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.