumulative incidence of major and minor vascular complications was higher among DAPT patients (13.3% vs 5%; P < .05).



Study Sample size Follow-up time	Treatment comparison N per treatment arm	Mortality (all-cause)	Thromboembolic Include all stroke except hemorrhagic	Major Hemorrhagic	Other benefits/harms:
				Major: 2 (3.3%) vs 2 (3.3%) Minor: 1 (1.7%) vs 3 (5%)	
Ussia, 2011 <sup>17</sup> RCT N=79 6 m follow-up	ASA = 39 DAPT = 40  Dosage: Aspirin 100 mg daily versus Aspirin 100 mg daily + Clopidogrel 75 mg daily (after initial loading dose of 300 mg the day prior to TAVR) Duration: ASA: ASA x lifelong DAPT: ASA x lifelong, Clopidogrel x 3 months	ASA (n= 39) vs DAPT (n = 40) At 30 days: All-cause: 10% vs 10% (P > .05) Cardiovascular: 0 vs 3% (P > .05) At 6 months: All-cause: 13% vs 10% (P > .05) Cardiovascular: 0 vs 3% (P > .05)	ASA (n= 39) vs DAPT (n = 40) At 30 days: Major Stroke: 5% vs 3% (P > .05) Minor Stroke: 0 vs 0 (P > .05) TIA: 3% vs 3% (P > .05) At 6 months: Major Stroke: 5% vs 3% (P > .05) Minor Stroke: 0 vs 0 (P > .05) TIA: 3% vs 3% (P > .05)	ASA (n= 39) vs DAPT (n = 40) At 30 days: Life-threatening bleeding: 5% vs 5% (P > .05) Major bleeding: 3% vs 5% (P > .05) Minor bleed: 10% vs 8% (P > .05) At 6 months: Life-threatening bleeding: 5% vs 5% (P > .05) Major bleeding: 3% vs 5% (P > .05) Minor bleed: 10% vs 8% (P > .05)	ASA (n = 78) vs DAPT (n = 66) Unmatched, 1 year: 9% vs 9% (P > .05) ASA (n = 44) vs DAPT (n = 44) Propensity Score Matched, 1 year: 10% vs 10% (P > .05)
<b>ASA vs DAPT: 1 cohort study</b>					
Ichibori, 2017 <sup>18</sup> Cohort N=144 1 y follow-up	ASA = 78 DAPT = 66  Dosage: ASA: 100 mg/d DAPT: Aspirin 100 mg daily + thienopyridine (ticlopidine 200 mg daily or clopidogrel 75 mg daily) Duration: In 2009-2012: 6 months DAPT, ASA lifelong, In 2012-2015: ASA lifelong	ASA (n = 78) vs DAPT (n = 66) Unmatched, 1 year: 7% vs 10% (P > .05)  ASA (n = 44) vs DAPT (n = 44) Propensity Score Matched, 1 year: 7% vs 7% (P > .05)	Stroke (Major + Minor): ASA (n = 78) vs DAPT (n = 66) Unmatched, 1 year: 9% vs 9% (P > .05)  ASA (n = 44) vs DAPT (n = 44) Propensity Score Matched, 1 year: 10% vs 10% (P > .05)	ASA (n = 78) vs DAPT (n = 66) <b>Unmatched, 1 year: 7.7% vs 21% (P = .019)</b> Intracranial bleeding 0 vs 4.5% (P > .05) Cardiac tamponade 2.6% vs 3.0% (P > .05) Gastrointestinal bleeding 1.3% vs 1.5% (P > .05) Hemorrhagic pleural effusion 0 vs 1.5% (P > .05) Access-related bleeding 3.8% vs 11% (P > .05)  ASA (n = 44) vs DAPT (n = 44) Propensity Score Matched, 1 year: 4.6 vs 18.2 (NS, P = .058)	Myocardial infarction: ASA (n = 78) vs DAPT (n = 66) Unmatched, at 1 year: 3% vs 5% (P > .05)  ASA (n = 44) vs DAPT (n = 44) Propensity Score Matched, 1 year: 3% vs 5% (P > .05)





Study Sample size Follow-up time	Treatment comparison N per treatment arm	Mortality (all-cause)	Thromboembolic Include all stroke except hemorrhagic	Major Hemorrhagic	Other benefits/harms:
<i>Other treatment comparisons: 4 cohort studies</i>					
<p>Abdul-Jawad Altisent, 2016<sup>21</sup> Cohort N=621 13 months</p>	<p>War monotherapy = 101 Multiple antithrombotic therapy (MAT) = 520</p> <p>MAT with War plus 1 or 2 antiplatelet agents (aspirin or clopidogrel): -Double therapy (War + only 1 antiplatelet): 463 -Triple therapy (War + ASA + clop): 57</p> <p>Dosage, mean duration: ASA 80 to 100 mg/d, 446 days Clopidogrel 75 mg/d, 407 days War: INR <math>\geq 2</math>, 289 days MAT: 394 days</p> <p>5 centers prescribed War plus at least 1 antiplatelet to all patients; 1 center prescribed War plus at least 1 antiplatelet agent until December 2011, thereafter patients were discharged with War alone if they had no other indication for APT; in all the others centers the strategy was at the treating physician's discretion.</p>	<p>War (n= 101) vs MAT (n = 520) All-cause: 22.8% vs 19.2% (P &gt; .05) Cardiovascular: 9.9% vs 10.2% (P &gt; .05) Adjusted HR (95% CI): 0.88 (0.54–1.44), P = .62</p>	<p>Ischemic stroke War vs MAT: N (%): 5 (5.0) vs 23 (5.0) Adjusted HR (95% CI): 1.10 (0.40–3.02), P = .85</p>	<p>VARC-2 major or life-threatening bleeding: War vs MAT: N (%): 15 (14.9) vs 118 (25.5) Adjusted HR (95% CI): 1.97 (1.11–3.51), P = .02</p>	<p>MI: 0 vs 12 (2.3%), P = .22 Acute kidney injury: 17 (16.8%) vs 93 (17.9%), P = .89 Pacemaker implant: 9 (8.9%) vs 72 (13.8%), P = .20</p>
<p>Durand, 2014<sup>19</sup> Cohort N=292 30 days</p>	<p>Strategy A =164 Strategy B = 128</p> <p>Complex and varied by baseline treatment: Strategy A was essentially SAPT either adding/maintaining ASA or maintaining clopidogrel; in patients with War aspirin was added.</p>	<p>A (n = 164) vs B (n = 91) <b>Unmatched, 30 days: 13.4% vs 23.4% (P = .026)</b></p> <p>A (n = 91) vs B (n = 91) Propensity Score Matched, 1 year: 8.8% vs 7.7% (P &gt; .05)</p>	<p>A (n = 164) vs B (n = 128) Unmatched, at 30 days: Major Stroke: 0 vs 2.3% (P &gt; .05) Minor Stroke: 0.6% vs 1.6% (P &gt; .05) TIA: 0.6% vs 0.8% (P &gt; .05)</p> <p>A (n = 91) vs B (n = 91) Propensity Score Matched, 30</p>	<p>A (n = 164) vs B (n = 128) <b>Unmatched, at 30 days: Bleeding complications (total): 8.5% vs 31.2% (p &lt; 0.0001)</b> <b>Life-threatening bleeding: 3.7% vs 12.5% (P = .005)</b> <b>Major bleeding: 2.4% vs 13.3% (p &lt; 0.0001)</b> Minor bleed: 2.4% vs 5.5%</p>	<p>A (n = 164) vs B (n = 128) Unmatched, at 30 days: <b>Vascular complications: 7.9% vs 19.5% (P = .003)</b> Acute Kidney Injury: 4.3% vs 9.4% (P &gt; .05) A (n = 91) vs B (n = 91)</p>



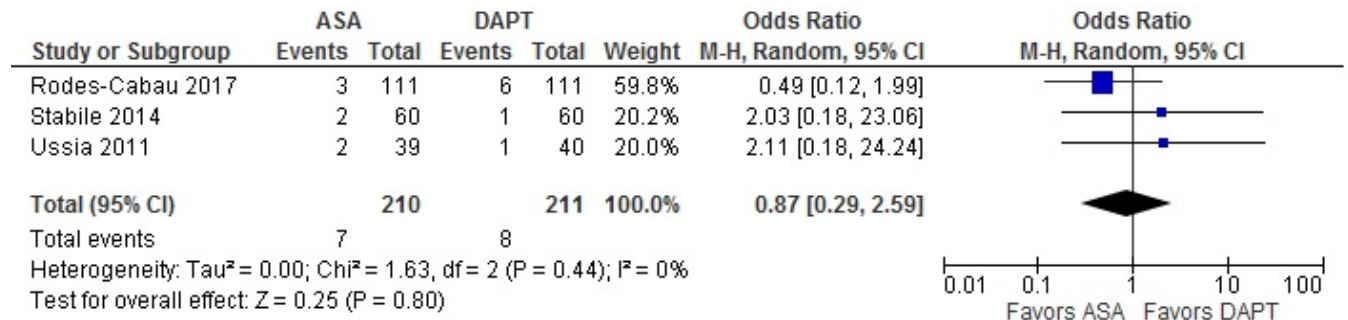
Study Sample size Follow-up time	Treatment comparison N per treatment arm	Mortality (all-cause)	Thromboembolic Include all stroke except hemorrhagic	Major Hemorrhagic	Other benefits/harms:
	<p>Strategy B was essentially DAPT with aspirin and clopidogrel; in patients with War the clopidogrel maintenance dose was excluded.</p> <p>Dosage, duration: ASA 75 mg/d, lifelong unless the patient was already on warfarin, in which case it was for 1 month. Clopidogrel 75 mg/d, 1 month unless the patient was already taking it, in which case it was continued beyond study period. Loading dose of clopidogrel (300 mg/d) was only used for transfemoral procedure</p>		<p>days: Major Stroke: 0 vs 1.1% (P &gt; .05) Minor Stroke: 1.1% vs 1.1% (P &gt; .05) TIA: 1.1% vs 0 (P &gt; .05)</p>	<p>(P &gt; .05) <b>Transfusions: 7.3% vs 25% (p &lt; 0.0001)</b> A (n = 91) vs B (n = 91) Propensity Score Matched, at 30 days: <b>-Bleeding Complications (total): 9.9% vs 30.8% (P = .002)</b> <b>Life-threatening bleeding: 3.3% vs 14.3% (P = .021)</b> <b>Major bleeding: 2.2% vs 12.1% (P = .022)</b> Minor bleed: 4.4% vs 4.4% (P &gt; .05) <b>Transfusions: 7.7% vs 25.3% (P = .005)</b></p>	<p>Propensity Score Matched, at 30 days: Vascular Complications: 8.8% vs 18.7% (P &gt; .05) Acute Kidney Injury: 2.2% vs 9.9% 9NS)</p>
Holy, 2017 <sup>20</sup> Cohort N=514 1 y follow-up	<p>DAPT = 315 OAC = 199 OAC included 188 phenprocoumon, 7 rivaroxaban, 4 dabigatran</p> <p>Dosage not specified. Duration: DAPT: life-long aspirin + clopidogrel x 3 months; x 6 months if concomitant PCI OAC: chronic OAC + clopidogrel x 3 months; x 6 months if concomitant PCI</p>	<p>DAPT (n = 315) vs OAC (n = 199) At 30 days: All-cause: 3.5% vs 3.5% (P &gt; .05) Cardiovascular: 3.5% vs 2.5% (P &gt; .05) At 6 months: All-cause: 7.9% vs 12.0% (P &gt; .05) Cardiovascular: 5.0% vs 7.0% (P &gt; .05) At 1 year: All-cause: 12.4% vs 17.6% (P &gt; .05)</p>	<p>DAPT (n = 315) vs OAC (n = 199) At 30 days: -All Stroke: 3.8% vs 3.5% (P &gt; .05) At 6 months: -All Stroke: 4.4% vs 4.0% (P &gt; .05)</p>	<p>DAPT (n = 315) vs OAC (n = 199) At 30 days: Life-threatening bleeding: 7.3% vs 9.6% (P &gt; .05) Major bleeding: 16.8% vs 15.1% (P &gt; .05) At 6 months: Life-threatening bleeding: NR Major bleeding: 17.5% vs 16.5% (P &gt; .05)</p>	<p>At 30 days: Myocardial Infarction: 0.9% vs 0.5% (P &gt; .05) At 6 months: MI: 1.6% vs 0.5% (P &gt; .05) At 1 year: Valve Thrombosis: 2.5% vs 0 (P = .02)</p>
Seeger, 2017 <sup>22</sup> Cohort N=617 12 m follow-up	<p>War = 131 DOAC (apixaban) = 141</p> <p>14/131 switched from War to apixaban. 5/141 switched from apixaban to War.</p>	<p>Apixaban (n = 141) vs War (n=131) At 30 days: All-cause: 1.4% vs 13.8% (P &gt; .05) Cardiovascular: NR</p>	<p>Apixaban (n = 141) vs War (n=131) At 30 days: Disabling and Non-disabling Stroke: 2.1% vs 5.3% (P &gt; .05)</p>	<p>Apixaban (n = 141) vs War (n=131) At 30 days: Life-threatening bleeding: 3.5% vs 5.3% (P &lt; .01) Intracerebral bleeding: 0.7% vs 0 (P &gt; .05)</p>	NR

Study Sample size Follow-up time	Treatment comparison N per treatment arm	Mortality (all-cause)	Thromboembolic Include all stroke except hemorrhagic	Major Hemorrhagic	Other benefits/harms:
	<p>SAPT used in patients in sinus rhythm                      DAPT used in patients in sinus rhythm and recent coronary stent                      Oral Anticoagulation was restarted 48 hours after TAVR in patients with pre-existing AF; patients with new-onset AF were transitioned to OAC before discharge.                      War (phenoprocumon) &amp; Apixaban were continued x lifelong.                      Apixaban (after November 2013; excluding valvular AF, severe liver dysfunction, or creatinine clearance &lt;15 mL/min)                      Patients in AF received OAC + SAPT for 4 weeks – except Boston Lotus recipients, who received OAC + DAPT for 4 weeks, then just OAC.</p>	<p>Apixaban (n= 81) vs War (n = 50)                      At 12 months:                      All-cause: 22.4% vs 12.0% (P &gt; .05)                      Cardiovascular: NR</p>	<p>Apixaban (n= 81) vs War (n = 50)                      At 12 months:                      Disabling and Non-disabling Stroke: 1.2% vs 2.0% (P &gt; .05)</p>	<p>Major vascular complications: 3.5% vs 7.6% (P &gt; .05)                       Authors report life-threatening bleeding and major vascular complications were independent of "triple therapy"</p>	

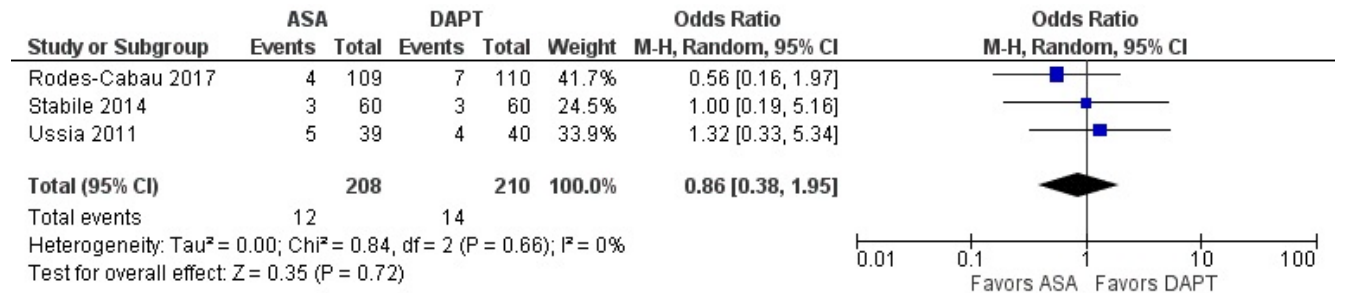
**Abbreviations:** AAR = Ascending aorta replacement; AC = Anticoagulation; AF = Atrial fibrillation; AP/APT = Antiplatelet therapy; ASA = Aspirin (acetylsalicylic acid); AVR = Aortic valve replacement; CAD = Coronary artery disease; CHF = Chronic heart failure; CKD = Chronic kidney disease; CV = Cardiovascular; DAPT = Dual antiplatelet therapy; DM = Diabetes mellitus; HR = Hazard ratio; HTN = Hypertension; INR = International Normalized Ratio; LIMA = left internal mammary artery (graft); LVEF = Left ventricular ejection fraction; MAT = Multiple antithrombotic therapy; MI = Myocardial infarction; MV = Mitral valve; NR = Not reported; OAC = Oral anticoagulation; P = P-value; RCT = Randomized controlled trial; ROB = Risk of bias; SVG = Saphenous vein graft; TAVR = Transcatheter aortic valve replacement; TIA = Transient ischemic attack; War = Warfarin.



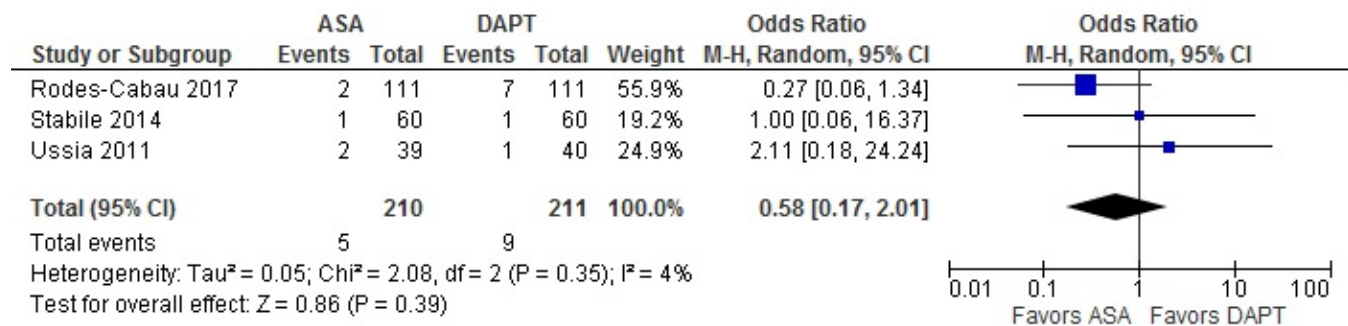
**Figure 5. Risk of Mortality at 30 Days in Trials that Compared ASA vs DAPT after TAVR**



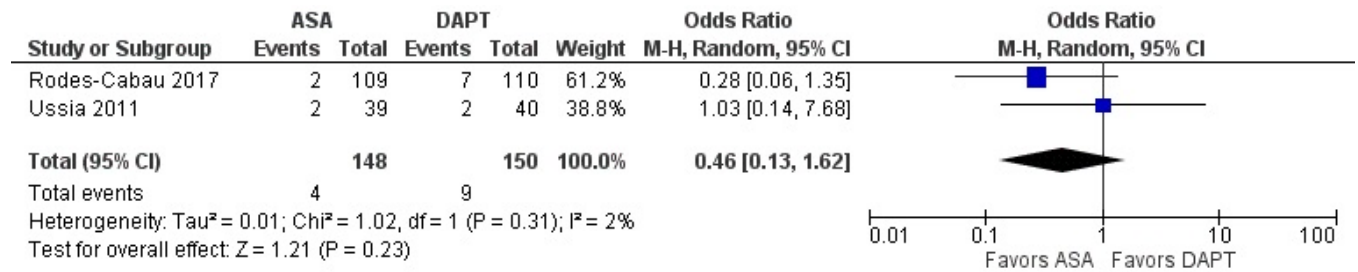
**Figure 6. Risk of Mortality at 3-6 Months in Trials that Compared ASA vs DAPT after TAVR**



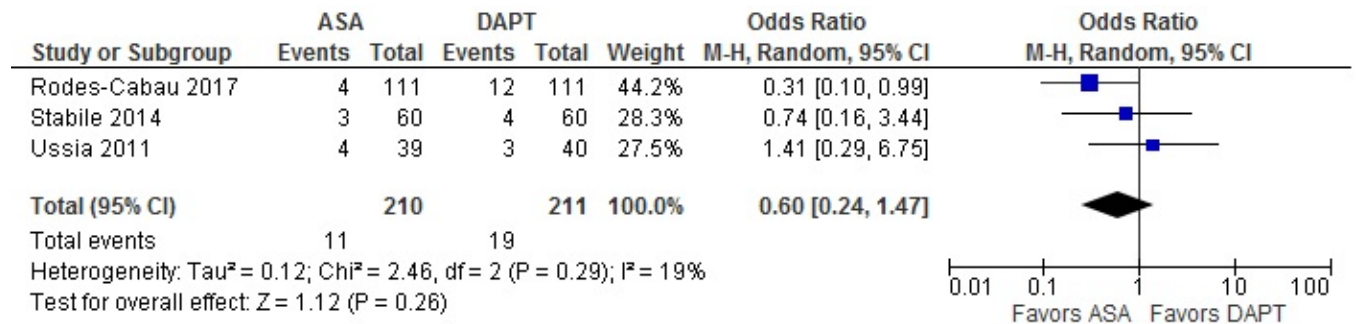
**Figure 7. Risk of TE Events (Includes Major Stroke and MI) at 30 Days in Trials that Compared ASA vs DAPT after TAVR**



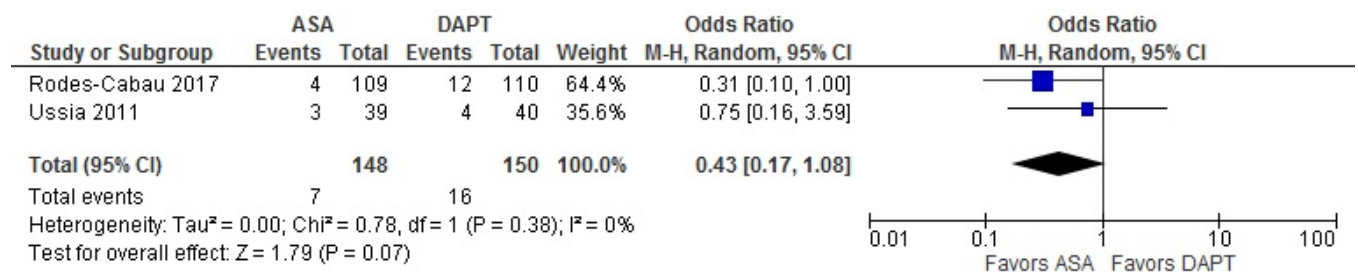
**Figure 8. Risk of TE Events (Includes Major Stroke and MI) at 3-6 Months in Trials that Compared ASA vs DAPT after TAVR**



**Figure 9. Risk of Major or Life-threatening Bleeding Events at 30 Days in Trials that Compared ASA vs DAPT after TAVR**



**Figure 10. Risk of Major or Life-threatening Bleeding Events at 3-6 Months in Trials that Compared ASA vs DAPT after TAVR**



## SUMMARY AND DISCUSSION

We systematically reviewed the literature and found 15 studies comparing different anticoagulation strategies in patients who had undergone surgical bAVR, and 8 studies comparing strategies in patients who had undergone transcatheter aortic valve replacement. Overall, there is consistent evidence from small trials and larger observational studies that aspirin and warfarin are associated with similar risks of mortality, thromboembolic events and bleeding after surgical bAVR (moderate-strength evidence). There was insufficient evidence to draw any conclusions about the effects of no treatment compared to aspirin or warfarin, and the effects of other antiplatelet agents in surgical bAVR.

Data from one large registry study of bAVR in the US found small but significant benefits of warfarin plus aspirin compared to aspirin alone, though the combination was associated with a substantial increase in bleeding risk. The same study, on the other hand, found that warfarin and aspirin alone were associated with similar mortality and thromboembolic event rates. No study compared warfarin plus aspirin to warfarin alone. The clinical importance of these findings is unclear. Even though the study was reasonably well-conducted and was broadly representative of the target population of interest, it only had information about discharge medications (so any subsequent outpatient changes in anticoagulation strategy would not have been captured) 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.

Interestingly, there is a stronger body of data emerging for TAVR patients. We found data from 3 open-label randomized trials and 2 observational studies that single antiplatelet therapy with aspirin was associated with similar mortality and thromboembolic event risk, but lower bleeding risk than dual-antiplatelet therapy with aspirin and clopidogrel. These findings may evolve as data from larger, in-progress trials<sup>46</sup> 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.

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. The reviewed studies did not clearly differentiate between pre- and post-operative atrial fibrillation. In patients with surgical bAVR, the main source for subgroup data comes from one large observational study<sup>5</sup> which found no difference between warfarin and aspirin monotherapy in benefits or harms according to thromboembolic risk factors including atrial fibrillation, reduced left ventricular ejection fraction, and prior stroke or thromboembolism. However, the same study found that among patients with risk factors (atrial fibrillation, depressed ejection fraction, or prior thromboembolism), the combination of warfarin and aspirin was associated with a substantially reduced risk of thromboembolism but was not associated with reduced mortality, and there was a substantially elevated bleeding risk. Of note, the authors used the term pre-discharge atrial fibrillation and did not further define pre-versus post-operative atrial fibrillation. Unfortunately, there are no studies comparing the combination of warfarin and aspirin to warfarin alone which would have been a clinically relevant comparison for many patients with chronic atrial fibrillation. It is possible that some

patients with substantially elevated thromboembolic risk who are not at high risk of bleeding might benefit from the combination of warfarin and aspirin after surgical bAVR.

We found no good evidence examining the relative benefits and harms of different strategies in patients who had concomitant procedures like CABG.

Our findings in surgical bAVR are congruent with some existing guideline recommendations. Recommendations from professional societies have varied. The ACCP currently recommends aspirin (50-100 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).<sup>25</sup> In 2017, the AHA/ACC released a focused update of the 2014 AHA/ACC guidelines for management of patients with valvular heart disease.<sup>30,31</sup> In this update, the prior recommendation for use of a vitamin K antagonist after bioprosthetic valve replacement were changed to include both aortic and mitral bioprosthesis, for 3 to 6 months after surgery, in patients at low risk of bleeding (Class IIa, level of evidence B-NR). This change was attributed to a lower stroke risk and mortality rate for patients receiving anticoagulation, and by reports of valve thrombosis for patients undergoing bioprosthetic surgical AVR or MVR. However, the studies on which this change was based were excluded from our review for either methodologic reasons<sup>47</sup> or because of a focus on imaging as opposed to clinical outcomes<sup>48</sup> as previously discussed. The recommendation of aspirin 75 mg to 100 mg per day in all patients with a bioprosthetic aortic or mitral valve was unchanged from the 2014 guidelines (Class IIa, level of evidence B). The 2012 guidelines on the management of valvular heart disease from the European Society of Cardiology suggested that a low-dose aspirin should be considered (Class IIa, level of evidence C) and an oral anticoagulation may be considered for the first 3 months after implantation of an aortic bioprosthesis (Class IIb, level of evidence C).<sup>32</sup>

The TAVR findings are novel and the clinical implications of this data should be discussed by clinical policy groups. Our findings are different than prior guideline recommendations in part because newer trial data have been published. However, the newer trials have small sample sizes and limited power to detect small differences in clinical outcomes. Unfortunately ongoing trials of TAVR are not designed to resolve the comparative benefits and harms of single versus dual antiplatelet therapy (Table 9). The 2014 ACC/AHA valvular disease guidelines give a class IIb recommendation (level of evidence C) for aspirin and clopidogrel for 6 months after TAVR.<sup>31</sup> The 2017 focused update includes a recommendation (Class IIb, level of evidence B-NR) that anticoagulation with warfarin to achieve an INR of 2.5 may be reasonable for at least 3 months after TAVR in patients at low risk of bleeding.<sup>30</sup> This recommendation is based in part on studies demonstrating valve thrombosis after TAVR as assessed by multidetector computerized tomographic scanning. These same guidelines also continue the previous recommendation that clopidogrel 75 mg daily may be reasonable for the first 6 months after TAVR in addition to life-long aspirin 75 mg to 100 mg daily (Class IIb, level of evidence C).<sup>30</sup> The 2012 ACCF/AATS/SCAI/STS panel consensus recommendations suggested DAPT with aspirin and clopidogrel after TAVR, but the duration and loading dose of clopidogrel were not specified.<sup>49</sup> The Canadian Cardiovascular Society statement on TAVR recommend the use of aspirin indefinitely and clopidogrel for 1 to 3 months.<sup>50</sup>

## LIMITATIONS

There are a number of limitations to this body of evidence. First, for most comparisons other than SAPT to DAPT after TAVR, there are simply too few studies to draw conclusions. Second, much of the evidence comes from observational studies and we found substantial variation in the methodologic rigor of these studies, even after excluding studies that did not adjust for confounding factors. As anticoagulation was typically left to the surgeon's discretion in bAVR studies (presumably based on the patient's risk for thromboembolism and bleeding), 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. Many studies did not report this data. The studies that did report this data found that target INR was not achieved 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, non-comparative cohort studies (N = 461 to 1260), the mean rate of 5-year thromboembolic events was 4% (range 3.4 – 5.9%).<sup>51-53</sup> Across 6 large cohort studies (N = 461 to 1594), the mean 5-year bleeding rate was 3.8% (range 1.4-6.2%).<sup>51-56</sup> In order to detect small differences in thromboembolic event 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 6226 subjects per arm to detect a 1% difference in thromboembolic events, and 1586 subjects per arm to detect a 2% difference.

On the other hand, given the low event rates and lack of demonstrable difference in available studies, it is reasonable to argue that the discovery of a significant effect in a large trial might have uncertain clinical importance as the number of patients to treat to achieve benefit would likely be large and, as the available studies suggest, offset by the risk of bleeding seen with more aggressive anticoagulation strategies. Large ongoing trials examining various anticoagulation strategies after TAVR are underway (Table 9), although most do not focus on single versus dual antiplatelet therapy.



**Table 9. Ongoing Clinical Trials Comparing Antithrombotic Strategies after bAVR/TAVR**

Trial	Study design	N	Procedure	Comparison	Primary outcomes
Anticoagulant after implantation of biological aortic valve comparing with aspirin (NCT01452568)	Randomized, open-label	370	B AVR	ASA 150mg daily vs warfarin target INR 2.0 to 3.0, starting day 1 after surgery, for 3 months.	Hemorrhagic complications; thromboembolic complications; registration of surgical data and postoperative complications; all-cause mortality
ATLANTIS (NCT02664649)	2 strata, 1:1 randomization per stratum	1,509	T AVR	Stratum 1 (indication for OAC): standard of care vs apixaban 5 mg bid for 6 months stratum 2 (no indication for OAC): standard of care —DAPT/SAPT vs apixaban 5 mg bid for 6 m.	MACE: all-cause death, MI, stroke/TIA/systemic embolism, intracardiac or bioprosthetic thrombus, DVT/PE; Safety: major bleeding
AUREA (NCT01642134)	Randomized, open-label (masked outcome assessor)	124	T AVR	ASA (100 mg) +clopidogrel (75 mg) for 3 vs ACENOCUMAROL, 3 months	Stroke at 3 months; cognitive function (MMSE) at 1, 3, and 6 months; quality of life (Euroqol EQ5) at 1, 3, and 6 months
AVATAR (NCT02735902)	Randomized (post-T AVR)	170	T AVR	War (INR of 2–3) for 12 months vs War (INR of 2–3) + ASA (75–100 mg/day) for 12 months	Composite outcome: death from any cause, MI, stroke, valve thrombosis, and hemorrhage as defined by the VARC-2 scale
ENVISAGE-TAVI AF (NCT02943785)	Randomized, open-label	1,400	T AVR	Edoxaban 15 mg, 30 mg and 60 mg vs War according to standard of care treatment in the country location (with antiplatelet therapy pre-declared at randomization if prescribed).	Net adverse clinical events (NACE), i.e., the composite of all-cause death, MI, ischemic stroke, systemic thromboembolism, valve thrombosis, and major bleeding
GALILEO (NCT02556203) PROBE	1:1 randomization	1,520	T AVR	Rivaroxaban 10 mg/day p ASA 75–100 mg/day for 3 months, then rivaroxaban 10 mg/day for 12–24 months vs DAPT for 3 months, then ASA 75–100mg/day for 12-24 months	MACE: all-cause death; stroke; MI; valve thrombosis; PE; DVT; systemic embolism Safety: life-threatening, disabling, or major bleeding
POPular-TAVI (NCT02247128)	Randomized Group A: T AVR patients with no indication for OAC Group B: T AVR patients with indication for OAC	1,000	T AVR	Group A: ASA (<100 mg/day) vs DAPT for 3 months, then continue ASA (<100 mg/day) 12 m Group B: warfarin (target INR of 2) vs clopidogrel 75 mg/day for 3 months p warfarin (target INR of 2), then continue warfarin alone through 12-month period	Safety: freedom from all bleeding complications Coprimary endpoint: freedom from non-procedure-related bleeding complications (defined according to BARC and VARC)

**Abbreviations:** ARTE = Aspirin Versus Aspirin + ClopidogRel Following Transcatheter Aortic Valve Implantation; ATLANTIS = Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis; ASA = Aspirin (acetylsalicylic acid); AUREA = Dual Antiplatelet Therapy Versus Oral Anticoagulation for a Short Time to Prevent Cerebral Embolism After TAVI; AVATAR = Anticoagulation Alone Versus Anticoagulation and Aspirin Following Transcatheter Aortic Valve Interventions (1:1); BARC = Bleeding Academic Research Consortium; bid = 2 times a day; DAPT = dual antiplatelet therapy; DVT = deep vein thrombosis; ENVISAGE-TAVI AF = Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation (ENVISAGE-TAVI AF); GALILEO = Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes; INR = international normalized ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction; MMSE = Mini-Mental State Examination; NCT = identification number registered in ClinicalTrials.gov; PE = pulmonary embolism; OAC = oral anticoagulation; POPular-TAVI = Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation; PROBE = prospective, randomized, open-label, blinded endpoint evaluation; SAPT = single-antiplatelet therapy; T AVR = transcatheter aortic valve replacement; VARC = Valve Academic Research Consortium; War = warfarin.

## CONCLUSIONS

We found moderate-strength evidence that use of aspirin or warfarin after surgical bAVR is associated with similar effects on mortality, thromboembolic events, and bleeding rates. Observational data suggest the combination of warfarin plus aspirin may be associated with lower mortality and thromboembolic events compared to 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. Use of aspirin alone after transcatheter aortic valve replacement is associated with similar short-term effects on mortality and stroke and possibly lower bleeding rates compared to use of dual-antiplatelet therapy, though larger trials are needed to exclude the possibility of small differences in comparative effects.

**Table 10. Summary of the Evidence on Antithrombotic Strategies after bAVR and TAVR**

Treatment comparison	N studies per outcome (N=combined participants)	Findings on mortality, thromboembolic events, and major hemorrhagic complications	Strength of Evidence*	Comments
<b>Surgical BAVR</b>				
<i>Warfarin vs ASA</i>				
• Mortality	3 RCTs <sup>1-3</sup> (N=355) 5 cohorts <sup>2,4-7</sup> (N=17,331)	No difference. Best evidence from 2 studies, at 3 months: <ul style="list-style-type: none"> <li>1 low-ROB RCT<sup>3</sup> (N=236): 3.8% vs 2.9%, P = .721</li> <li>1 large cohort study<sup>5</sup> (N=15,456): 4.0% vs 3.0%, P &gt; .05</li> </ul>	Moderate	Small RCTs, likely underpowered, but results are consistent with one large, well-conducted cohort study
• TE events	3 RCTs <sup>1-3</sup> (N=355) 8 cohorts <sup>2,4-10</sup> (N=18,506)	No difference. Best evidence from 2 studies, at 3 months: <ul style="list-style-type: none"> <li>1 low-ROB RCT<sup>3</sup> (N=236): 3.8% vs 2.9%, P = .721</li> <li>1 large cohort study<sup>5</sup> (N=15,456): 1.0% vs 1.0%, P &gt; .05</li> </ul>	Moderate	
• Major bleeding	3 RCTs <sup>1-3</sup> (N=355) 7 cohorts <sup>2,4-7,9,10</sup> (N=18,212)	No difference. Best evidence from 2 studies, at 3 months: <ul style="list-style-type: none"> <li>1 low-ROB RCT<sup>3</sup> (N=236): 2.9% vs 1.9%, P = .683</li> <li>1 large cohort study<sup>5</sup> (N=15,456): 1.0% vs 1.4%, P &gt; .05</li> </ul>	Moderate	
<i>Warfarin + ASA vs ASA</i>				
• Mortality	1 RCT <sup>3</sup> (N=119) 2 cohorts <sup>5,11</sup> (N=18,485)	Best evidence from 1 large cohort <sup>5</sup> RR (95% CI): 0.80 (0.66 to 0.96), NNT 153	Low	Findings are based mostly on one 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.
• TE events	1 RCT <sup>3</sup> (N=119) 4 cohorts <sup>3,5,11,12</sup> (N=19,551)	Best evidence from 1 large cohort <sup>5</sup> RR (95% CI): 0.52 (0.35 to 0.76), NNT 212	Low	
• Major bleeding	1 RCT <sup>3</sup> (N=135) 1 cohort <sup>5</sup> (N=18,429)	Best evidence from 1 large cohort <sup>5</sup> RR (95% CI): 2.80 (2.18 to 3.60), NNH 55	Low	
<i>Warfarin + ASA vs Warfarin</i>	0 studies	---	Insufficient	No evidence currently available.
<i>Warfarin vs no treatment</i>				
• Mortality	2 cohorts <sup>4,13</sup> (N=210)	Short-term: no differences at 3 months <sup>4</sup> Long-term: poorer survival with warfarin: 67.9% vs 76.1% at 8 years (P = .03) <sup>13</sup>	Insufficient	Evidence from smaller retrospective studies. INR generally not reported
• TE events	2 cohorts <sup>4,8</sup> (N=347)	Elevated TE risk with warfarin in one study with 4.2 years follow-up. <sup>8</sup> Adjusted RR (95% CI): 3.0 (1.5 to 6.3), P = .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	
• Major bleeding	1 cohort <sup>4</sup> (N=88)	No difference by treatment group in long-term freedom from hemorrhage.	Insufficient	

Treatment comparison	N studies per outcome (N=combined participants)	Findings on mortality, thromboembolic events, and major hemorrhagic complications	Strength of Evidence*	Comments
<i>ASA vs no treatment</i>				
• Mortality	1 cohort <sup>4</sup> (N=360)	No difference.	Insufficient	ASA dose and duration were reported in only study
• TE events	3 cohorts <sup>4,8,12</sup> (N=1983)	No difference.	Insufficient	
• Major bleeding	1 cohort <sup>4</sup> (N=360)	No difference.	Insufficient	
<i>Triflusal v. Acenocoumarol</i>				
• Mortality	1 RCT <sup>14</sup> (N=200)	No difference. 30-day mortality: 8.3% vs 3.2%, P = .15	Insufficient	Evidence is from one study. Treatments not available in the US
• TE events	1 RCT <sup>14</sup> (N=200)	No difference. TE at 3 months: 6.3% vs 3.2%, P = .50	Insufficient	
• Major bleeding	1 RCT <sup>14</sup> (N=200)	Risk of bleeding lower with triflusal: 3% vs 10%, P = .048	Insufficient	
<b>TAVR:</b>				
<i>ASA vs DAPT</i>				
• Mortality	3 RCTs <sup>15-17</sup> (N=421) 1 cohort <sup>18</sup> (N=144)	No difference. Combined estimate (95% CI) at 3-6 months from meta-analysis of all 3 trials, ASA vs DAPT: 0.86 (0.38 to 1.95)	Moderate	Consistent findings of no difference among 3 low ROB trials. Sample sizes limit power to detect small differences in treatment effect.
• TE events	3 RCTs <sup>15-17</sup> (N=421) 1 cohort <sup>18</sup> (N=144)	No difference. Combined estimate (95% CI) at 3-6 months from meta-analysis of 2 trials, <sup>15,17</sup> ASA vs DAPT: 0.46 (0.13 to 1.62)	Moderate	
• Major bleeding	3 RCTs <sup>15-17</sup> (N=421) 1 cohort <sup>18</sup> (N=144)	Marginally significant increased risk with DAPT vs ASA in one trial <sup>15</sup> (N=222): 10.9% vs 3.6%, P = .038 Combined estimate (95% CI) at 3-6 months from meta-analysis of 2 trials, <sup>15,17</sup> ASA vs DAPT: 0.43 (0.17 to 1.08)	Moderate	
<i>APT vs APT + OAC</i>				
• Mortality	2 cohorts <sup>19,20</sup> (N=806)	No difference.	Insufficient	Treatment arms contain a mix of antithrombotic regimens.
• TE events	2 cohorts <sup>19,20</sup> (N=806)	No difference.	Insufficient	
• Major bleeding	2 cohorts <sup>19,20</sup> (N=806)	No difference at 1 year for DAPT (N=315) vs OAC (N=199, includes 188 warfarin, 7 rivaroxaban, and 4 dabigatran) <sup>20</sup> More bleeding complications at 30 days with DAPT (ASA+clopidogrel) vs SAPT (adding/maintaining ASA or maintaining clopidogrel), propensity score-matched (N=182) <sup>19</sup> : 30.8% vs 9.9%, P = .002.	Insufficient	

Treatment comparison	N studies per outcome (N=combined participants)	Findings on mortality, thromboembolic events, and major hemorrhagic complications	Strength of Evidence*	Comments
<i>Warfarin monotherapy vs Warfarin + APT</i>				
• Mortality	1 cohort <sup>21</sup> (N=621)	No difference.	Insufficient	Evidence is from one study.
• TE events	1 cohort <sup>21</sup> (N=621)	No difference.	Insufficient	
• Major bleeding	1 cohort <sup>21</sup> (N=621)	Increased risk of hemorrhage with Warfarin + APT vs warfarin monotherapy: Adjusted HR (95% CI) for VARC-2 major or life-threatening bleeding, median 13 months follow-up: 1.85 (1.05 to 3.28), P = .04	Insufficient	
<i>Warfarin vs DOAC (apixaban):</i>				
• Mortality	1 cohort <sup>22</sup> (N=272)	No difference.	Insufficient	Evidence is from one study.
• TE events	1 cohort <sup>22</sup> (N=272)	No difference.	Insufficient	
• Major bleeding	1 cohort <sup>22</sup> (N=272)	No difference.	Insufficient	

<sup>a</sup>The 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:<sup>41</sup>

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.

Insufficient = Any estimate of effect is very uncertain.

**Abbreviations:** APT = Antiplatelet therapy; ASA = Aspirin (acetylsalicylic acid); BAVR = Bioprosthetic aortic valve replacement; DAPT = Dual antiplatelet therapy; DOAC = Direct oral anticoagulant; N = Number; NNH = Number needed to harm; NNT = Number needed to treat; RCT = Randomized controlled trial; ROB = Risk of bias; RR = Relative risk; TE = Thromboembolism; War = warfarin.

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