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

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PREFACE

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

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

Develop clinical policies informed by evidence;

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

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

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

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

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

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EXECUTIVE SUMMARY

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