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

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PREFACE

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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.

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

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INTRODUCTION

The use of bioprosthetic aortic valves placed surgically and with a transcatheter approach is a common treatment for valvular heart disease. While most patients are treated with anticoagulant and/or antiplatelet therapy for a period of time after the procedure, the optimal antithrombotic regimen and duration after placement of a bioprosthetic aortic valve is unclear, and both guideline recommendations and practice patterns vary significantly. 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

We searched MEDLINE, PubMed, EMBASE, EMB Reviews (CDSR, DARE, HTA, Cochrane CENTRAL, *etc*), and grey literature sources from database inception through January 2017, with a search for new/in-process citations in June 2017, and reviewed the bibliographies of relevant articles to identify additional studies. We included controlled clinical trials and cohort 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. 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.

From each study, we abstracted data on study design, setting, sample size, population characteristics, duration of follow-up, dosage and duration of treatment, concomitant procedures, clinical outcomes, and adverse events. We used standardized assessment tools to determine the risk of bias in each study. We qualitatively synthesized the evidence on benefits and harms, and combined trials with comparable interventions and outcomes in meta-analyses. We assessed the overall strength of evidence for outcomes using a standardized approach.

RESULTS

We included 23 primary studies reported in 22 publications after reviewing 4,554 titles and abstracts. We identified 4 RCTs and 11 cohort studies that compared antithrombotic strategies in bAVR patients (KQs 1 and 2). We found 3 RCTs and 5 cohort studies assessing various antiplatelet and anticoagulation strategies in patients who have undergone TAVR (KQ 3). The results are summarized below according to treatment comparison.

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

Warfarin vs ASA

Three randomized controlled trials and 8 observational studies evaluated the benefits and harms of a vitamin K antagonist compared with aspirin after bioprosthetic aortic valve replacement (bAVR). 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).

Warfarin Combined with ASA vs ASA Monotherapy

One randomized controlled trial 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.

Warfarin vs No Treatment

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

Aspirin vs No Treatment

Three cohort studies compared aspirin with no treatment. No differences by treatment were found in the risk of thromboembolic events, mortality, or hemorrhage. The strength of evidence for these findings is insufficient given the paucity of available data, insufficient detail about dose and/or duration of treatment, and other methodologic limitations.

Triflusal vs Acenocoumarol

One randomized controlled trial 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 the 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. Furthermore, neither medication is currently used in the US, therefore applicability of these findings to practice in the US is limited.

KQ1-2 A. Do the benefits/harms differ according to thromboembolic risk profile?

In one large observational trial comparing warfarin alone to aspirin alone, there was no difference in benefits or harms according to thromboembolic risk factors including atrial fibrillation, reduced left ventricular ejection fraction, and prior stroke or thromboembolism. The same study found 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.

KQ1-2 B. Do the benefits/harms differ according to concomitant procedure (*eg* CABG)?

Among all comparisons, we found insufficient evidence to determine whether treatment effects differed according to receipt of concomitant procedures like CABG.

Key Question 3: What are the comparative benefits and harms of antithrombotic strategies for patients who have TAVR?

In 3 small, open-label, randomized controlled trials and one cohort study of patients without atrial fibrillation undergoing transcatheter aortic valve replacement (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).

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

In the TAVR trials, patients with atrial fibrillation were largely excluded and the cohort studies provided insufficient evidence to draw conclusions of comparative benefits and harms of different strategies according to thromboembolic risk profile.

KQ3B. Do the benefits/harms differ according to concomitant procedure (*eg*, CABG)?

Among all comparisons, we found insufficient evidence to determine whether treatment effects differed according to receipt of concomitant procedures like coronary artery bypass grafting (CABG).

SUMMARY AND DISCUSSION

We found moderate-strength evidence that use of aspirin or warfarin after surgical bAVR are 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.

We found insufficient evidence to draw conclusions about the optimal anticoagulation strategy according to thromboembolic risk or receipt of concomitant procedures.

In TAVR patients, the strategy of adding a second antiplatelet agent to aspirin for 3 to 6 months 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).

CURRENT PRACTICE AND OUTCOMES IN VA

In a companion project, we partnered with the PRISM QUERI to complete a retrospective cohort to better understand practice patterns in VA, how practice differs across VA facilities, and to describe post-bAVR outcomes in VA patients. A detailed report explaining the study's methods and describing all findings is posted alongside this report.[1]

In brief, the VA cohort study found that the number of bAVR procedures has doubled between 2005 and 2015. Nearly half of all patients received aspirin alone, but practice patterns differed substantially across facilities. For example, the use of aspirin and warfarin together varied from 10% to about 70% of patients across facilities; there were clinical differences among groups of patients receiving different anticoagulation, but the variation in practice was not entirely attributable to comorbidities such as atrial fibrillation. Outcomes in VA patients were similar to non-VA cohorts: 90-day mortality after bAVR ranged 1.2-2.2%, 90-day thromboembolism rates ranged 0.9-2.5%, and 90-day major bleeding ranged 0.6-2.2% depending on the anticoagulation strategy chosen.

LIMITATIONS

Much of the current evidence came from observational studies that had substantial variation in methodologic rigor. 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 ways that may not have been adequately captured in adjusted analyses. Furthermore, 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 information and those that did 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 inadequate dosing 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.

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. Larger trials of TAVR are underway, and their findings may have a significant impact on clinical management.

[1] Bravata D, Coffing J, Kansagara D, Myers J, Murphy L, Homoya B, Snow K, Ying Z, Myers L. Antithrombotic Use in the Year After Bioprosthetic Aortic Valve Replacement in the Veterans Health Administration System. VA ESP Project #05-225; 2017.

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.

Clinical outcomes post-bAVR in VA were similar to those reported in non-VA cohorts. There is substantial variation in anticoagulation practice patterns across VA facilities.

Table. 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
Surgical BAVR				
Warfarin vs ASA				
• Mortality	3 RCTs[1-3] (N=355) 5 cohorts[2,4-7] (N=17,331)	No difference. Best evidence from 2 studies, at 3 months: ▪ 1 low-ROB RCT[3] (N=236): 3.8% vs 2.9%, P = .721 ▪ 1 large cohort study[5] (N=15,456): 4.0% vs 3.0%, P > .05	Moderate	Small RCTs, likely underpowered, but results are consistent with one large, well-conducted cohort study
• TE events	3 RCTs[1-3] (N=355) 8 cohorts[2,4-10] (N=18,506)	No difference. Best evidence from 2 studies, at 3 months: ▪ 1 low-ROB RCT[3] (N=236): 3.8% vs 2.9%, P = .721 ▪ 1 large cohort study[5] (N=15,456): 1.0% vs 1.0%, P > .05	Moderate	
• Major bleeding	3 RCTs[1-3] (N=355) 7 cohorts[2,4-7,9,10] (N=18,212)	No difference. Best evidence from 2 studies, at 3 months: ▪ 1 low-ROB RCT[3] (N=236): 2.9% vs 1.9%, P = .683 ▪ 1 large cohort study[5] (N=15,456): 1.0% vs 1.4%, P > .05	Moderate	
Warfarin + ASA vs ASA				
• Mortality	1 RCT[3] (N=119) 2 cohorts[5,11] (N=18,485)	Best evidence from 1 large cohort[5] 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[3] (N=119) 4 cohorts[3,5,11,12] (N=19,551)	Best evidence from 1 large cohort[5] RR (95% CI): 0.52 (0.35 to 0.76), NNT 212	Low	
• Major bleeding	1 RCT[3] (N=135) 1 cohort[5] (N=18,429)	Best evidence from 1 large cohort[5] RR (95% CI): 2.80 (2.18 to 3.60), NNH 55	Low	
Warfarin + ASA vs Warfarin	0 studies	---	Insufficient	No evidence currently available.
Warfarin vs no treatment				
• Mortality	2 cohorts[4,13] (N=210)	Short-term: no differences at 3 months[4] Long-term: poorer survival with warfarin: 67.9% vs 76.1% at 8 years (P = .03)[13]	Insufficient	Evidence from smaller retrospective studies. INR generally not reported
• TE events	2 cohorts[4,8](N=347)	Elevated TE risk with warfarin in one study with 4.2 years follow-up.[8] 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[4](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
ASA vs no treatment				
• Mortality	1 cohort[4] (N=360)	No difference.	Insufficient	ASA dose and duration were reported in only study
• TE events	3 cohorts[4,8,12] (N=1983)	No difference.	Insufficient	
• Major bleeding	1 cohort[4] (N=360)	No difference.	Insufficient	
Triflusal v. Acenocoumarol				
• Mortality	1 RCT[14] (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[14] (N=200)	No difference. TE at 3 months: 6.3% vs 3.2%, P = .50	Insufficient	
• Major bleeding	1 RCT[14] (N=200)	Risk of bleeding lower with triflusal: 3% vs 10%, P = .048	Insufficient	
TAVR:				
ASA vs DAPT				
• Mortality	3 RCTs[15-17] (N=421) 1 cohort[18] (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[15-17] (N=421) 1 cohort[18] (N=144)	No difference. Combined estimate (95% CI) at 3-6 months from meta-analysis of 2 trials,[15,17] ASA vs DAPT: 0.46 (0.13 to 1.62)	Moderate	
• Major bleeding	3 RCTs[15-17] (N=421) 1 cohort[18] (N=144)	Marginally significant increased risk with DAPT vs ASA in one trial[15] (N=222): 10.9% vs 3.6%, P = .038 Combined estimate (95% CI) at 3-6 months from meta-analysis of 2 trials,[15,17] ASA vs DAPT: 0.43 (0.17 to 1.08)	Moderate	
APT vs APT + OAC				
• Mortality	2 cohorts[19,20] (N=806)	No difference.	Insufficient	Treatment arms contain a mix of antithrombotic regimens.
• TE events	2 cohorts[19,20] (N=806)	No difference.	Insufficient	
• Major bleeding	2 cohorts[19,20] (N=806)	No difference at 1 year for DAPT (N=315) vs OAC (N=199, includes 188 warfarin, 7 rivaroxaban, and 4 dabigatran)[20] More bleeding complications at 30 days with DAPT (ASA+clopidogrel) vs SAPT (adding/maintaining ASA or maintaining clopidogrel), propensity score-matched (N=182)[19]: 30.8% vs 9.9%, P = .002.	Insufficient	
Warfarin monotherapy vs Warfarin + APT				
• Mortality	1 cohort[21] (N=621)	No difference.	Insufficient	Evidence is from one study.
• TE events	1 cohort[21] (N=621)	No difference.	Insufficient	

Treatment comparison	N studies per outcome (N=combined participants)	Findings on mortality, thromboembolic events, and major hemorrhagic complications	Strength of Evidence*	Comments
• Major bleeding	1 cohort[21] (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	
Warfarin vs DOAC (apixaban):				
• Mortality	1 cohort[22] (N=272)	No difference.	Insufficient	Evidence is from one study.
• TE events	1 cohort[22] (N=272)	No difference.	Insufficient	
• Major bleeding	1 cohort[22] (N=272)	No difference.	Insufficient	

[a] 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:

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.

ABBREVIATIONS TABLE

Abbreviation	Term
AAR	Ascending aorta replacement
AC	Anticoagulation
Adj	Adjusted
AE	Adverse event
AF	Atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality
AP/APT	Antiplatelet therapy
ASA	Aspirin (acetylsalicylic acid)
AVR	Aortic valve replacement
bAVR	Bioprosthetic aortic valve replacement
BID	Two times a day
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CHF	Chronic heart failure
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
D	Days
DAPT	Dual antiplatelet therapy
DM	Diabetes mellitus
DoD	Department of Defense
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DVT	Deep vein thrombosis
EGFR	Estimated glomerular filtration rate
HR	Hazard ratio
HTN	Hypertension
Hx	History (of)
ICD	International Statistical Classification of Diseases and Related Health Problems
INR	International Normalized Ratio
IOM	Institute of Medicine
ITT	Intention to treat
KQ	Key question
LIMA	Left internal mammary artery (graft)
LOS	Length of stay
LTB	Life-threatening bleeding
LVEF	Left ventricular ejection fraction
M	Months
MAT	Multiple antithrombotic therapy
MES	Microembolic signal
MI	Myocardial infarction

MOF	Multi-organ failure
MV	Mitral valve
N	Number
NNH	Number needed to harm
NNT	Number needed to treat
NR	Not reported
NYHA	New York Heart Association functional classification
OAC	Oral anticoagulation
OR	Odds ratio
P	P-value
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PICOTS	Patient population, intervention, comparator, outcome, timing parameters, and study designs
PSM	Propensity score matching
QD	Once a day
QOL	Quality of life
RCT	Randomized controlled trial
RIND	Reversible ischemic neurologic deficit
ROB	Risk of bias
RR	Relative risk
SAPT	Single antiplatelet therapy
SVG	Saphenous vein graft
TAVR	Transcatheter aortic valve replacement
TE	Thromboembolism
TIA	Transient ischemic attack
Tx	Treatment
UK	United Kingdom
US	United States
VA	Department of Veterans Affairs
VARC	Valve Academic Research Consortium
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
War	Warfarin
Y	Years

EVIDENCE REPORT

INTRODUCTION

The use of bioprosthetic aortic valve replacement (bAVR) has become a common solution for the treatment of valvular heart disease.[23] 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.[24] 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.[25-27]

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.[25,26,28] 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.[5,25,29-32]

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,[33,34] 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,[35] 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) before the study was initiated.[36]

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)	KQ1: What are the comparative benefits of antithrombotic strategies for patients who have had bAVR? KQ1A: Do the benefits differ according to thromboembolic risk profile? KQ1B: Do the benefits differ according to concomitant procedure (*eg*, 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 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*, PTCA with stent)?
Population	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.		Adult patients who have had TAVR with stenting of aortic valves. Exclude: pregnant women
Intervention/ Comparators	Agents: • Warfarin • Warfarin plus ASA or other antiplatelet agents • ASA or other antiplatelet agents • Dual antiplatelet therapy • Direct oral anticoagulants (DOACs) • No therapy Duration of antithrombotic therapy: • < 90 days • ≥ 90 days		
Outcomes	• Mortality • Thromboembolic events • Stroke • Myocardial infarction • Heart failure • Readmission rates • Need for valve reoperation (*eg*, valve thrombosis) • Length of stay • Need for change in antithrombotic strategy	• Major bleeding events - GI bleeds - Intracranial hemorrhage - Other (*eg*, retroperitoneal) • Other/minor bleeding • Readmission rates • Pericardial or pleural effusion* *We will prioritize effusions requiring intervention.	Benefits and harms listed under KQs 1 and 2.
Timing	• Perioperative, defined as in-hospital or within 30 days. • Long-term, defined as >30 days to 1-year or longer. Both timeframes are of interest for each outcome.		
Study design	• Randomized controlled trials • Non-randomized controlled trials • Cohort studies (retrospective or prospective) or case-control studies that adequately control for important confounders		

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 Abstrackr.[37] 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.[38] 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.[39,40]

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).[41] 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.[42] 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

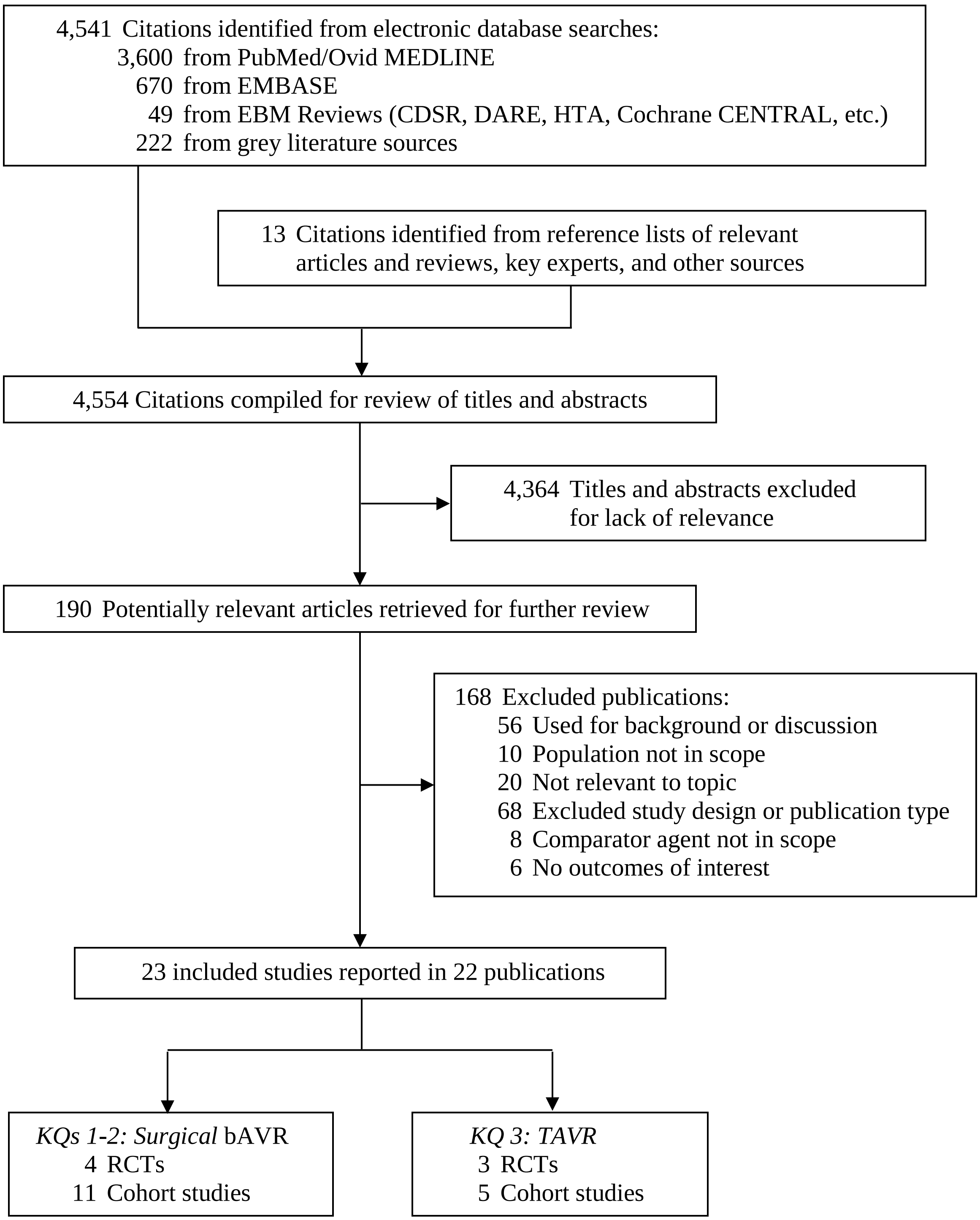
A draft version of this report was reviewed by technical experts and key stakeholders. Reviewer comments and our responses are provided in Appendix D.

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
Randomized controlled trials (N=4)					
Aramendi, 2005[14] 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[1] 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[2] RCT, Single center, Italy April-Oct 2005 N=250 3 m follow-up	War ASA	**APMES vs ACMES** 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[3] 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).
Cohort studies (N=11)					
Al-Atassi, 2012[11] 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[4] 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[5] 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[6] 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[2] Cohort, prospective Single center, Italy 2002-2005 N=250 24±14 m follow-up	War ASA	**Group 1 (ASA) vs Group 2 (AC)** 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 sufficently adjusted for potential confounders. Used mixed outcome assessment methods; unclear if complete and consistent.
Gherli, 2004 #552[7] 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 theASA 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[12] 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[9] 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[13] 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[8] 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[10] 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.

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
		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[5] 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.[3] 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±4d vs 9±3d, P = .96).[1,2] 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.[1,3] 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.[5] 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.[2,4,6,7,9]

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.[8] 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, $P = .7$).[10]

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.[43]

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
Randomized controlled trials (N=3)					
Colli, 2007[1] 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[2] 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[3] 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
Cohort studies (N=8)					
Blair, 1994[4] 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[5] Cohort N=15,456 3 m	ASA = 12457 Warfarin = 2999 ASA + warfarin = 5972 Dosage not specified. Duration 3 months	Watfarin: 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[6] 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[2] 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[7] 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[9] 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[8] 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		
van der Wall, 2016[10] Cohort, retrospective N=402 1 year follow-up	Before policy change (War) = 163 After policy change (ASA) = 239 Nadroparin was started on the first postoperative day followed by acenocoumarol (INR target range 2.5-3.5), or ASA. 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. 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).	NR	Risk of TE events 1 year after BAVRwas not significantly associated with current acenocoumarol use (Adj RR 1.2 0.47 to 3.02, P = .7). Risk of TE was increased with prior acenocoumarol use: Adj RR (95% CI): 3.1 (1.37 to 7.4), P = .007	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 < .001. Prior acenocoumarol use also had higher risk of bleeding: Adj RR 2.46 (95% CI 1.32to4.56) P = .004 Adj RR (95% CI) for 'major' bleedings associated with acenocoumarol: 14.60 (1.95 to 109.37)	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

Study or Subgroup	Warfarin Events	Warfarin Total	ASA Events	ASA Total	Weight	Odds Ratio M-H, Random, 95% CI
Colli 2007	2	34	2	35	36.2%	1.03 [0.14, 7.77]
Rafiq 2017	4	104	3	105	63.8%	1.36 [0.30, 6.23]
Total (95% CI)		**138**		**140**	**100.0%**	**1.23 [0.36, 4.15]**
Total events	6		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

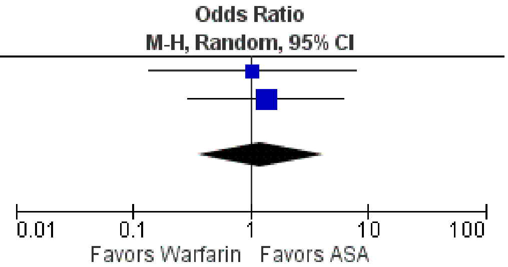


Figure 3. TE Events at 90 Days in Trials that Compared Warfarin with ASA after Surgical bAVR

Study or Subgroup	Warfarin Events	Warfarin Total	ASA Events	ASA Total	Weight	Odds Ratio M-H, Random, 95% CI
Colli 2007	1	34	1	35	22.7%	1.03 [0.06, 17.16]
Rafiq 2017	4	104	3	105	77.3%	1.36 [0.30, 6.23]
Total (95% CI)		**138**		**140**	**100.0%**	**1.28 [0.33, 4.87]**
Total events	5		4			

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)

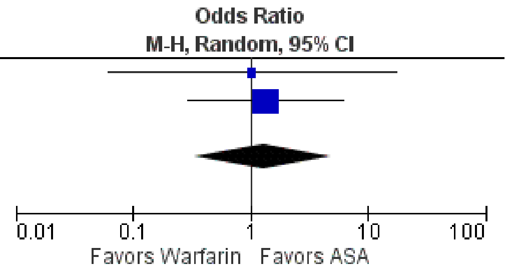
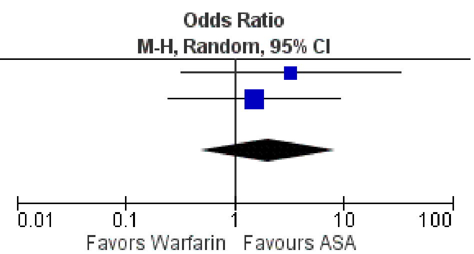


Figure 4. Major Bleeding Complications at 90 days in Trials that Compared Warfarin with ASA after Surgical bAVR

Study or Subgroup	Warfarin Events	Warfarin Total	ASA Events	ASA Total	Weight	Odds Ratio M-H, Random, 95% CI
Colli 2007	3	34	1	35	37.9%	3.29 [0.32, 33.31]
Rafiq 2017	3	104	2	105	62.1%	1.53 [0.25, 9.35]
Total (95% CI)		**138**		**140**	**100.0%**	**2.05 [0.49, 8.51]**
Total events	6		3			

Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.98 (P = 0.33)



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[5,11,12] and one RCT[3] 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%)[12] 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%).[5] 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.[3] 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.[5] 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. [25] 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.[11] 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.[12] 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; $P < .0001$).[5] 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.[12] 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
Randomized controlled trial (N=1)					
Rafiq, 2017[3] 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
Cohort studies (N=3)					
Al-Atassi, 2012[11] 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[5] 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[12] 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.[13] Another study found elevated risk of TE associated with warfarin after 4.2 years.[8] Only one study provided data on bleeding risk, and reported no difference between treatment groups.[4] 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.[8]

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[4] and 24 in another.[13] A third study included 74 patients treated with warfarin.[8] 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.[4] Another study found poorer long-term survival with warfarin compared with no treatment (67.9% vs 76.1% survival at 8 years, P = .03).[13]

TE risk did not significantly differ between warfarin and no treatment in one small study (N=18 patients on warfarin).[4] 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).[8] 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.[4]

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).[8] 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[4] 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[13] 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[8] 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,[4,8,12] mortality,[4] or hemorrhage.[4] 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.[8]

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).[4,8,12] These studies had fairly large samples of patients in the ASA arm, numbering 220,[8] 290,[4] and 912.[12] ASA dose and duration were reported in only study.[8]

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.[4]

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).[8] 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[4] 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[12] 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 3rd 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[8] 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).[14] 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).[14]

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),[16,17] intermediate (3-6 month),[15-17] and longer term (1 year)[18] 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 3rd general CoreValve Revalving System (Medtronic, Minneapolis, Minnesota).[17] 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).[16] 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.[16]

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).[15] 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).[15] 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).[15] 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.[15-17] 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.[15,17] 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).[18] 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).[18] 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).[19] 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).[20] 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) .[20] 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.[19] 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.[44] 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[16,17] and 2 cohort studies[19,45] 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[45] 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 CHADS2-VASc >1) or DAPT (*ie*, recent PCI).[15-17] 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.[19] 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.[21] Another cohort study compared warfarin monotherapy to direct oral anticoagulant (DOAC) monotherapy.[22]

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).[21] 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 or 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.[22] 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%, $p < 0.01$).[22] 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.[22] 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)
ASA vs DAPT: 3 trials						
Rodes-Cabau, 2017[15] 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[16] 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[17] 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.
ASA vs DAPT: 1 cohort study						
Ichibori, 2017[18] 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) **Prior PCI 14.1% vs 37.8% (P = .0018)** **CHF (NYHA III or IV): 47.4% vs 66.7% (P = .028)** CKD (EGFR, mL/min/1.73m2): 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			
Other treatment comparisons: 4 cohort studies						
Abdul-Jawad Altisent, 2016[21] 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[19] 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) **Age: 82.7 ± 6.3 vs 84.6±5.8 (P = .001)** **Male: 54.9% vs 39.1% (P = .007)** DM: 24.4% vs 23.4% (P > .05) **CAD: 50.0% vs 30.5% (P = .001)** **Prior Cardiac Surgery: 18.3% vs 7.8 (P = .01)** 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 **PAD: 17.1% vs 7.8% (P = .020)** 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 **Aspirin: 56.1% vs 35.9% (P = .001)** Clopidogrel: 7.9% vs 6.3% (P > .05) War: 28.0% vs 32.8% (P > .05) **ASA or Clop and War: 15.9% vs 5.5% (P = .005)**	NR	Methodologically sound but limited applicability: follow-up was only 30 days
Holy, 2017[20] 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) **Staged PCI 40.1% vs 28.3% (p < 0.01)** 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) **Atrial Fibrillation 10.5% vs 69.2% (p < 0.01)**	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) **BMI: 26.4 ± 4.9 vs 27.5 ± 4.8 (p < 0.01)**			
Seeger, 2017[22] Cohort N=617 12 m follow-up	TAVR SAPIEN (Edwards Lifesciences, Irvine, California) Boston Lotus (Boston Scientific, Marlborough, Massacusetts) CoreValve (Medtronic, Minneapolis, Minnesota) Evolute (Medtronic, Minneaspolis, 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:
ASA vs DAPT: 3 trials					
Rodes-Cabau, 2017[15] 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: **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 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[16] 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[17] 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)
ASA vs DAPT: 1 cohort study					
Ichibori, 2017[18] 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) **Unmatched, 1 year: 7.7% vs 21% (P = .019)** 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:
Other treatment comparisons: 4 cohort studies					
Abdul-Jawad Altisent, 2016[21] Cohort N=621 13 months	War monotherapy = 101 Multiple antithrombotic therapy (MAT) = 520 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 Dosage, mean duration: ASA 80 to 100 mg/d, 446 days Clopidogrel 75 mg/d, 407 days War: INR ≥2, 289 days MAT: 394 days 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.	War (n= 101) vs MAT (n = 520) All-cause: 22.8% vs 19.2% (P > .05) Cardiovascular: 9.9% vs 10.2% (P > .05) Adjusted HR (95% CI): 0.88 (0.54–1.44), P = .62	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	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	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
Durand, 2014[19] Cohort N=292 30 days	Strategy A =164 Strategy B = 128 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.	A (n = 164) vs B (n = 91) **Unmatched, 30 days: 13.4% vs 23.4% (P = .026)** A (n = 91) vs B (n = 91) Propensity Score Matched, 1 year: 8.8% vs 7.7% (P > .05)	A (n = 164) vs B (n = 128) Unmatched, at 30 days: Major Stroke: 0 vs 2.3% (P > .05) Minor Stroke: 0.6% vs 1.6% (P > .05) TIA: 0.6% vs 0.8% (P > .05) A (n = 91) vs B (n = 91) Propensity Score Matched, 30	A (n = 164) vs B (n = 128) **Unmatched, at 30 days: Bleeding complications (total): 8.5% vs 31.2% (p < 0.0001)** **Life-threatening bleeding: 3.7% vs 12.5% (P = .005)** **Major bleeding: 2.4% vs 13.3% (p < 0.0001)** Minor bleed: 2.4% vs 5.5%	A (n = 164) vs B (n = 128) Unmatched, at 30 days: **Vascular complications: 7.9% vs 19.5% (P = .003)** Acute Kidney Injury: 4.3% vs 9.4% (P > .05) A (n = 91) vs B (n = 91)

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:
	Strategy B was essentially DAPT with aspiring and clopidogrel; in patients with War the clopidogrel maintenance dose was excluded. 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		days: Major Stroke: 0 vs 1.1% (P > .05) Minor Stroke: 1.1% vs 1.1% (P > .05) TIA: 1.1% vs 0 (P > .05)	(P > .05) **Transfusions: 7.3% vs 25% (p < 0.0001)** A (n = 91) vs B (n = 91) Propensity Score Matched, at 30 days: **-Bleeding Complications (total): 9.9% vs 30.8% (P = .002)** **Life-threatening bleeding: 3.3% vs 14.3% (P = .021)** **Major bleeding: 2.2% vs 12.1% (P = .022)** Minor bleed: 4.4% vs 4.4% (P > .05) **Transfusions: 7.7% vs 25.3% (P = .005)**	Propensity Score Matched, at 30 days: Vascular Complications: 8.8% vs 18.7% (P > .05) Acute Kidney Injury: 2.2% vs 9.9% 9NS)
Holy, 2017[20] Cohort N=514 1 y follow-up	DAPT = 315 OAC = 199 OAC included 188 phenoprocoumon, 7 rivaroxaban, 4 dabigatran 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	DAPT (n = 315) vs OAC (n = 199) At 30 days: All-cause: 3.5% vs 3.5% (P > .05) Cardiovascular: 3.5% vs 2.5% (P > .05) At 6 months: All-cause: 7.9% vs 12.0% (P > .05) Cardiovascular: 5.0% vs 7.0% (P > .05) At 1 year: All-cause: 12.4% vs 17.6% (P > .05)	DAPT (n = 315) vs OAC (n = 199) At 30 days: -All Stroke: 3.8% vs 3.5% (P > .05) At 6 months: -All Stroke: 4.4% vs 4.0% (P > .05)	DAPT (n = 315) vs OAC (n = 199) At 30 days: Life-threatening bleeding: 7.3% vs 9.6% (P > .05) Major bleeding: 16.8% vs 15.1% (P > .05) At 6 months: Life-threatening bleeding: NR Major bleeding: 17.5% vs 16.5% (P > .05)	At 30 days: Myocardial Infarction: 0.9% vs 0.5% (P > .05) At 6 months: MI: 1.6% vs 0.5% (P > .05) At 1 year: Valve Thrombosis: 2.5% vs 0 (P = .02)
Seeger, 2017[22] Cohort N=617 12 m follow-up	War = 131 DOAC (apixaban) = 141 14/131 switched from War to apixaban. 5/141 switched from apixaban to War.	Apixaban (n = 141) vs War (n=131) At 30 days: All-cause: 1.4% vs 13.8% (P > .05) Cardiovascular: NR	Apixaban (n = 141) vs War (n=131) At 30 days: Disabling and Non-disabling Stroke: 2.1% vs 5.3% (P > .05)	Apixaban (n = 141) vs War (n=131) At 30 days: Life-threatening bleeding: 3.5% vs 5.3% (P < .01) Intracerebral bleeding: 0.7% vs 0 (P > .05)	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:
	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 (phenoprocuomon) & Apixaban were continued x lifelong. Apixaban (after November 2013; excluding valvular AF, severe liver dysfunction, or creatinine clearance <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.	Apixaban (n= 81) vs War (n = 50) At 12 months: All-cause: 22.4% vs 12.0% (P > .05) Cardiovascular: NR	Apixaban (n= 81) vs War (n = 50) At 12 months: Disabling and Non-disabling Stroke: 1.2% vs 2.0% (P > .05)	Major vascular complications: 3.5% vs 7.6% (P > .05) Authors report life-threatening bleeding and major vascular complications were independent of "triple therapy"	

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

	ASA		DAPT			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Rodes-Cabau 2017	3	111	6	111	59.8%	0.49 [0.12, 1.99]
Stabile 2014	2	60	1	60	20.2%	2.03 [0.18, 23.06]
Ussia 2011	2	39	1	40	20.0%	2.11 [0.18, 24.24]
Total (95% CI)		**210**		**211**	**100.0%**	**0.87 [0.29, 2.59]**
Total events	7		8			

Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)

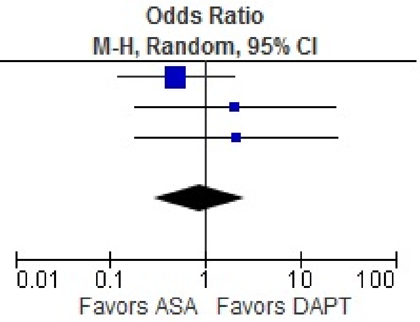


Figure 6. Risk of Mortality at 3-6 Months in Trials that Compared ASA vs DAPT after TAVR

	ASA		DAPT			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Rodes-Cabau 2017	4	109	7	110	41.7%	0.56 [0.16, 1.97]
Stabile 2014	3	60	3	60	24.5%	1.00 [0.19, 5.16]
Ussia 2011	5	39	4	40	33.9%	1.32 [0.33, 5.34]
Total (95% CI)		**208**		**210**	**100.0%**	**0.86 [0.38, 1.95]**
Total events	12		14			

Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.72)

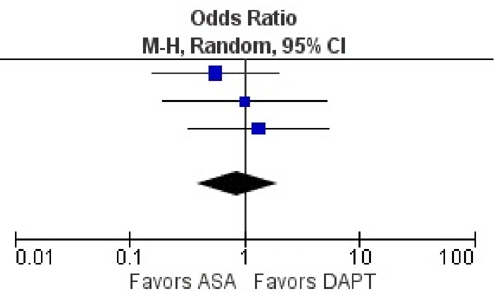


Figure 7. Risk of TE Events (Includes Major Stroke and MI) at 30 Days in Trials that Compared ASA vs DAPT after TAVR

	ASA		DAPT			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Rodes-Cabau 2017	2	111	7	111	55.9%	0.27 [0.06, 1.34]
Stabile 2014	1	60	1	60	19.2%	1.00 [0.06, 16.37]
Ussia 2011	2	39	1	40	24.9%	2.11 [0.18, 24.24]
Total (95% CI)		**210**		**211**	**100.0%**	**0.58 [0.17, 2.01]**
Total events	5		9			

Heterogeneity: Tau² = 0.05; Chi² = 2.08, df = 2 (P = 0.35); I² = 4%
Test for overall effect: Z = 0.86 (P = 0.39)

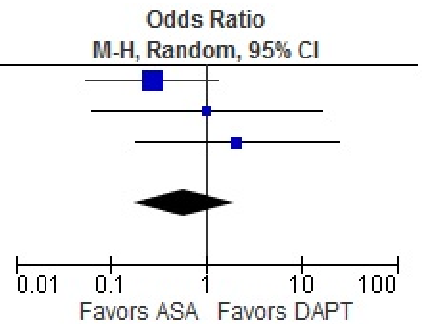


Figure 8. Risk of TE Events (Includes Major Stroke and MI) at 3-6 Months in Trials that Compared ASA vs DAPT after TAVR

	ASA		DAPT			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Rodes-Cabau 2017	2	109	7	110	61.2%	0.28 [0.06, 1.35]
Ussia 2011	2	39	2	40	38.8%	1.03 [0.14, 7.68]
Total (95% CI)		**148**		**150**	**100.0%**	**0.46 [0.13, 1.62]**
Total events	4		9			

Heterogeneity: Tau² = 0.01; Chi² = 1.02, df = 1 (P = 0.31); I² = 2%
Test for overall effect: Z = 1.21 (P = 0.23)

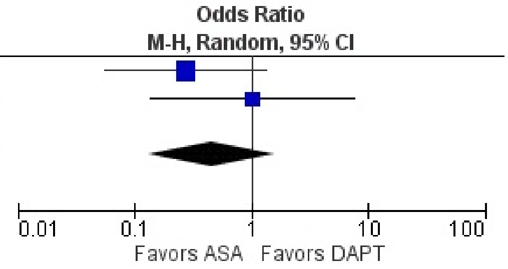


Figure 9. Risk of Major or Life-threatening Bleeding Events at 30 Days in Trials that Compared ASA vs DAPT after TAVR

	ASA		DAPT			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Rodes-Cabau 2017	4	111	12	111	44.2%	0.31 [0.10, 0.99]
Stabile 2014	3	60	4	60	28.3%	0.74 [0.16, 3.44]
Ussia 2011	4	39	3	40	27.5%	1.41 [0.29, 6.75]
Total (95% CI)		**210**		**211**	**100.0%**	**0.60 [0.24, 1.47]**
Total events	11		19			

Heterogeneity: Tau² = 0.12; Chi² = 2.46, df = 2 (P = 0.29); I² = 19%
Test for overall effect: Z = 1.12 (P = 0.26)

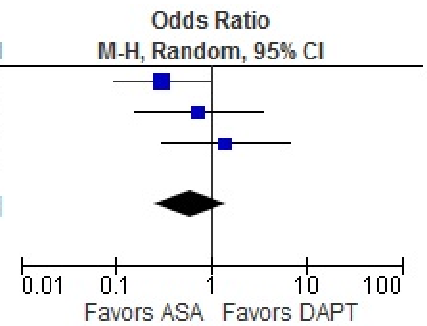
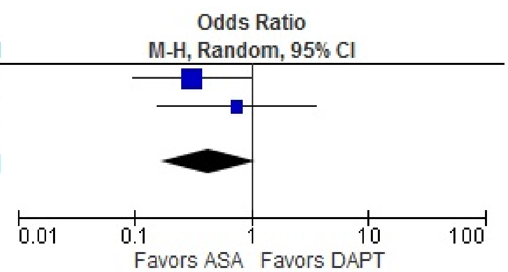


Figure 10. Risk of Major or Life-threatening Bleeding Events at 3-6 Months in Trials that Compared ASA vs DAPT after TAVR

	ASA		DAPT			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Rodes-Cabau 2017	4	109	12	110	64.4%	0.31 [0.10, 1.00]
Ussia 2011	3	39	4	40	35.6%	0.75 [0.16, 3.59]
Total (95% CI)		**148**		**150**	**100.0%**	**0.43 [0.17, 1.08]**
Total events	7		16			

Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 1.79 (P = 0.07)



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[46] 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[5] 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).[25] In 2017, the AHA/ACC released a focused update of the 2014 AHA/ACC guidelines for management of patients with valvular heart disease.[30,31] 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 changed was based were excluded from our review for either methodologic reasons[47] or because of a focus on imaging as opposed to clinical outcomes[48] 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 bioprothesis (Class IIb, level of evidence C).[32]

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.[31] 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.[30] 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).[30] 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.[49] The Canadian Cardiovascular Society statement on TAVR recommend the use of aspirin indefinitely and clopidogrel for 1 to 3 months.[50]

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%).[51-53] Across 6 large cohort studies (N = 461 to 1594), the mean 5-year bleeding rate was 3.8% (range 1.4-6.2%).[51-56] 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	BAVR	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	TAVR	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	TAVR	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 (Euroquol EQ5) at 1, 3, and 6 months
AVATAR (NCT02735902)	Randomized (post-TAVR)	170	TAVR	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	TAVR	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	TAVR	Rivaroxaban 10 mg/day þ 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: TAVR patients with no indication for OAC Group B: TAVR patients with indication for OAC	1,000	TAVR	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 þ 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.govPE = 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; TAVR = 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
Surgical BAVR				
Warfarin vs ASA				
• Mortality	3 RCTs[1-3] (N=355) 5 cohorts[2,4-7] (N=17,331)	No difference. Best evidence from 2 studies, at 3 months: ▪ 1 low-ROB RCT[3] (N=236): 3.8% vs 2.9%, P = .721 ▪ 1 large cohort study[5] (N=15,456): 4.0% vs 3.0%, P > .05	Moderate	Small RCTs, likely underpowered, but results are consistent with one large, well-conducted cohort study
• TE events	3 RCTs[1-3] (N=355) 8 cohorts[2,4-10] (N=18,506)	No difference. Best evidence from 2 studies, at 3 months: ▪ 1 low-ROB RCT[3] (N=236): 3.8% vs 2.9%, P = .721 ▪ 1 large cohort study[5] (N=15,456): 1.0% vs 1.0%, P > .05	Moderate	
• Major bleeding	3 RCTs[1-3] (N=355) 7 cohorts[2,4-7,9,10] (N=18,212)	No difference. Best evidence from 2 studies, at 3 months: ▪ 1 low-ROB RCT[3] (N=236): 2.9% vs 1.9%, P = .683 ▪ 1 large cohort study[5] (N=15,456): 1.0% vs 1.4%, P > .05	Moderate	
Warfarin + ASA vs ASA				
• Mortality	1 RCT[3] (N=119) 2 cohorts[5,11] (N=18,485)	Best evidence from 1 large cohort[5] 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[3] (N=119) 4 cohorts[3,5,11,12] (N=19,551)	Best evidence from 1 large cohort[5] RR (95% CI): 0.52 (0.35 to 0.76), NNT 212	Low	
• Major bleeding	1 RCT[3] (N=135) 1 cohort[5] (N=18,429)	Best evidence from 1 large cohort[5] RR (95% CI): 2.80 (2.18 to 3.60), NNH 55	Low	
Warfarin + ASA vs Warfarin	0 studies	---	Insufficient	No evidence currently available.
Warfarin vs no treatment				
• Mortality	2 cohorts[4,13] (N=210)	Short-term: no differences at 3 months[4] Long-term: poorer survival with warfarin: 67.9% vs 76.1% at 8 years (P = .03)[13]	Insufficient	Evidence from smaller retrospective studies. INR generally not reported
• TE events	2 cohorts[4,8](N=347)	Elevated TE risk with warfarin in one study with 4.2 years follow-up.[8] 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[4](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
ASA vs no treatment				
• Mortality	1 cohort[4] (N=360)	No difference.	Insufficient	ASA dose and duration were reported in only study
• TE events	3 cohorts[4,8,12] (N=1983)	No difference.	Insufficient	
• Major bleeding	1 cohort[4] (N=360)	No difference.	Insufficient	
Triflusal v. Acenocoumarol				
• Mortality	1 RCT[14] (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[14] (N=200)	No difference. TE at 3 months: 6.3% vs 3.2%, P = .50	Insufficient	
• Major bleeding	1 RCT[14] (N=200)	Risk of bleeding lower with triflusal: 3% vs 10%, P = .048	Insufficient	
TAVR:				
ASA vs DAPT				
• Mortality	3 RCTs[15-17] (N=421) 1 cohort[18] (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[15-17] (N=421) 1 cohort[18] (N=144)	No difference. Combined estimate (95% CI) at 3-6 months from meta-analysis of 2 trials,[15,17] ASA vs DAPT: 0.46 (0.13 to 1.62)	Moderate	
• Major bleeding	3 RCTs[15-17] (N=421) 1 cohort[18] (N=144)	Marginally significant increased risk with DAPT vs ASA in one trial[15] (N=222): 10.9% vs 3.6%, P = .038 Combined estimate (95% CI) at 3-6 months from meta-analysis of 2 trials,[15,17] ASA vs DAPT: 0.43 (0.17 to 1.08)	Moderate	
APT vs APT + OAC				
• Mortality	2 cohorts[19,20] (N=806)	No difference.	Insufficient	Treatment arms contain a mix of antithrombotic regimens.
• TE events	2 cohorts[19,20] (N=806)	No difference.	Insufficient	
• Major bleeding	2 cohorts[19,20] (N=806)	No difference at 1 year for DAPT (N=315) vs OAC (N=199, includes 188 warfarin, 7 rivaroxaban, and 4 dabigatran)[20] More bleeding complications at 30 days with DAPT (ASA+clopidogrel) vs SAPT (adding/maintaining ASA or maintaining clopidogrel), propensity score-matched (N=182)[19]: 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
Warfarin monotherapy vs Warfarin + APT				
• Mortality	1 cohort[21] (N=621)	No difference.	Insufficient	Evidence is from one study.
• TE events	1 cohort[21] (N=621)	No difference.	Insufficient	
• Major bleeding	1 cohort[21] (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	
Warfarin vs DOAC (apixaban):				
• Mortality	1 cohort[22] (N=272)	No difference.	Insufficient	Evidence is from one study.
• TE events	1 cohort[22] (N=272)	No difference.	Insufficient	
• Major bleeding	1 cohort[22] (N=272)	No difference.	Insufficient	

[a] 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:[41]

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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APPENDIX A. SEARCH STRATEGIES

DATABASES/WEBSITES:
Ovid Medline 1946 to June 19, 2017
PubMed (non-Medline materials) January 9, 2017
Elsevier EMBASE February 1, 2017
EBM Reviews (CDSR, DARE, HTA, Cochrane CENTRAL, etc.) January 24, 2017
Clinicaltrials.gov January 24, 2017
RoPR (Registry of Patient Registries January 24, 2017

SEARCH STRATEGIES

Updated search strategy – 9Jan2017, after adding "placement" based on Stevenson editorial:

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date Searched: January 9, 2017
Searched by: Robin Paynter, MLIS

1	Heart Valve Prosthesis/ or Heart Valve Prosthesis Implantation/ or Transcatheter Aortic Valve Replacement/ or (((aort* or valve*) adj3 (implant* or replac* or graft*)) or AVR or AVRs or mini-AVR* or "surgical AVR*" or SAVR or SAVRs or "bioprosthe* AVR*" or "bio-prosthe* AVR*" or "biologic* AVR*" or bAVR* or TAVI* or TAVR* or PAVR* or ((transcatheter* or trans-catheter* or transfemoral* or trans-femoral* or transapical* or trans-apical* or transaxillar* or trans-axillar* or transvascular* or trans-vascular* or percutaneous* or bioprosthet* or bio-prosthet* or biologic*) adj3 (implant* or placement* or replac* or graft*))).tw,kf.	80730
2	aortic valve/ or (aort* or answer or "Anticoagulation Treatment Influence on Postoperative Patients" or action).tw,kf.	998641
3	bioprosthesis/ or (bioprosthe* or bio-prosthe* or ((biologic* or tissue* or prosthe*) adj3 (aort* or valv* or graft*)) or bovine* or porcine* or equine* or xenograft* or xenogen* or heterograft* or xenobioprosthe* or 3F* or ACURATE-TA* or Biocor* or Carpentier-Edwards* or COLIBRI* or CoreValve* or Crown PRT* or DOKIMOS* or Engager* or EPIC* or Freestyle* or FS or HANCOCK* or INSPIRIS* or J-Valve* or JENAVALVE* or MITROFLOW* or MOSAIC* or MYVAL* or Perceval* or Perimount* or Sapien* or SOLO or TLPB* or TRIFECTA*).tw,kf.	512785
4	exp Anticoagulants/ or exp Platelet Aggregation Inhibitors/ or exp Antithrombins/	322966
5	(anti-coagul* or anticoag* or antiplatelet* or antiplatelet* or (platelet* adj2 (aggregat* or anti-aggregat* or antiaggregat* or inhibit*)) or anti-thromb* or antithromb* or NOAC* or ((new or novel) adj3 (anti-coagul* or anticoagul*)) or DOAC* or "direct oral anti-coagul*" or "direct oral anticoagul*" or AVK or AVKs or "anti-vitamin k" or "antivitamin k" or VKA or VKAs or "vitamin k antagonist*" or coumarin* or acenocoumarol* or phenprocoumon* or fluindione*).tw,kf.	174660
6	4-hydroxycoumarins/ or acenocoumarol/ or dicumarol/ or ethyl biscoumacetate/ or phenprocoumon/	5484
7	warfarin/ or (warfarin* or Coumadin*).tw,kf.	28607
8	Thienopyridines/ or (Clopidogrel* or Plavix*).tw,kf.	11380
9	(Ticagrelor* or Brilinta*).tw,kf.	1519
10	Ticlopidine/ or (ticlopidine* or Ticlid* or prasugrel* or cangrelor*).tw,kf.	12168
11	Dipyridamole/ or (dipyridamole* or Persantine*).tw,kf.	11573
12	Aspirin, Dipyridamole Drug Combination/ or ((aspirin* adj2 dipyridamole) or Aggrenox*).tw,kf.	969
13	(Edoxaban* or Savaysa* or Lixiana*).tw,kf.	814
14	(Apixaban* or Eliquis*).tw,kf.	1906

15	Dabigatran/ or (dabigatran* or Pradaxa*).tw,kf.	3910
16	Rivaroxaban/ or (Rivaroxaban* or Xarelto*).tw,kf.	3457
17	Aspirin/ or ("acetylsalicylic acid" or "acetyl salicylic acid" or aspirin*).tw,kf.	69828
18	and/1-3	15004
19	or/4-17	434099
20	18 and 19	1740
21	limit 20 to english language	1480
22	limit 21 to animals	165
23	limit 22 to humans	93
24	22 not 23	72
25	21 not 24	1408
26	remove duplicates from 25	1317

EBM Reviews: (Cochrane trials, SRs; HTA; NHS econ)
Cochrane Central Register of Controlled Trials November 2016,
Cochrane Database of Systematic Reviews 2005 to January 18, 2017,
Health Technology Assessment 4th Quarter 2016,
NHS Economic Evaluation Database 1st Quarter 2015
Date Searched: January 24, 2017
Searched by: Robin Paynter, MLIS

1	Heart Valve Prosthesis/ or Heart Valve Prosthesis Implantation/ or Transcatheter Aortic Valve Replacement/ or (((aort* or valve*) adj3 (implant* or replac* or graft*)) or AVR or AVRs or mini-AVR* or "surgical AVR*" or SAVR or SAVRs or "bioprosthe* AVR*" or "bio-prosthe* AVR*" or "biologic* AVR*" or bAVR* or TAVI* or TAVR* or PAVR* or ((transcatheter* or trans-catheter* or transfemoral* or trans-femoral* or transapical* or trans-apical* or transaxillar* or trans-axillar* or transvascular* or trans-vascular* or percutaneous* or bioprosthet* or bio-prosthet* or biologic*) adj3 (implant* or placement* or replac* or graft*))).tw,kf.	3064
2	aortic valve/ or (aort* or answer or "Anticoagulation Treatment Influence on Postoperative Patients" or action).tw,kf.	33128
3	bioprosthesis/ or (bioprosthe* or bio-prosthe* or ((biologic* or tissue* or prosthe*) adj3 (aort* or valv* or graft*)) or bovine* or porcine* or equine* or xenograft* or xenogen* or heterograft* or xenobioprosthe* or 3F* or ACURATE-TA* or Biocor* or Carpentier-Edwards* or COLIBRI* or CoreValve* or Crown PRT* or Cryo-Life O'Brien or DOKIMOS* or Engager* or EPIC* or Freestyle* or FS or HANCOCK* or INSPIRIS* or Ionescu-Shiley* or J-Valve* or JENAVALVE* or MITROFLOW* or MOSAIC* or MYVAL* or Perceval* or Perimount* or Sapien* or SOLO or TexMi* or TLPB* or TRIFECTA* or Xenomedica*).tw,kf.	7797
4	exp Anticoagulants/ or exp Platelet Aggregation Inhibitors/ or exp Antithrombins/	16171
5	(anti-coagul* or anticoag* or antiplatelet* or antiplatelet* or (platelet* adj2 (aggregat* or anti-aggregat* or antiaggregat* or inhibit*)) or anti-thromb* or antithromb* or NOAC* or ((new or novel) adj3 (anti-coagul* or anticoagul*)) or DOAC* or "direct oral anti-coagul*" or "direct oral anticoagul*" or AVK or AVKs or "anti-vitamin k" or "antivitamin k" or VKA or VKAs or "vitamin k antagonist*" or coumarin* or acenocoumarol* or phenprocoumon* or fluindione*).tw,kf.	13560
6	4-hydroxycoumarins/ or acenocoumarol/ or dicumarol/ or ethyl biscoumacetate/ or phenprocoumon/	210
7	warfarin/ or (warfarin* or Coumadin*).tw,kf.	2850
8	Thienopyridines/ or (Clopidogrel* or Plavix*).tw,kf.	2334

9	(Ticagrelor* or Brilinta*).tw,kf.	387
10	Ticlopidine/ or (ticlopidine* or Ticlid* or prasugrel* or cangrelor*).tw,kf.	2003
11	Dipyridamole/ or (dipyridamole* or Persantine*).tw,kf.	1106
12	Aspirin, Dipyridamole Drug Combination/ or ((aspirin* adj2 dipyridamole) or Aggrenox*).tw,kf.	299
13	(Edoxaban* or Savaysa* or Lixiana*).tw,kf.	146
14	(Apixaban* or Eliquis*).tw,kf.	302
15	Dabigatran/ or (dabigatran* or Pradaxa*).tw,kf.	404
16	Rivaroxaban/ or (Rivaroxaban* or Xarelto*).tw,kf.	519
17	Aspirin/ or ("acetylsalicylic acid" or "acetyl salicylic acid" or aspirin*).tw,kf.	9850
18	and/1-3	509
19	or/4-17	28997
20	18 and 19	79

ESP SEARCHES: BAVR AND ANTICOAGULATION: CLINICALTRIALS.GOV SEARCH RESULTS

ClinicalTrials.gov
Date Searched: January 24, 2017
Searched by: Robin Paynter, MLIS

Search #1:	
bioprosthetic OR bio-prosthetic OR bovine OR porcine OR equine OR xenograft OR heterograft OR xenobioprosthetic | aortic OR heart OR valve OR valvular | anticoagulation OR antiplatelet OR antithromb OR antiaggregation OR VKA OR coumarin OR warfarin OR NOAC OR DOAC OR Clopidogrel OR Ticagrelor OR ticlopidine OR prasugrel OR dipyridamole OR Edoxaban OR Apixaban OR dabigatran OR Rivaroxaban	8 studies found

Search #2	
3F OR ACURATE-TA OR BiocOR OR Carpentier-Edwards OR COLIBRI OR COReValve OR Crown PRT OR Cryo-Life O'Brien OR DOKIMOS OR Engager OR EPIC OR Freestyle OR FS OR HANCOCK OR INSPIRIS OR Ionescu-Shiley OR J-Valve OR JENAVALVE OR MITROFLOW OR MOSAIC | aortic OR heart OR valve OR valvular	128 studies found

Search #3	
MYVAL OR Perceval OR Perimount OR Sapien OR SOLO OR TexMi OR TLPB OR TRIFECTA OR Xenomedica | aortic OR heart OR valve OR valvular	78 studies found

ESP SEARCHES: BAVR + ANTICOAGULATION: REGISTRY OF PATIENT REGISTRIES

RoPR (Registry of Patient Registries, https://patientregistry.ahrq.gov/search)
Date Searched: January 24, 2017
Searched by: Robin Paynter, MLIS

Search terms: bioprosthetic AND aortic
EMBASE.COM

Date Searched: February 1, 2017
Searched by: Robin Paynter, MLIS

1	'aorta valve prosthesis'/exp OR 'aorta valve replacement'/exp OR ((aort* OR valve*) NEAR/3 (implant* OR replac* OR graft*)):ab,ti OR avr:ab,ti OR avrs:ab,ti OR 'mini avr*':ab,ti OR 'surgical avr*':ab,ti OR savr:ab,ti OR savrs:ab,ti OR 'bioprosthe* avr*':ab,ti OR 'bio-prosthe* avr*':ab,ti OR 'biologic* avr*':ab,ti OR bAVR*:ab,ti OR tavi*:ab,ti OR tavr*:ab,ti OR pavr*:ab,ti OR ((transcatheter* OR 'trans catheter*' OR transfemoral* OR 'trans femoral*' OR transapical* OR 'trans apical*' OR transaxillar* OR 'trans axillar*' OR transvascular* OR 'trans vascular*' OR percutaneous* OR bioprosthet* OR 'bio prosthet*' OR biologic*) NEAR/3 (implant* OR replac* OR graft*)):ab,ti	78,179
2	'aorta valve'/exp OR aort*:ab,ti OR answer:ab,ti OR 'anticoagulation treatment influence on postoperative patients':ab,ti OR action:ab,ti	1,085,625
3	'bioprosthesis'/exp OR 'heart valve bioprosthesis'/exp OR 'carpentier edwards bioprosthesis'/exp OR 'hancock valve prosthesis'/exp OR 'mosaic bioprosthesis'/exp OR 'percutaneous aortic valve'/exp OR (bioprosthe*:ab,ti OR 'bio prosthe*':ab,ti OR ((biologic* OR tissue* OR prosthe*) NEAR/3 (aort* OR valv* OR graft*)):ab,ti OR bovine*:ab,ti OR porcine*:ab,ti OR equine*:ab,ti OR xenograft*:ab,ti OR xenogen*:ab,ti OR heterograft*:ab,ti OR xenobioprosthe*:ab,ti OR 3f*:ab,ti OR 'acurate ta*':ab,ti OR biocor*:ab,ti OR 'carpentier edwards*':ab,ti OR colibri*:ab,ti OR corevalve*:ab,ti OR crown:ab,ti AND prt*:ab,ti) OR dokimos*:ab,ti OR engager*:ab,ti OR epic*:ab,ti OR freestyle*:ab,ti OR fs:ab,ti OR hancock*:ab,ti OR inspiris*:ab,ti OR 'j valve*':ab,ti OR jenavalve*:ab,ti OR mitroflow*:ab,ti OR mosaic*:ab,ti OR myval*:ab,ti OR perceval*:ab,ti OR perimount*:ab,ti OR sapien*:ab,ti OR solo:ab,ti OR tlpb*:ab,ti OR trifecta*:ab,ti	128,669
4	'anticoagulant agent'/exp OR 'antithrombocytic agent'/exp OR 'blood clotting inhibitor'/exp	572,738
5	'anti coagul*':ab,ti OR anticoagul*:ab,ti OR 'anti platelet*':ab,ti OR antiplatelet*:ab,ti OR (platelet* NEAR/2 (aggregat* OR 'anti aggregat*' OR antiaggregat* OR inhibit*)):ab,ti OR 'anti thromb*':ab,ti OR antithromb*:ab,ti OR noac*:ab,ti OR ((new OR novel) NEAR/3 ('anti coagul*' OR anticoagul*)):ab,ti OR doac*:ab,ti OR 'direct oral anti-coagul*':ab,ti OR 'direct oral anticoagul*':ab,ti OR avk:ab,ti OR avks:ab,ti OR 'anti-vitamin k':ab,ti OR 'antivitamin k':ab,ti OR vka:ab,ti OR vkas:ab,ti OR 'vitamin k antagonist*':ab,ti OR coumarin*:ab,ti OR acenocoumarol*:ab,ti OR phenprocoumon*:ab,ti OR fluindione*:ab,ti	222,158
6	'coumarin derivative'/exp OR '4 hydroxycoumarin'/exp OR 'acenocoumarol'/exp OR 'dicoumarol'/exp OR'ethyl biscoumacetate'/exp OR 'phenprocoumon'/exp	111,728
7	'warfarin'/exp OR warfarin*:ab,ti OR coumadin*:ab,ti	79,840
8	'thienopyridine derivative'/exp OR clopidogrel*:ab,ti OR plavix*:ab,ti	20,571
9	'ticagrelor'/exp OR ticagrelor*:ab,ti OR brilinta*:ab,ti	4,835
10	'ticlopidine'/exp OR ticlopidine*:ab,ti OR ticlid*:ab,ti OR prasugrel*:ab,ti OR cangrelor*:ab,ti	16,536
11	'dipyridamole'/exp OR dipyridamole*:ab,ti OR persantine*:ab,ti	23,918
12	'acetylsalicylic acid plus dipyridamole'/exp OR (aspirin* NEAR/2 dipyridamole):ab,ti OR aggrenox*:ab,ti	1,837
13	'edoxaban'/exp OR edoxaban*:ab,ti OR savaysa*:ab,ti OR lixiana*:ab,ti	2,104
14	'apixaban'/exp OR apixaban*:ab,ti OR eliquis*:ab,ti	5,957
15	'dabigatran'/exp OR dabigatran*:ab,ti OR pradaxa*:ab,ti	9,218
16	'rivaroxaban'/exp OR rivaroxaban*:ab,ti OR xarelto*:ab,ti	9,238
17	'acetylsalicylic acid'/exp OR 'acetylsalicylic acid':ab,ti OR 'acetyl salicylic acid':ab,ti OR aspirin*:ab,ti	192,267
18	#1 AND #2 AND #3	9,238
19	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	674,206
20	#18 AND #19	810
21	#20 AND [English]/lim	735

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date Searched: June 19, 2017

Searched by: Robin Paynter, MLIS

1	Heart Valve Prosthesis/ or Heart Valve Prosthesis Implantation/ or Transcatheter Aortic Valve Replacement/ or (((aort* or valve*) adj3 (implant* or replac* or graft*)) or AVR or AVRs or mini-AVR* or "surgical AVR*" or SAVR or SAVRs or "bioprosthe* AVR*" or "bio-prosthe* AVR*" or "biologic* AVR*" or bAVR* or TAVI* or TAVR* or PAVR* or ((transcatheter* or trans-catheter* or transfemoral* or trans-femoral* or transapical* or trans-apical* or transaxillar* or trans-axillar* or transvascular* or trans-vascular* or percutaneous* or bioprosthet* or bio-prosthet* or biologic*) adj3 (implant* or placement* or replac* or graft*))).tw,kf.	77787
2	aortic valve/ or (aort* or answer or "Anticoagulation Treatment Influence on Postoperative Patients" or action).tw,kf.	925458
3	bioprosthesis/ or (bioprosthe* or bio-prosthe* or ((biologic* or tissue* or prosthe*) adj3 (aort* or valv* or graft*)) or bovine* or porcine* or equine* or xenograft* or xenogen* or heterograft* or xenobioprosthe* or 3F* or ACURATE-TA* or Biocor* or Carpentier-Edwards* or COLIBRI* or CoreValve* or Crown PRT* or Cryo-Life O'Brien or DOKIMOS* or Engager* or EPIC* or Freestyle* or FS or HANCOCK* or INSPIRIS* or Ionescu-Shiley* or J-Valve* or JENAVALVE* or MITROFLOW* or MOSAIC* or MYVAL* or Perceval* or Perimount* or Sapien* or SOLO or TexMi* or TLPB* or TRIFECTA* or Xenomedica*).tw,kf.	476257
4	exp Anticoagulants/ or exp Platelet Aggregation Inhibitors/ or exp Antithrombins/	292022
5	(anti-coagul* or anticoag* or antiplatelet* or antiplatelet* or (platelet* adj2 (aggregat* or anti-aggregat* or antiaggregat* or inhibit*)) or anti-thromb* or antithromb* or NOAC* or ((new or novel) adj3 (anti-coagul* or anticoagul*)) or DOAC* or "direct oral anti-coagul*" or "direct oral anticoagul*" or AVK or AVKs or "anti-vitamin k" or "antivitamin k" or VKA or VKAs or "vitamin k antagonist*" or coumarin* or acenocoumarol* or phenprocoumon* or fluindione*).tw,kf.	167816
6	4-hydroxycoumarins/ or acenocoumarol/ or dicumarol/ or ethyl biscoumacetate/ or phenprocoumon/	5251
7	warfarin/ or (warfarin* or Coumadin*).tw,kf.	27383
8	Thienopyridines/ or (Clopidogrel* or Plavix*).tw,kf.	11048
9	(Ticagrelor* or Brilinta*).tw,kf.	1580
10	Ticlopidine/ or (ticlopidine* or Ticlid* or prasugrel* or cangrelor*).tw,kf.	11737
11	Dipyridamole/ or (dipyridamole* or Persantine*).tw,kf.	10369
12	Aspirin, Dipyridamole Drug Combination/ or ((aspirin* adj2 dipyridamole) or Aggrenox*).tw,kf.	881
13	(Edoxaban* or Savaysa* or Lixiana*).tw,kf.	814
14	(Apixaban* or Eliquis*).tw,kf.	1993
15	Dabigatran/ or (dabigatran* or Pradaxa*).tw,kf.	3964
16	Rivaroxaban/ or (Rivaroxaban* or Xarelto*).tw,kf.	3563
17	Aspirin/ or ("acetylsalicylic acid" or "acetyl salicylic acid" or aspirin*).tw,kf.	65868
18	and/1-3	14497
19	or/4-17	398605
20	18 and 19	1692
21	limit 20 to english language	1432
22	limit 21 to animals	154
23	limit 22 to humans	90
24	22 not 23	64

25	21 not 24	1368
26	remove duplicates from 25	1347
27	Heart Valve Prosthesis/ or Heart Valve Prosthesis Implantation/ or Transcatheter Aortic Valve Replacement/ or (((aort* or valve*) adj3 (implant* or replac* or graft* or repair*)) or "bioprosthe* AVR*" or "bio-prosthe* AVR*" or "biologic* AVR*" or bAVR* or TAVI* or TAVR* or PAVR* or ((transcatheter* or trans-catheter* or transfemoral* or trans-femoral* or transapical* or trans-apical* or transaxillar* or trans-axillar* or transvascular* or trans-vascular* or percutaneous* or bioprosthet* or bio-prosthet* or biologic*) adj3 (implant* or placement* or replac* or graft* or repair*))).tw,kf.	90097
28	2 and 27	53970
29	19 and 28	3275
30	limit 29 to english language	2815
31	limit 30 to animals	241
32	limit 31 to humans	115
33	31 not 32	126
34	30 not 33	2689
35	remove duplicates from 34	2622
36	35 not 26	1277
37	from 36 keep 1-1277	1277

APPENDIX B. STUDY SELECTION

INCLUSION CODES, CODE DEFINITIONS, AND CRITERIA

Does the population include non-pregnant adults who have had bioprosthetic aortic valve replacement, which may include transcatheter **aortic** valve implantation?

Exclusions: patients with valve replacement in areas other than/in addition to aortic (*eg*, mitral valve); Ross procedure; Bentall procedure; and aortic root repair.

Exclude: studies that do not report outcomes of interest for patients who underwent isolated aortic valve replacement (*eg* mixed mitral & aortic population).

Yes → Proceed to 2.

No → STOP. **Code X1** (Excluded population)

For reference, below is a list of bioprosthetic and mechanical valves. Please note any other valves occurring in the literature that should be added to the list.

BIOPROSTHETIC VALVES
3F (Medtronic)
ACURATE-TA
Biocor
Carpentier-Edwards
COLIBRI
CoreValve (Medtronic)
Crown PRT
Cryo-Life O'Brien Stentless
DOKIMOS
Edwards-Sapien XT
Engager
EPIC (St. Jude Medical)
EVOLUTE-R™ (MCV)
Freestyle (Medtronic)
FS
Hancock, Hancock II (Medtronic)
INSPIRIS
Ionescu-Shiley
JENAVALVE
J-Valve
LOTUS (Boston)
Mitroflow (Sorin)
MOSAIC (Medtronic)
MYVAL
Perceval
Perimount/Perimount Magna (Carpentier-Edwards)
Sapien (Edwards)
SAPIEN 3
SOLO
SORIN Freedom SOLO
TexMi
TLPB
TRIFECTA (St. Jude)
Xenomedica
Zorin

MECHANICAL VALVES
ATS
Beall
Bicarbon
Bjork
Bjork-Shiley/Delrin
Bjork-Shiley/Integral Monostrut
Braunwald-Cutter
CarboMedics bileaflet
Chitra tilting disc valve
Cross–Jones
DeBakey–Surgitool
Edwards MIRA
Edwards-Duromedics
Edwards-Tekna
Harken
Hufnagel–Lucite
Kay-Sheiley
Lillehei-Kaster
Magovern–Cromie
Medtronic-Hall
Monostrut (Sorin)
Omnicarbon
Omniscience
On-X
Smeloff-Cutter
Sorin Bicarbon
Sorin tilting-disc
St. Jude Medical (SJM)

Star-GK
Starr
Starr-Edwards
Ultracor

Wada-Cutter

Is the intervention an anticoagulant, antiplatelet, antithrombotic, or direct oral anticoagulant (DOAC) agent, used alone or in combination? We are interested only in post-procedure anticoagulation strategies, rather than strategies used before or during surgery (*eg*, heparin use intraoperatively).

Yes → Proceed to 3.

No → STOP. **Code X2** (Not relevant to topic)

Note: If the study doesn't compare with appropriate control intervention, go to Q4

Is the article any of the following study designs or publication types:

- Randomized controlled trial
- Non-randomized controlled trial

Case-control or cohort study that adequately controls for important confounders. Cohort studies would include registry studies with comparative analyses.

Yes → Proceed to 4.

No → STOP. **Code X3** (Excluded study design or publication type)

X3 examples: Narrative or non-systematic review; opinion/editorial; cross-sectional study; case report; non-consecutive case series; or consecutive case series with fewer than 500 subjects.

Note: Systematic reviews, meta-analyses, large (N ≥500) non-comparative registry studies, large (N ≥500) consecutive case series, and any other important background/discussion papers should be coded **B-X3**, with notes/keywords**.**

Examples:

B-X3 – consecutive case series, N>1000

B-X3 – non-comparative registry study, N>4000

B-X3 – SR, pearl references

B-X3 – narrative review with good background

Is the intervention compared with no therapy or with another anticoagulant, antiplatelet, antithrombotic, or direct oral anticoagulant (DOAC) agent, used alone or in combination?

Yes → Proceed to 5.

No → STOP. **Code X4** (Comparator agent not in scope)

Are any of the following outcomes reported:

- Mortality
- Thromboembolic events
- Stroke
- Myocardial infarction
- Heart failure
- Readmission rates
- Need for valve reoperation (*eg*, valve thrombosis)
- Length of stay
- Need for change in antithrombotic strategy
- Major bleeding events
  - GI bleeds
  - Intracranial hemorrhage
  - Other (*eg*, retroperitoneal)
- Other/minor bleeding
- Readmission rates
- Pericardial or pleural effusion (requiring intervention where specified, rather than detected solely by imaging)

Excluded outcomes:

Imaging findings (including echocardiogram, CT, MRI); pleural effusions seen on X-ray but not requiring intervention

Low platelet count (thrombocytopenia)

Lab abnormalities not requiring intervention values in general (high INR, or anemia)

Subclinical thrombosis

Vascular complications, *eg*, AV fistula, local thrombosis, vascular dissection, vascular perforation, access-site hematoma, aortic dissection, left ventricle perforation, other peri-procedural complications

Atrial fibrillation

Yes → STOP. **Code I** (Include: study contains primary data addressing one or more KQs)

No → STOP. **Code X5** (No outcomes of interest)

APPENDIX C. QUALITY ASSESSMENT CRITERIA AND TABLES

Domain	Criteria
Trials: Cochrane Risk of Bias assessment[38]	
Sequence generation	Was the allocation sequence adequately generated?
Allocation concealment	Was allocation adequately concealed?
Blinding	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data	Were incomplete outcome data adequately addressed? Consider attrition, intention-to-treat analysis.
Selective outcome reporting	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	Was the study apparently free of other problems that could put it at a high risk of bias?
Overall assessment of potential for bias	Low/Unclear/High
Observational studies: criteria based on the Newcastle-Ottawa scale[39]	
Representativeness of the exposed cohort	Enter 0 or 1: 1 = truly representative of the average patient in the community 1 = somewhat representative of the average patient in the community 0 = selected group of users (eg, nurses, volunteers) 0 = no description of the derivation of the cohort
Selection of the non-exposed cohort	Enter 0 or 1: 1 = drawn from the same community as the exposed cohort 0 = drawn from a different source 0 = no description of the derivation of the non-exposed cohort
Ascertainment of exposure	Enter 0 or 1: 1 = secure record (*eg* surgical records; chart review; database) 0 = no description
Precision of Exposure Dose Ascertainment	Enter 0 or 1: 1 = both criteria satisfied for warfarin & aspirin: For warfarin, they reported duration of exposure and some measure of achieved INR or % time in range (dose of warfarin not meaningful). For aspirin, need to specify range of dose, as well as duration. 1 = amount and duration of exposure, other drugs studied (INR not needed) – applies to DOACS. 0 = if exposure category is simply “warfarin” or “aspirin” with duration noted, but without dose. 0 = no information about amount and time.
Demonstration that outcome of interest was not present at start of study, or baseline assessment	Enter 0 or 1: 1= yes 0 = no *Note: we are prioritizing symptomatic outcomes; MRI outcomes found 6 months later might be problematic (stroke present at baseline) but not applicable to our outcomes of interest.*
Adjustment for confounding (rendering comparability of cohorts on the basis of the design or analysis)	Enter 0 or 1: 1 = study accounts/controls for key factors (age, sex, atrial fibrillation; other cardiovascular risk factors; previous thromboembolic event) 0 = study controls for other factors but lacks key factors listed above

Domain	Criteria
	Notes: propensity score matching – variables associated with receipt of a given therapy (eg, CABG; end up on dual AP because of procedure); multivariate regression
Assessment of outcome	Enter 0 or 1: 1 = independent assessment/chart review – investigators aren't assessing patient themselves 1 = record linkage (*eg* administrative data, registry data) 0 = no description; unspecified; non-specific patient self-report without chart review or clinical assessment
Adequacy of follow-up of cohorts	Enter 0 or 1: 1 = complete follow-up, all subjects accounted for 1 = subjects lost to follow-up unlikely to introduce bias; small number lost (select an adequate % follow-up), or description of those lost 0 = follow-up rate < 80%, and no description of those lost 0 = no statement

QA Tables for RCTs

Quality assessment criteria	**Aramendi, 2005[14]**	**Colli, 2007[1]**	**DiMarco 2007[2]**	**Rafiq 2017[3]**
Randomization/ allocation sequence adequately generated? Yes/No	Yes: Statistical significance between groups' baseline characteristics not reported, but appear similar. Note: 5% of included pts had mitral valve or both aortic and mitral valve replacement.	No: 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."	Unclear: method of randomization not reported. Authors note in discussion: "the randomization methods (especially in group 1) might imply some bias"	Unclear - exact method of randomization not reported ("randomly sequenced opaque sealed envelopes," but method of generating sequence or assigning them to a group was not reported). Groups were balanced at baseline.
Allocation adequately concealed? Yes/No	Yes	Unclear: not reported	Unclear: method not reported	Yes: opaque sealed envelopes
Blinding? Yes/No	No for patients: randomized open pilot trial. Yes for outcome assessors: All reported primary and secondary end-points were validated by all 4 investigators without unblinding the treatment assigned.	No, not reported whether blinding was attempted	No, there is no mention of the providers or outcome assessors being blinded	No: open-label trial (although data analysis blinded to group allocation); however, outcome data appears to have been collected in an objective manner (clear criteria)
Incomplete outcome data adequately addressed? Yes/No	Yes: 191 analyzed of 200 randomized; 18% withdrew but reported reasons for withdrawal	Yes. Only 8% were excluded because they developed afib and were treated with VKA.	Yes, no loss to follow up	Yes: 11% attrition (even among groups), ITT analysis
Free of suggestion of selective outcome reporting? Yes/No	Yes: protocol published prior to study	Yes	No: overly favorable: "Aspirin therapy appears to be the appropriate response to both cardiac surgeons' and patients' needs in the early postoperative course after aortic valve replacement with tissue valves"	Yes: ClinicalTrials.gov record available, does not appear to have been any selective outcome reporting
Free of other problems that could put it at a high risk of bias? Yes/No	Unclear - authors call analysis ITT but excluded those who did not receive medication. Post-randomization exclusions: 3.5% because they did not receive medication	Unclear. "The sample size was underpowered to demonstrate statistical differences between the 2 groups."	Yes	Yes: updated INR charts provided by 79% of warfarin group (Table 5), although the study admits there was some difficulty staying within range
Overall risk of bias: Low/ Unclear/ High	Low ROB	Unclear	Unclear. Randomized, but no efforts at concealment discussed, would pose risk	Low
Comments	INR out of range was reported (147 instances where INR values were >3; mean period when patients out of INR range was 11.8±7 days).	Non-blinded, but similar allocation strategy for embolic events	50 of 250 patients were in RCT arm with little explanation of methods and 0 events for outcomes	Unclear (because open-label trial with no blinding)

QA Table for RCTs, Continued

Quality assessment criteria	**Rodes-Cabau, 2017[15]**	**Stabile, 2014[16]**	**Ussia, 2011[17]**
Randomization/ allocation sequence adequately generated? Yes/No	Unclear: no description of sequence generation but no significant differences in table 1	Unclear - Randomized trial, does not report sequence generation -- groups are well balanced	Unclear: no description of sequence generation but groups were balanced.
Allocation adequately concealed? Yes/No	Yes: "random block sizes were used to conceal Tx allocation and randomization was stratified by clinical center	Unclear	No: no description
Blinding? Yes/No	No: open label	Unclear - Physicians were blinded. It does not state whether patients were blinded.	No: open-label
Incomplete outcome data adequately addressed? Yes/No	Yes: at 3 months, 98.6% included in analysis; states no loss to follow-up.	Yes: No attrition was reported, however, outcomes data is only to 30 days.	Yes: full follow-up + ITT
Free of suggestion of selective outcome reporting? Yes/No	Yes: all events were adjudicated by an independent committee. Pts with serious AEs were systematically monitored for source data verification. Protocol as posted and amended with updates.	No: most outcomes only report 30 day data (except mortality). Methods state 6-month follow-up, but reports only mortality at 6 months. Other outcomes only 30 days presented.	Yes: conclusions match data
Free of other problems that could put it at a high risk of bias? Yes/No	No: Sample size calculation was for 300 pts; only 222 enrolled because of slow enrollment and financial constraints.	No: Short-term follow-up biases towards vascular complications which are increased with DAPT, but may be insufficient to capture thromboembolic events. Not powered to assess clinical endpoints based on author's assessment. Small sample size.	Unclear: an exploratory paper and, hence, a formal sample size estimation was not performed. The authors acknowledge the main limitation of the study was the small number of randomized subjects.
Overall risk of bias: Low/ Unclear/ High	Low	High ROB	Unclear
Comments	Study prematurely ended (anticipated 300 patients) due to slow enrollment and lack of continued financial support.	Authors note: "…caution should be applied when interpreting the study results, which should be considered hypothesis generating rather than offering a definitive answer."	

QA Table for Cohort Studies

Quality assessment criteria	**Abdul-Jawad Altisent, 2016[21]**	**Al-Atassi, 2012[11]**	**Blair, 1994[4]**	**Brennan, 2012[5]**
Representativeness of the exposed cohort	1 - multiple sites, probably typical of patients selected for TAVR	1	0 = Highly selected sample, excluded 115 patients (13% of 881 operated) who died before discharge. Patients who got AVR+MVR were included in both AVR and MVR	1 = sampling of large number of institutions
Selection of the non-exposed cohort	1 - drawn from same sites	1	0 = Not specified whether ASA or No Tx pts differed from War pts, or why treated differently	1 = drawn from same database (same consortium of hospitals)
Ascertainment of exposure	1 - database, prospectively collected data including on antithrombotic strategy	1	1 = chart review	1 = discharge records
Precision of Exposure Dose Ascertainment	0 - specified for aspirin, but not INR for warfarin	1	0 = Specifies prothrombin time for Warfarin, but not duration. ASA dosage and duration NR	0 = based on discharge medications without clear exposure dose
Demonstration that outcome of interest was not present at baseline	1	1	1 = Outcomes well defined, not likely to be present at baseline.	1 = based on record review
Adjustment for confounding (rendering comparability of cohorts on the basis of the design or analysis)	1 - accounts for CAD, center, strategy and explored other key differences between groups	1 – propensity score model	0 = key factors were examined via univariate analysis, but not signif so excluded from multivariate model.	1 = propensity scoring done
Assessment of outcome	0 - unclear - chart review or telephone interview, but unclear how many patients were called or how outcomes were assessed over telephone.	1	0 = chart review "supplemented by patient contact"; possible non-independence, and lack of information about how often they needed to contact people, who was contacting them, what they asked, etc.	1 = administrative data based on ICD9
Adequacy of follow-up of cohorts	1- person-time outcome so would have censored for loss to follow-up; however, # patients lost to follow-up NR. Median f/u 13 months and no one followed for less than 3 months	1 No loss	1	1 = Medicare administrative data
Comments	Moderate-quality study. Main limitations include lack of specific information on exact outcome assessment procedures and baseline imbalance in proportion of patients with CAD suggesting potential for confounding by indication, though crude and adjusted HR were very similar	Small sample size (N=56)	Poor quality study.	7 = high quality with the notable exception of exposure risk. Some bias likely in selection. Tx choice varied among institutions.

QA Table for Cohort Studies, Continued

Quality assessment criteria	**Colli, 2013**[6]	**di Marco, 2007**[2]	**Durand, 2014**[19]	**Gherli, 2004**[7]
Representativeness of the exposed cohort	1	1 consecutive patients	1 = consecutive TAVR at 3 sites	1
Selection of the non-exposed cohort	0 = War population differed from ASA treated pts, with higher prevalence of Periphral vascular dz, CKD, and CAD.	1 consecutive patients	0 = Tx group individually determined by pt's previous use of same drug. SAPT pts were from 2 of the centers whereas DAPT pts were predominantly from a single center.	1 = treatment assignment depended on which surgeon was on duty the day the patient underwent surgery.
Ascertainment of exposure	1	1 = chart review and in person visits	1 = registry	1
Precision of Exposure Dose Ascertainment	0 = target INR for War was 2.5; dose and duration of ASA or War not otherwise specified	0 = time in INR not reported, though authors mention that all events occurred when patient INR was in range	1	0 = Warfarin maintained for 3 months then substituted with ASA; NOS
Demonstration that outcome of interest was not present at baseline	1	1 = based on clinical review	1 = prospective study; major clinical events as primary end point	1 = major health outcomes, clinically assessed.
Adjustment for confounding	1 = propensity score matching	0 : 200 patients assigned to anticoagulation strategy by surgeon preference with no mention of adjustment for confounders	1 = multivariate analysis and propensity score matching	1 = Cox model used to adjust for possible confounders.
Assessment of outcome	1	0 = some chart review administrative data; then ambulatory clinical evaluation and phone interviews. Unclear if clinical evaluations by independent assessor.	1	0 = 2nd author performed all clinical evaluations for study outcomes.
Adequacy of follow-up of cohorts	0: Follow-up was uneven: 78% in War vs 89% in ASA	1 = no patient lost to follow up	1	1 = survival analysis with person-time-at risk
Comments	Registry industry-sponsored by St. Jude. Conclusions don't fit data. Significant results only with combined endpoints or small subgroups. 16% attrition	5, appears to have low risk of bias but there is not clear adjustment for confounders and the assessment of outcome was somewhat unclear, likely clinical	Limited applicability: follow-up was only 30 days	Sum = 6

QA Table for Cohort Studies, Continued

Quality assessment criteria	**Holy, 2017[20]**	**Ichibori, 2017[18]**	**Jamieson, 2007[12]**	**Lee, 2017[9]**
Representativeness of the exposed cohort	1 =All Ss from a single site	1 = consecutive TAVR pts	1 = a matched group within 2 regional teaching hospitals	1
Selection of the non-exposed cohort	1 = All Ss from a single site, but Tx groups differed: more AF in the OAC group; more staged PCI in DAPT group (P = .01). AF was adjusted for in analysis	1 = same source; treatment based on year of surgery.	1 = all from same database	1 = treatment by surgeon's preference, but pts with indications for warfarin (*eg*, afib) received warfarin.
Ascertainment of exposure	0 = no description	0 = no description	1 = UBC cardiac valve database	1 = clinical database
Precision of Exposure Dose Ascertainment	0 = dose not specified, only duration	1	0 = unclear exposure; describes only the antithrombotic therapy during the study era	1
Demonstration that outcome of interest was not present at baseline	1 = clinical exams and imaging performed at multiple time points	1	1 = from chart review	1 = clinical presentation, primarily.
Adjustment for confounding	1 = adjusted for age, sex, BMI, AF, and staged PCI	1 = Cox proportional hazards regression	1 = multivariate regression	1 = propensity score matching
Assessment of outcome	0 = not clear if investigators performed the clinical exams	0 = no description on how outcome data was gathered	0 = no information about how they assessed outcomes.	0 = investigators also treated patients, examined patients for outcomes
Adequacy of follow-up of cohorts	1 = no mention of follow-up completeness, but mentions Tx changes and ITT approach.	1 = follow-up data on all patients	0 = no statement on % follow-up.	1 = All but one pt were followed up for 3 months
Comments	Insufficient detail on dose and/or duration of treatment; method of exposure ascertainment not described.	Dr. Y Sakata and Dr. Y Sawa received research grants from Edwards Lifesciences and Dr. S Nakatani received lecture fees from Edwards Lifesciences.	Lack of information about outcome assessment and follow-up are important flaws.	Very small study after the propensity score matching

QA Table for Cohort Studies, Continued

Quality assessment criteria	**Lytle, 1988**[13]	**Mistiaen, 2004**[8]	**Seeger, 2017**[22]	**van der Wall, 2016**[10]
Representativeness of the exposed cohort	1 = consecutive patients, 294 identified as having a preoperative aortic valve lesion that was a 'pure' aortic stenosis (1+ aortic insufficiency)	0 = 500 consecutive patients getting a CEP valve. Doesn't say where patients were drawn from	1 = single site, large N.	1
Selection of the non-exposed cohort	1 = patients were subgrouped looking at valve-anticoagulation subgroups using a cox multivariate model.	0 = Difficult to tell how the groups are derived	1 = Pts with Hx or new onset AF after TAVR were given War or apixaban (with use at institution beginning Nov 2013)	1
Ascertainment of exposure	0 = anticoagulation strategy was 'warfarin', not otherwise specified	1 = probably Rx from hospital database	0 = no description	1 = In all 3 hospitals, postoperative medical files were obtained and evaluated.
Precision of Exposure Dose Ascertainment	0 = Time on warfarin, INR range or % time spent in range NR	0 = no description, not even sure if all received ASA in the ASA group	0 = dose not specified, only duration, which varied according to: dialysis status	1 = postoperative medical files obtained and evaluated; thrombosis service was consulted about Tx duration, INRs and target values of pts who received acenocoumarol.
Demonstration that outcome of interest was not present at baseline	1	1 = Previous stroke was present in some patients; Hx stroke was analyzed as a predictive variable.	1 = early safety endpoint at 30 days appear to be all major clinical outcomes	1
Adjustment for confounding	1 = Multivariate analysis performed	1 = univariate and multivariate analysis	1 = multivariate analyses using stepwise forward regression: age, sex, DM, renal insufficiency, DAPT, STS score for mortality, and AF.	1 = multivariable Poisson regression was performed using all potential risk factors simultaneously.
Assessment of outcome	1: chart review	0 = cardiologist filling out questionaire, but then all those with events underwent CT	0 = "Patients were followed up by assessing their clinical histories at scheduled outpatient controls or through telephone contact after 1 and 12 months."	1
Adequacy of follow-up of cohorts	1 = 1 patient lost to follow up after 29 months.	0 = unclear outcome ascertainment, proportion of questionnaires returned NR.	0 = differential loss to follow-up between Tx groups. Twelve-month follow-up was available in 131 in AF (48% of 272 at baseline): 81 (57.4%) of 141 apixaban 50 (31.7%) of 131 War	1 = 5% excluded due to missing Tx data
Comments	Total: 6/8	1/8, high risk of selection and ascertainment bias	The afib 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.	For the RR analyses separation of War vs ASA use for bleeding and TE isn't possible as they analyzed the data differently.

APPENDIX D. PEER REVIEWER COMMENTS

Reviewer Number	Comment	Authors' response
Are the objectives, scope, and methods for this review clearly described?		
2-6	All responded, "Yes."	Noted.
Is there any indication of bias in our synthesis of the evidence?		
2-6	All responded, "No."	Noted.
Are there any published or unpublished studies that we may have overlooked?		
2-6	All responded, "No."	Noted.
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.		
2	N/A	Noted.
3	1- The methods do not mention the review period (years) of the published articles 2- I suspect that there might be studies published in the 1960's that might not have been included	We have clarified in the Methods that we searched all available years of publication from database inception (1946 for Ovid MEDLINE) through January 2017. Our initial search yield contained 48 publications published during 1964-1969.
4	The authors present a thorough assessment of the literature regarding varying risk-benefit ratios of different antithrombotic strategies after bioprosthetic aortic valve replacement (bAVR; surgical or transcatheter). Their systematic search strategy included multiple data sources, a detailed algorithm of their inclusion/exclusion criteria for literature selection, including a consort diagram, and comprehensive tables outlining the details of the studies reviewed. Based on the literature reviewed, the investigators conclude that aspirin (ASA) and VitaminK antagonist administration after bAVR appear to show a similar risk profile with regard to mortality, bleeding and thromboembolism study. They note that the optimal anti-thrombotic strategy in other situations (*eg*, concomitant thrombotic conditions and procedures) is not clear as the evidence is very limited but that large scale studies in the transcatheter (TAVR) population are forthcoming.	Noted.
4	Comments: The search presented by the authors is a comprehensive one which explores all aspects of bAVR including both surgical and transcatheter approaches, and the 2 of the most common accompanying clinical circumstances: concomitant ischemic heart and/or atrial fibrillation. The review illustrates the challenges is studying optimal anticoagulation strategies for the diverse and dynamic population of patients undergoing bAVR regardless of the approach. The review is well written and comprehensive. Comments/suggestions are only minor, as follow:	Noted.
4	The rationale for not including the study by Merie and colleagues (ref 35) in the current analysis is clear; however, the AHA/ACC appears to have considered the findings of this study in their 2017 updated guidelines for pts with valve disease (it is reasonable to anticoagulate with a VKA for 3-6 months after valve replacement for patients at low risk for bleeding), the authors might consider including a little more information on this study than what is currently written (p 16, lines 33-38).	
4	In the Introduction section, the sentence, "Bioprosthetic valves carry a significant advantage over mechanical aortic valve replacement…." (p 3, line 11), as written, seems to imply that that	We agree and have clarified that there may be a lower need for long term anticoagulation with bioprosthetic valves.

Reviewer Number	Comment	Authors' response
	bioprosthetic valves are preferable to mechanical valves. While it is not necessary to note that mechanical valves have a significant advantage over bioprosthetic valves in that they are at almost zero risk of structural deterioration, consider revising this sentence.	
4	The sentence, "However, in the first 3 months after implantation…."(p. 3, line 15) may be slightly overstated since it these studies include prosthetic mitral valves which are known to have a higher risk of thromboembolism relative to valves in the aortic positions - *eg*, in the study by Heras et al, (ref 5) the thromboembolism rate from 11-90 days was comparatively higher for mitral valves as was stated in their conclusions.	We agree and have reworded the sentence to convey the risk as theoretical rather than established.
4	Where possible, it might be helpful to distinguish between pre and postoperative AFib (e.g, on p. 23, lines 25 and 46; p 24, line 23, etc) or state that this information was not clarified in the reviewed study. In most of these cases, it appears that the afib was pre-existing although not clearly stated. Similarly, in reading the paragraph synopsis of the anticoagulation regimens in the study by Brannan and colleagues (p. 24, lines 22-42), the reader would likely wonder what percentages of preop Afib patients were in each of the anticoagulation arms (i.e., how many of the 49% ASA only patients had Afib, etc). Even though the authors imply that there were more Afib patients in the Warfarin/ASA group (p. 24, lines 33-35), more details might be appreciated.	We agree and have revised the summary of the Brennan 2012 paper (in the Results section for for Warfarin combined with ASA vs ASA monotherapy) to clarify 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- vs post-operative atrial fibrillation.
4	Although the RCT comparing trifusal vs. acenocoumarol met study criteria inclusion, the study might not have much direct application in the VA population (I could not find information on either drug at FDA.gov. in my limited search on US availability).	We have added clarification that the drugs used in this trial are not currently used in the US, therefore applicability to practice is limited.
4	On 6 line 15: the phrase "warfarin plus was" should probably read "warfarin plus aspirin was"	We have made the correction as suggested.
4	Although the relevant studies for each of the sub analyses are more readily available for review when included within each section (rather than altogether as an appendix at the end of the statement), the tables distract from the flow of the document to a degree	Noted. We have relocated the tables to occur together after the text for each treatment comparison.
5	Overall, the authors are to be commended for a thorough overview of the topic that provides a trove of available data supporting current recommendations. Overall, the evidence review appears complete and the findings and conclusions of the paper appear reasonable.	Noted.
5	My preference in evidence reviews is to better separate and distinguish evidence/data from non-RCT observational data, whether in large populations or small populations, from evidence from RCT data. In this review, evidence from these 2 types of data are often presented together. Eg, Table 10 has both RCT and cohort data presented together. Could there be a separate column for RCT versus cohort data (ie N studies per outcome separated into 2 columns, one for RCT, one for the rest)?	We have revised each table by grouping studies together by study design, and listing RCTs first, followed by cohort studies, for each drug comparison. For the summary of evidence table, all of the information was used to determine the strength of evidence, so both study designs contributed to the summary findings for each drug comparison.
5	Of the various guidelines cited by the authors, the AHA/ACC focused update of the 2014 AHA/ACC guidelines for management of patients with valvular heart disease may be of greatest relevance for the practice in the VA setting of clinicians licensed in the USA. Thus, agree with the decision to highlight	We strengthened the discussion of the guidelines, as noted in the Discussion, (2nd to last paragraph).

Reviewer Number	Comment	Authors' response
	the conclusions regarding warfarin plus aspirin benefit/risk in BAVR and the review might further emphasize the concordance of this conclusion with the AHA/ACC guidelines in particular.	
5	The novel TAVR data are an important focus of this review. The review would also benefit from a stronger statement about the limited data available from adequately sized RCTs and a comment about the gaps that need to be addressed by ongoing or currently unplanned trials in addition to the listing of ongoing trials in Table 9.	We agree and have added a statement in the Discussion as suggested.
6	None	Noted.