Antithrombotic Agents in the Medical Management of Patients with Valvular Disease

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Learning Objectives for Pharmacists & Nurses

Recall current guideline recommendations on the use of antithrombotic agents in the medical management of patients with valve replacement procedures

Identify thrombotic risk based on valve position and type of valve utilized in patients with valve replacement procedures

Recognize the optimal antithrombotic agent and duration of therapy for patients post-valve replacement to balance incidences of thromboembolic and bleeding events

Learning Objectives for Pharmacy Techs

Recall current guideline recommendations on the use of antithrombotic agents in the medical management of patients with valve replacement procedures

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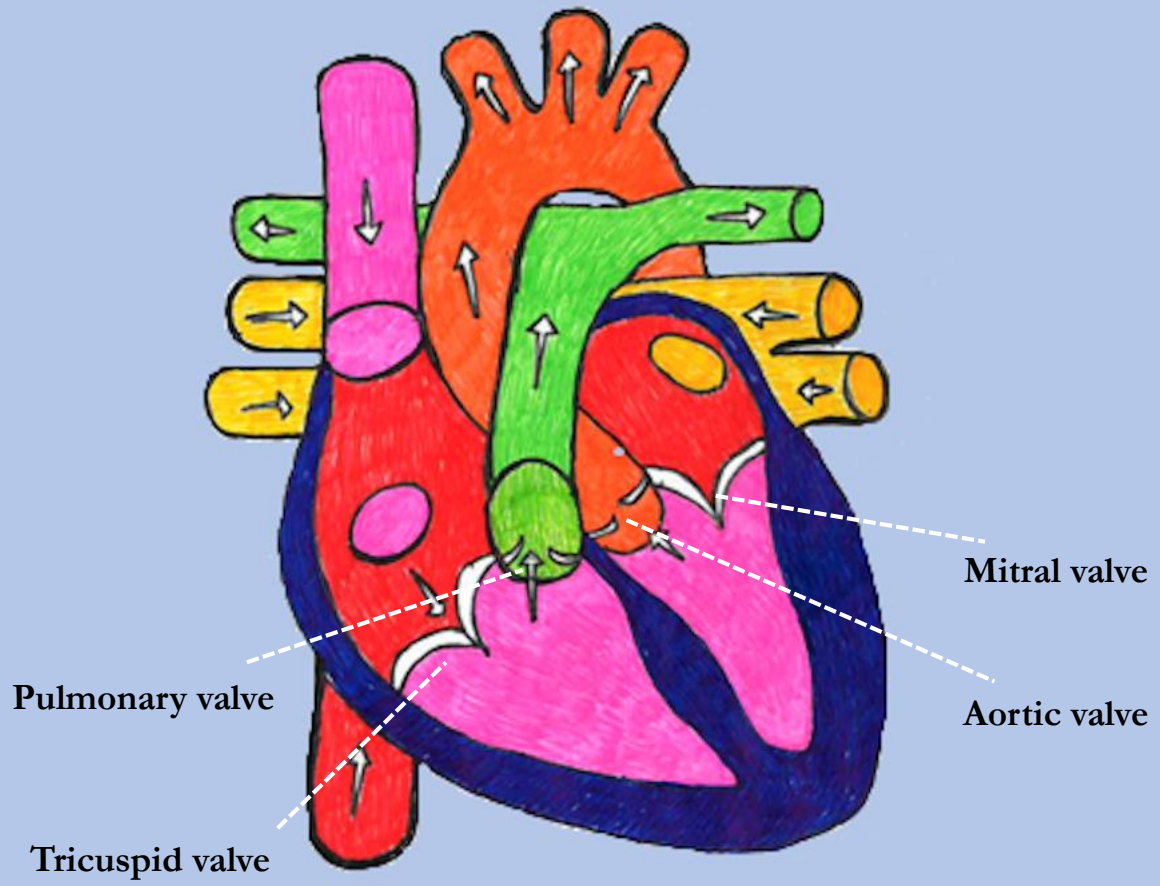
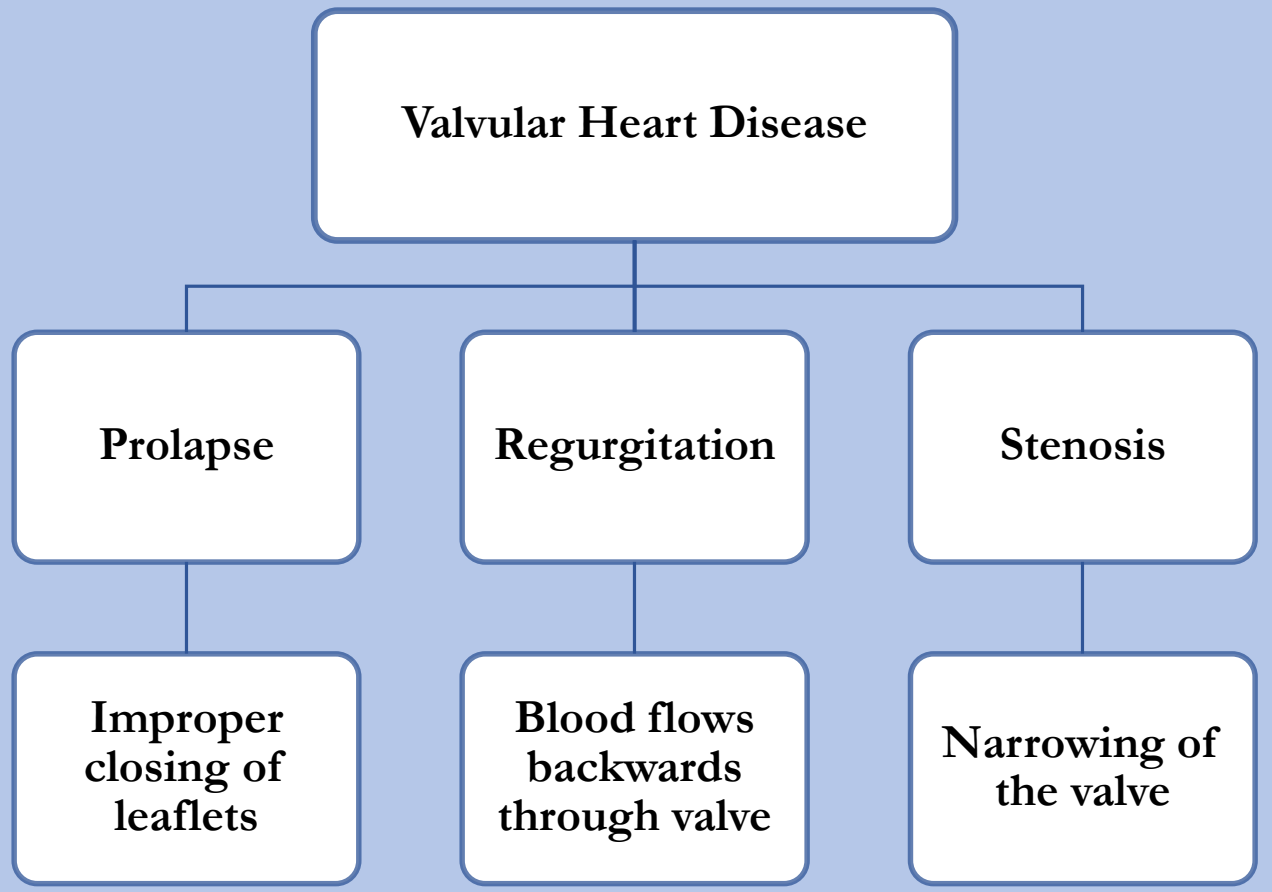
Definitions

AF: Atrial Fibrillation
ASA: Aspirin
AT: Antithrombin
AVR: Aortic Valve Replacement
CABG: Coronary Artery Bypass Graft
CAD: Coronary Artery Disease
CKD: Chronic Kidney Disease
DAPT: Dual Antiplatelet Therapy
HFrEF: Heart Failure Reduced Ejection Fraction
HTN: Hypertension
LV: Left Ventricular
LVEF: Left Ventricular Ejection Fraction
MI: Myocardial Infarction
MS: Mitral Stenosis
MVR: Mitral Valve Replacement
PMH: Past Medical History
RCT: Randomized Control Trial
SAPT: Single Antiplatelet Therapy
SAVR: Surgical Aortic Valve Replacement
SD: Standard Deviation
T2DM: Type 2 Diabetes Mellitus
TAVI: Transcatheter Aortic Valve Implantation
TAVR: Transcatheter Aortic Valve Replacement
TFPI: Tissue Factor Pathway Inhibitor
TIA: Transient Ischemic Attack
VHD: Valvular Heart Disease
VKA: Vitamin K Antagonist
VTE: Venous Thromboembolism
Yr: Year

Valvular Disease





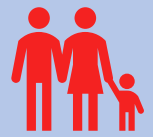
Source(s): Annu Rev Physiol. 2011;73:29-46.

Valvular Disease

Risk Factors

Older age

- Increased calcium deposits on aortic valve



Family history

- Coronary heart disease
- Mitral valve prolapse
- Bicuspid aortic valve dysfunction

Lifestyle habits

- Lack of physical activity
- Smoking

Medical Devices

- Defibrillators
- Pacemakers

Concomitant Heart Disease

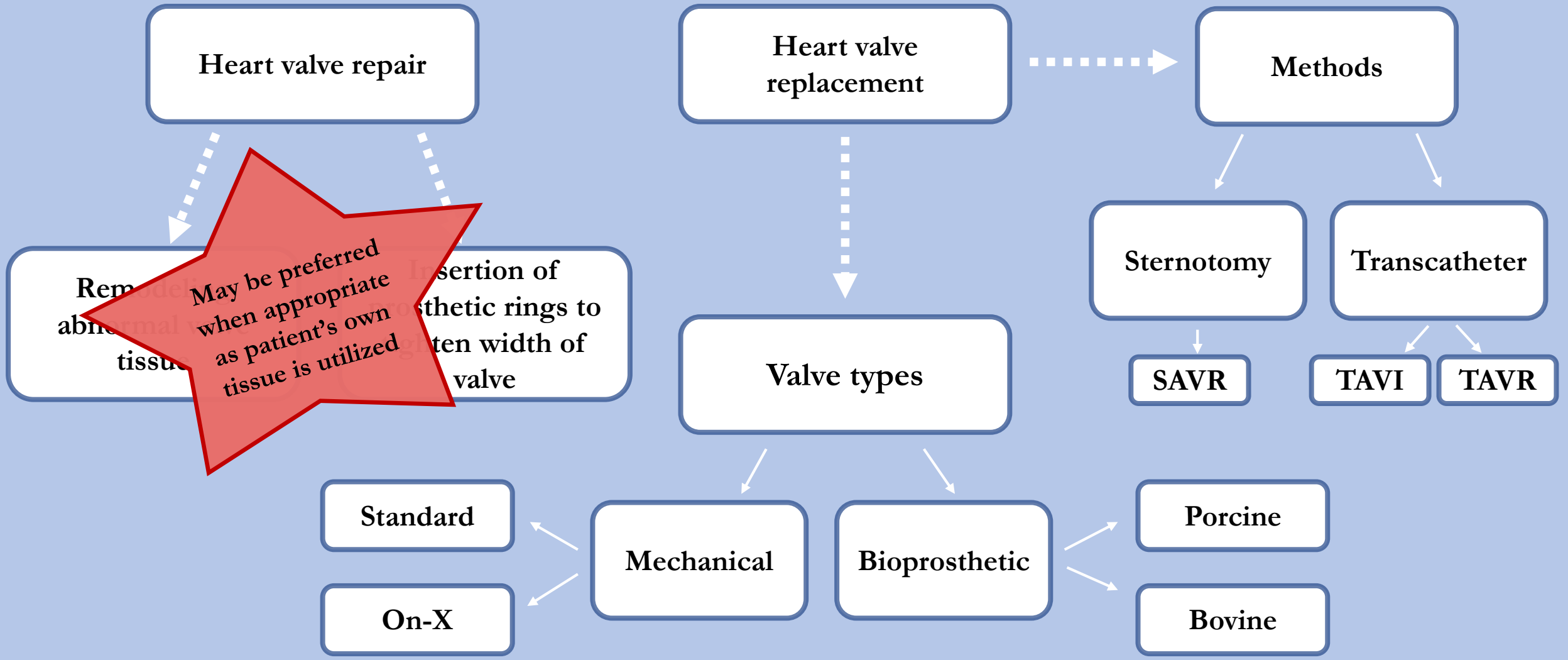
- Hypertension
- CAD, history of MI

Source(s): Med Sci (Basel). 2022 Jun 15;10(2):32

Complications of Valvular Disease

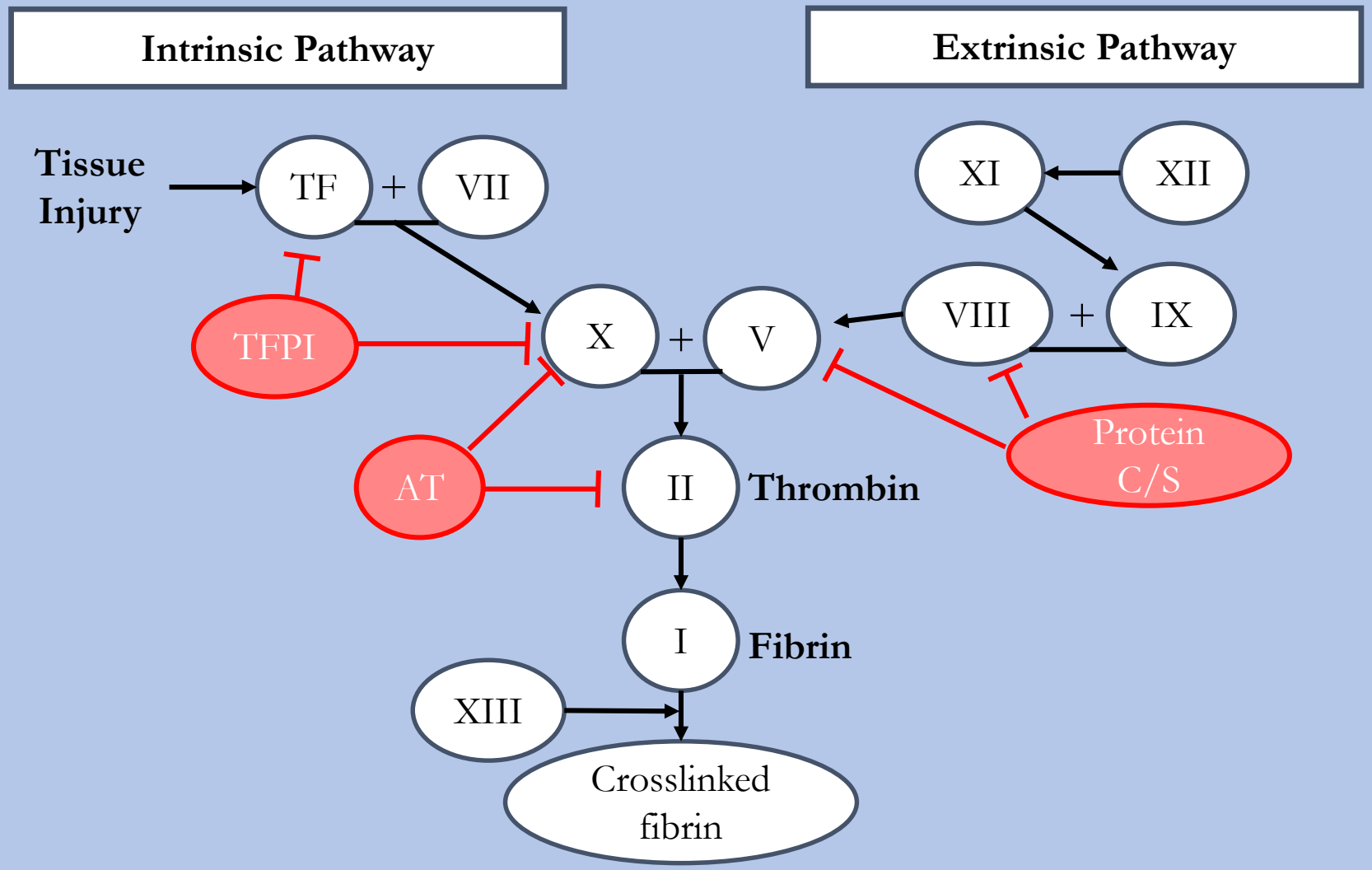
Source(s): Med Sci (Basel). 2022 Jun 15;10(2):32

Intervention



Source(s): Exp Ther Med. 2016 Apr;11(4):1184-1188.

Role of Antithrombotic Therapy



Patients with valve replacement

↓

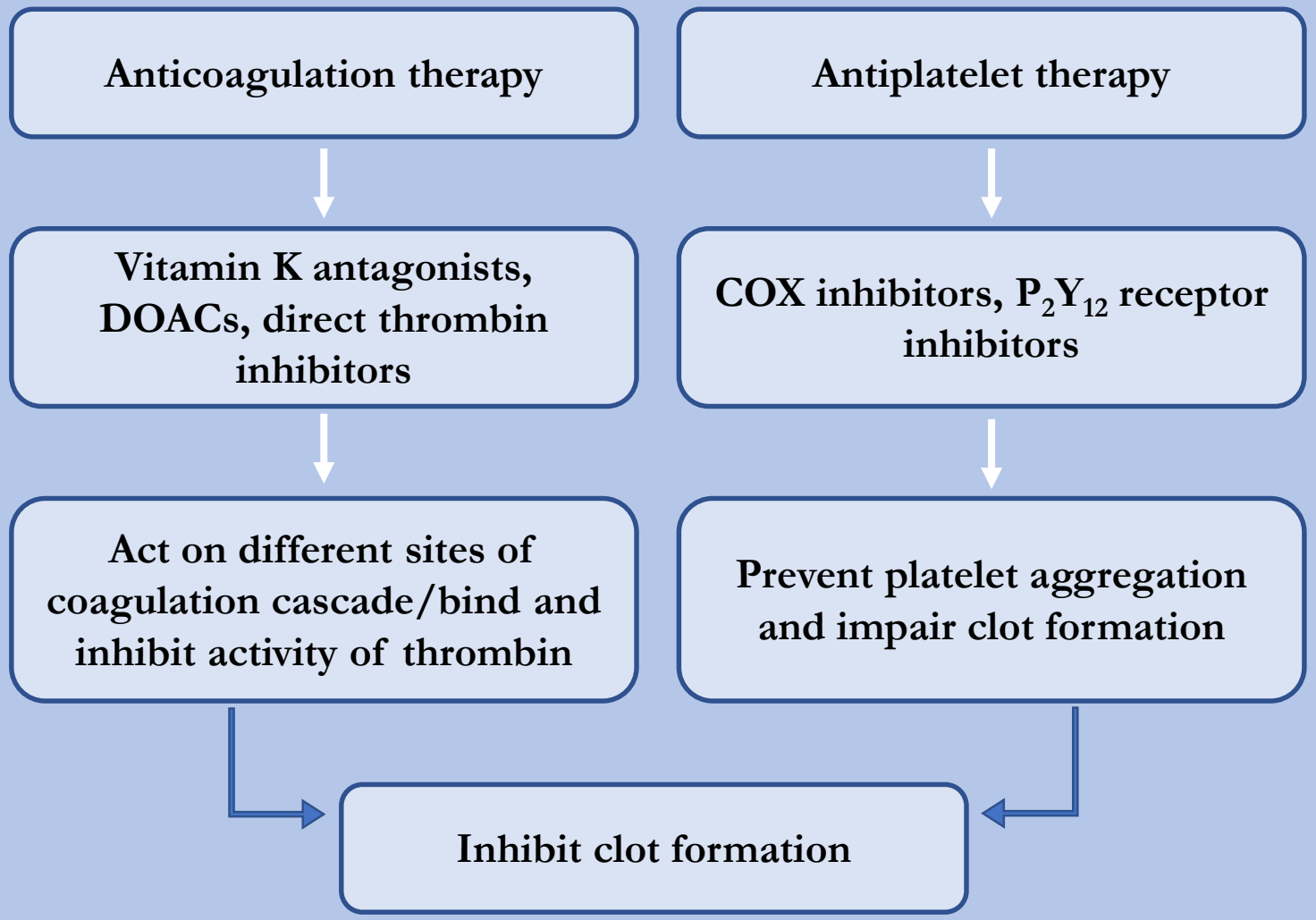
Presence of foreign body and turbulent blood flow

↓

High risk of thromboembolic events and thrombosis of valve

Source(s): Ann Thorac Surg. 2019 May;107(5):1571-1581.

Role of Antithrombotic Therapy

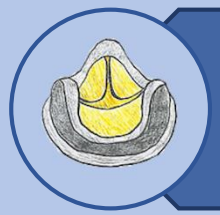


Source(s): Ann Thorac Surg. 2019 May;107(5):1571-1581.

Choice of Mechanical vs. Bioprosthetic Valve

Mechanical

- Younger age with no contraindication to anticoagulation
- Compliant patient with access to INR monitoring
- Separate indication for anticoagulation such as AF
- Low risk of long-term anticoagulation



Bioprosthetic

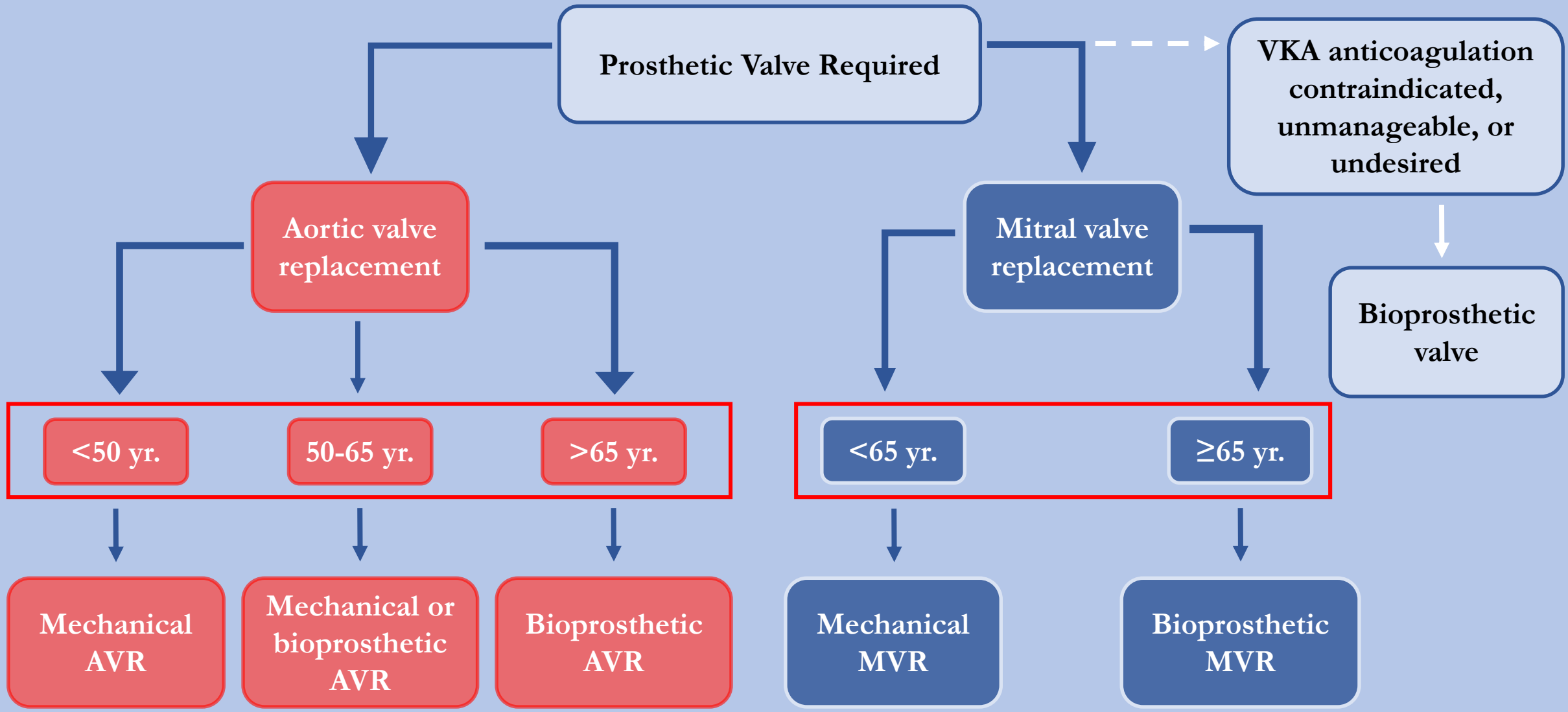
- Advanced age
- Limited access to medical care
- Patients whom VKA anticoagulation therapy is contraindicated, unmanageable, or not desired
- Higher risk of complications from anticoagulation

Based on individual patient factors

- Patients 50-65 years of age with no contraindication to anticoagulation

Source(s): Circulation. 2021 Feb 2;143(5):e35-e71.

Choice of Mechanical vs. Bioprosthetic Valve



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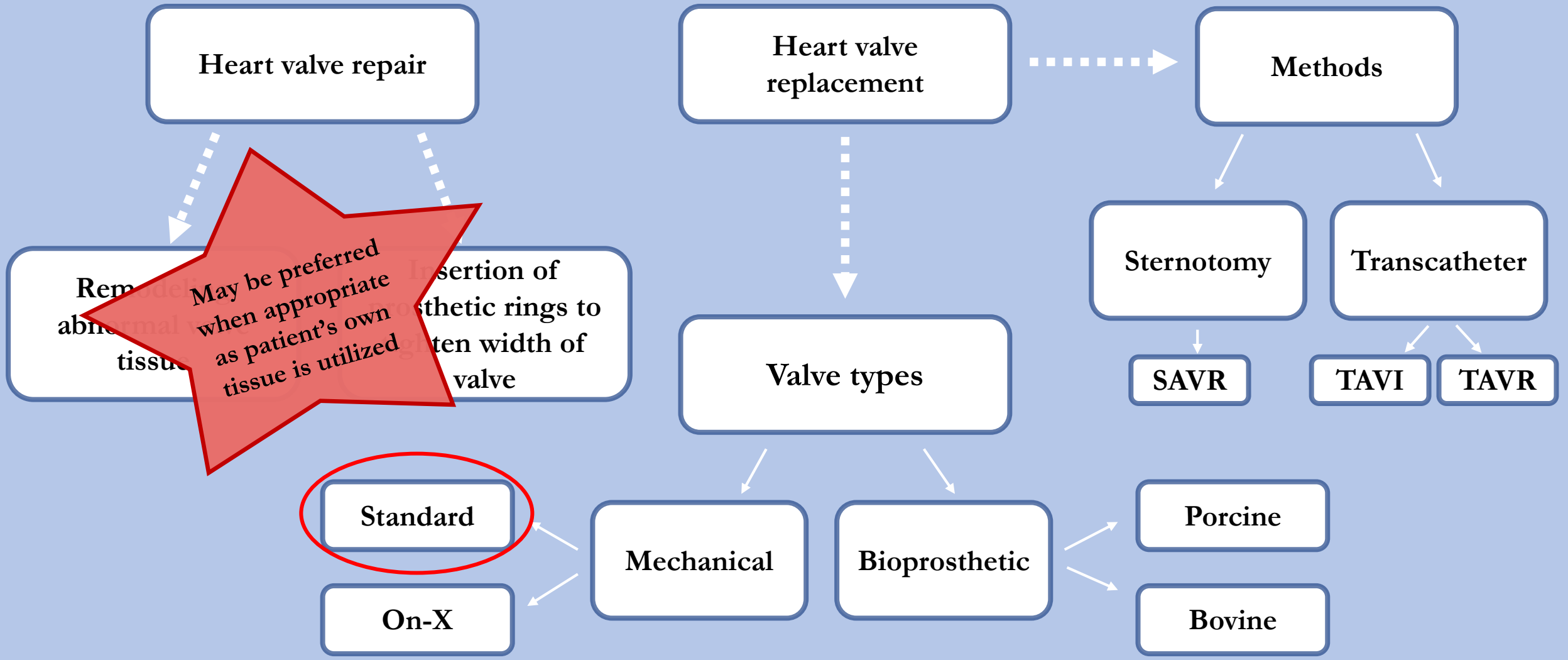
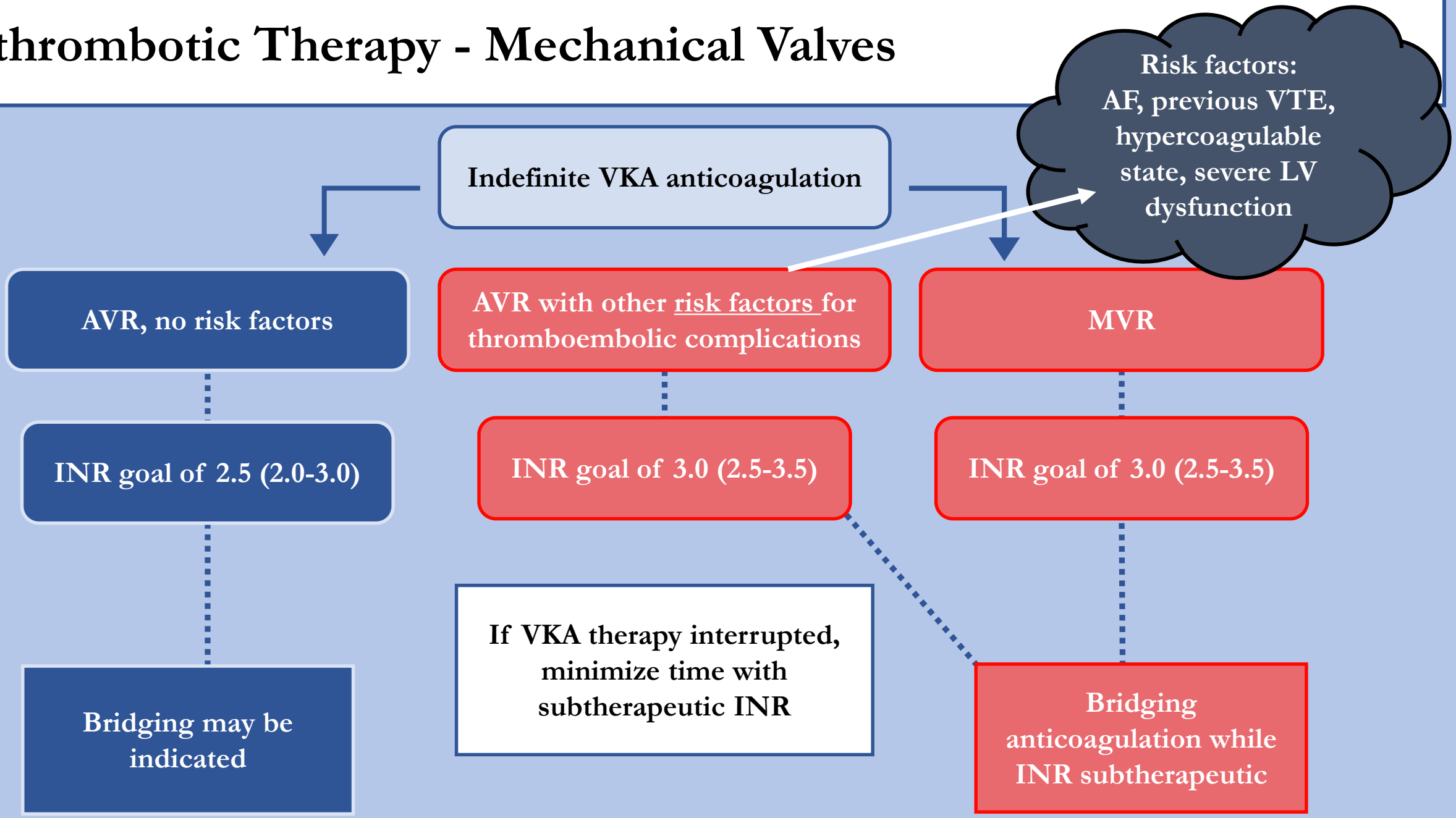


Source(s): Exp Ther Med. 2016 Apr;11(4):1184-1188.

Mechanical Valves – warfarin for all!

Antithrombotic Therapy - Mechanical Valves



Source(s): Circulation. 2021 Feb 2;143(5):e35-e71.

Antithrombotic Therapy - Mechanical Valves

DOAC therapy

Dabigatran	→	Contraindicated in mechanical valve prosthesis
Factor Xa Inhibitors	→	Not studied

Antiplatelet therapy

If antiplatelet agent indicated, add ASA 75-100 mg to warfarin therapy

Source(s): Circulation. 2021 Feb 2;143(5):e35-e71.

RE-ALIGN Trial: Study Design

Prospective, randomized, phase 2 dose-validation study

Objective

Validate a new dabigatran dosing regimen for the prevention of thromboembolic complications in patients with mechanical heart valves

Inclusion

- 18-75 years of age
- Undergoing implantation of a mechanical bileaflet valve in aortic or mitral valve position or both
- OR undergone implantation of mechanical bileaflet mitral valve more than 3 months before randomization

Exclusion

- Previous prosthetic heart valve replacement
- Aortic root replacement
- Replacement of ascending aorta
- Concomitant bioprosthetic valve replacement
- History of hemorrhagic stroke
- Active hepatitis
- CrCl <40 mL/min
- Clear indication for DAPT or oral anticoagulation therapy for indications in which dabigatran is not approved

Source(s): N Engl J Med 2013;369:1206-14.

RE-ALIGN Trial: Intervention

Patients post aortic or mitral valve replacement

Population A:	Population B:
Within past 7 days	≥ 3 months prior

Randomized in ratio of 2:1

Dabigatran (N = 168)

150, 220, or 300 mg BID
Based on kidney function

Doses adjusted to obtain trough plasma level of ≥ 50 mcg/mL

vs.

Warfarin (N = 84)

Dose adjusted to obtained INR of 2 to 3 or 2.5 to 3.5

Goal INR based on patient's thromboembolic risk

Based on data from RE-LY trial

Patients changed to non study vitamin K antagonist if:

- Dabigatran level <50 mcg/mL on highest dose
- CrCl fell below 30 mL/min or decrease ≥50% from baseline
- Participant choice

Source(s): N Engl J Med 2013;369:1206-14.
N Engl J Med. 2009;361(12):1139-51.

RE-ALIGN Trial: Outcomes

Primary Outcome → Trough plasma level of dabigatran

Secondary Outcome → Stroke, systemic embolism, TIA, valve thrombosis, bleeding, VTE, MI, and death

Source(s): N Engl J Med 2013;369:1206-14.

RE-ALIGN Trial: Results

Outcome	Dabigatran (N = 168)	Warfarin (N = 84)	Hazard Ratio	P Value
Composite CV outcome – No. (%)	15 (9)	4 (5)	1.94 (0.64-5.86)	0.24
Valve thrombosis – No. (%)	5 (3)	0 (0)	NA	NA
Bleeding – No. (%)				
Any	45 (27)	10 (12)	2.45 (1.23-4.86)	0.01
Major	7 (4)	2 (2)	1.76 (0.37-8.46)	0.48
Major with pericardial location	7 (4)	2 (2)	1.76 (0.36-8.45)	0.48

Majority of thromboembolic events in dabigatran group occurred in <u>Population A</u>

<u>Population A:</u>
Patients with valve replacement within past 7 days

Source(s): N Engl J Med 2013;369:1206-14.

RE-ALIGN Trial: Conclusion

Trial terminated early

Excess thromboembolic and bleeding events in dabigatran group > warfarin group

Possible explanations

Inadequate plasma levels of the drug

Levels in population A lower during first few weeks post surgery than subsequently

Mechanism of action differs from warfarin

However

Also occurred with higher trough plasma levels + population B

Source(s): N Engl J Med 2013;369:1206-14.

RE-ALIGN Trial: Conclusion

Dabigatran

Not as effective as warfarin in preventing thromboembolism

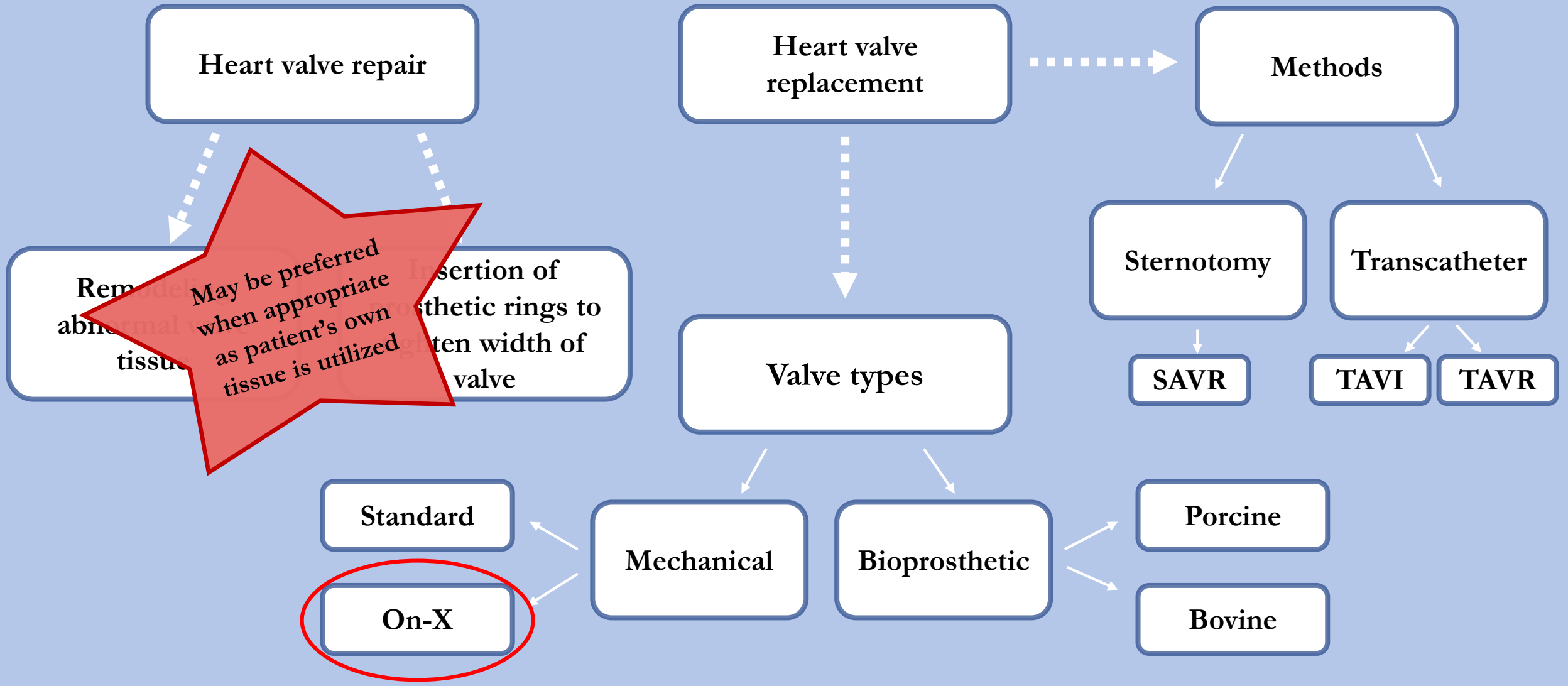
Associated with increased risk of bleeding

Conclusion:
Dabigatran is not appropriate as an alternative to warfarin for prevention of thromboembolic complications in prosthetic heart valve replacement

- Outcomes directly related to contraindication of dabigatran
- DOACs not studied in mechanical valve replacement

Source(s): N Engl J Med 2013;369:1206-14.

Intervention



Source(s): Exp Ther Med. 2016 Apr;11(4):1184-1188.

On-X Mechanical Aortic Valve Replacement

- Newly designed commercial valve
- Less turbulent blood flow
- ✓ May be less susceptible to thrombosis

On-X Aortic Valve Replacement

ACC/AHA Guidelines

Mechanical On-X Aortic valve replacement + **No thromboembolic risk factors**

First 3 months post surgery

VKA antagonist + ASA 81 mg daily → **INR goal 2.0-3.0**

Design characteristics of valve may make it less susceptible to thrombosis than other mechanical heart valves

Long-term Management

VKA antagonist + ASA 81 mg daily → **INR goal 1.5-2.0** → **Starting ≥ 3 months post surgery**

Source(s): Circulation. 2021 Feb 2;143(5):e35-e71.

Assessment Question

A 65 yo female with PMH of MI, AF, HTN, T2DM, and HFrEF with LVEF of 35-40% undergoes an aortic valve replacement with a mechanical valve.

Which antithrombotic regimen is most appropriate for the patient?

A. Warfarin with INR goal 2.5 (2.0-3.0)

B. ASA 81 mg daily + clopidogrel 75 mg daily x 3 months then lifelong ASA 81 mg daily

C. Warfarin with INR goal of 3.0 (2.5-3.5) + ASA 81 mg daily

D. Apixaban 5 mg BID + ASA 81 mg daily x 3 months

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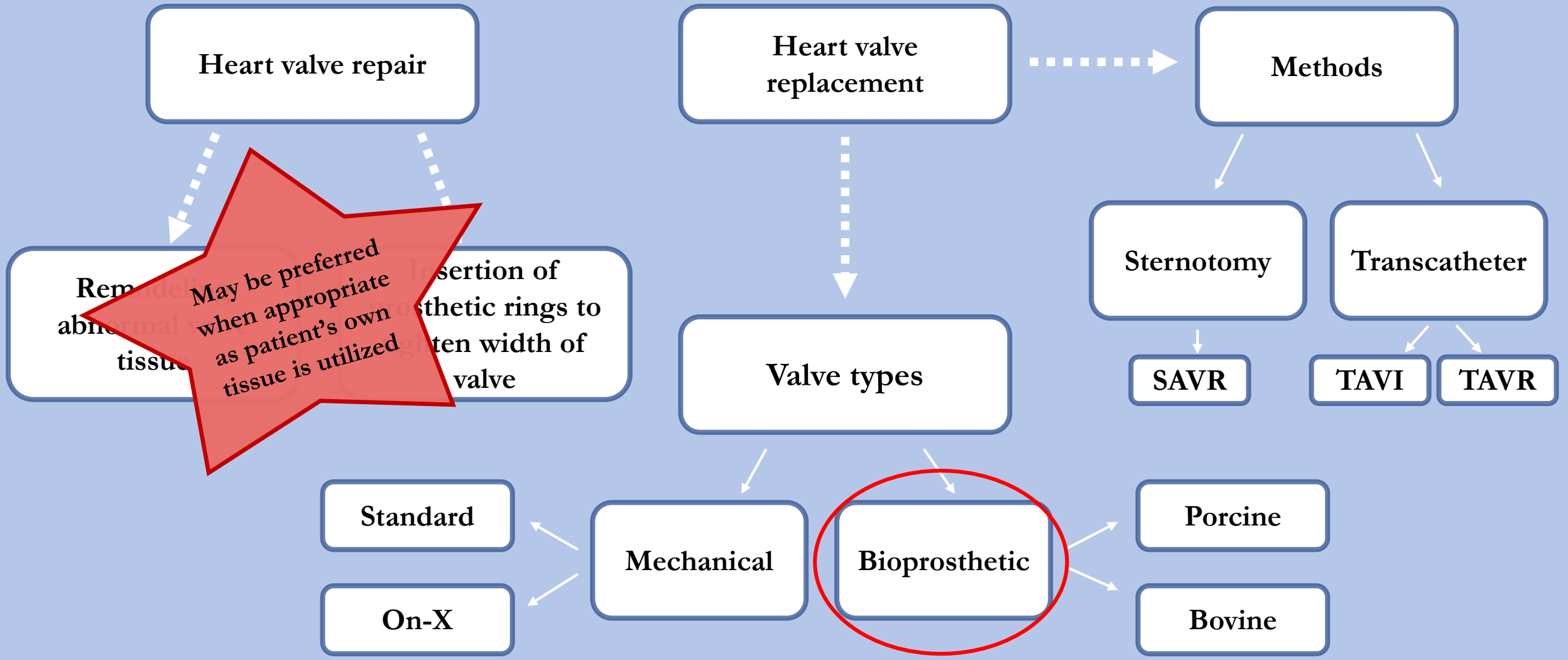
Intervention



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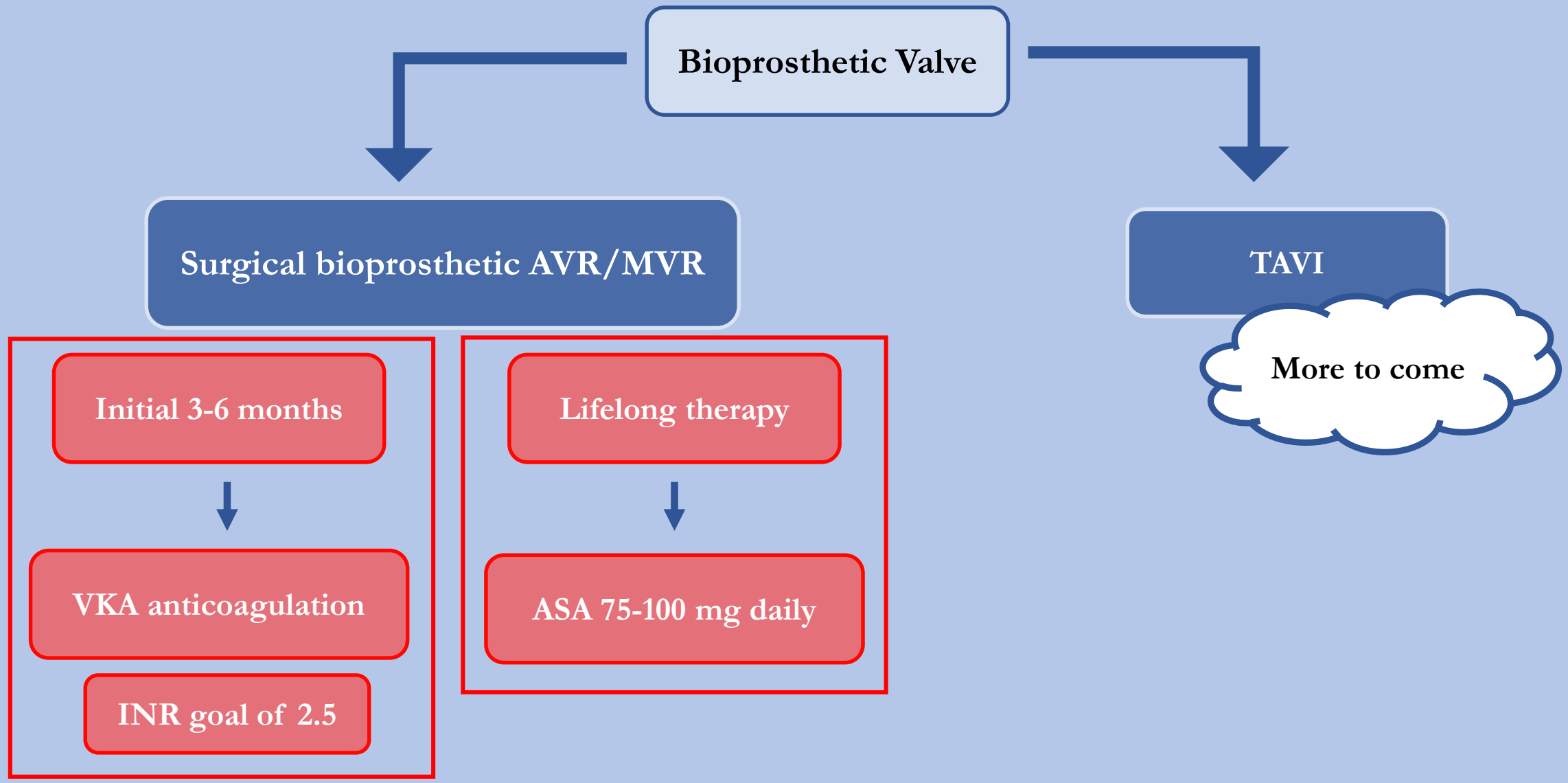
Bioprosthetic Valves

Antithrombotic Therapy - Bioprosthetic Valves



Source(s): Circulation. 2021 Feb 2;143(5):e35-e71.

River Trial: Study Design

Multicenter, noninferiority RCT

Objective

"Assess the efficacy and safety of rivaroxaban as compared with warfarin in patients with atrial fibrillation and a bioprosthetic mitral valve"

Inclusion

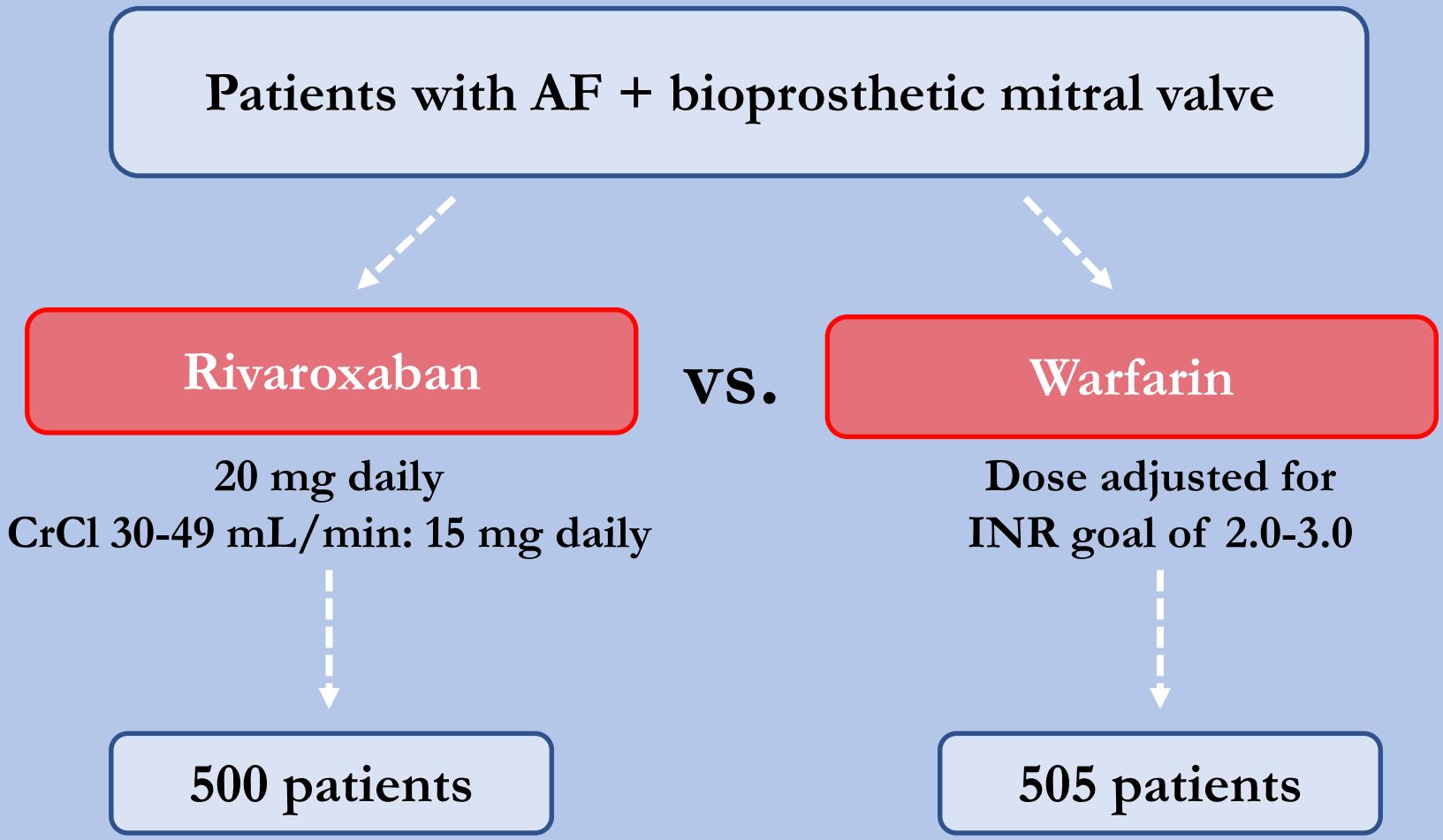
- ≥ 18 years of age
- Permanent, paroxysmal, or persistent AF or atrial flutter
- Bioprosthetic mitral valve
- Receiving/planning to receive oral anticoagulation
- ≥ 48 hours after mitral-valve surgery

Exclusion

- Contraindication to rivaroxaban or warfarin
- Extremely high risk of bleeding
- Transient AF caused by surgery
- Placement of mechanical valves

Source(s): N Engl J Med. 2020 Nov 26;383(22):2117-2126.

River Trial: Intervention



Source(s): N Engl J Med. 2020 Nov 26;383(22):2117-2126.

River Trial: Endpoints

✓ Efficacy

- Composite outcome of CV death or thromboembolic events (stroke, TIA, valve thrombosis, venous thromboembolism, non-CNS systemic embolism)
- Individual components of combined endpoints

Safety

- Bleeding events (major, minor, minimal, fatal)

Source(s): N Engl J Med. 2020 Nov 26;383(22):2117-2126.

River Trial: Baseline Characteristics

Characteristic	Rivaroxaban (N = 100)	Warfarin (N = 505)	All Patients (N = 1005)
Age			
Mean – yr ± SD	59.4±2.4	59.2±11.8	59.3±12.1
≥65 yr – no. (%)	179 (35.8)	176 (34.9)	355 (35.3)
Female – no. (%)	311 (62.2)	296 (58.6)	607 (60.4)
White – no. (%)	294 (58.8)	270 (53.5)	564 (56.1)
Type of atrial rhythm – no. (%)			
Paroxysmal fibrillation	114 (22.8)	109 (21.6)	223 (22.2)
Permanent fibrillation	311 (62.2)	310 (61.4)	621 (61.7)
Persistent fibrillation	55 (10.9)	62 (12.3)	117 (11.6)
Flutter	20 (4.0)	24 (4.8)	44 (4.3)
Mean CHA_2DS_2VASc score* ± SD	2.7±1.5	2.5±1.3	2.6±1.4

*Values ranging from 0 to 9 with higher scores indicating greater risk of stroke

Source(s): N Engl J Med. 2020 Nov 26;383(22):2117-2126.

River Trial: Efficacy Outcomes

Mean time to primary outcome event

Warfarin	340.1 days
Rivaroxaban	347.5 days

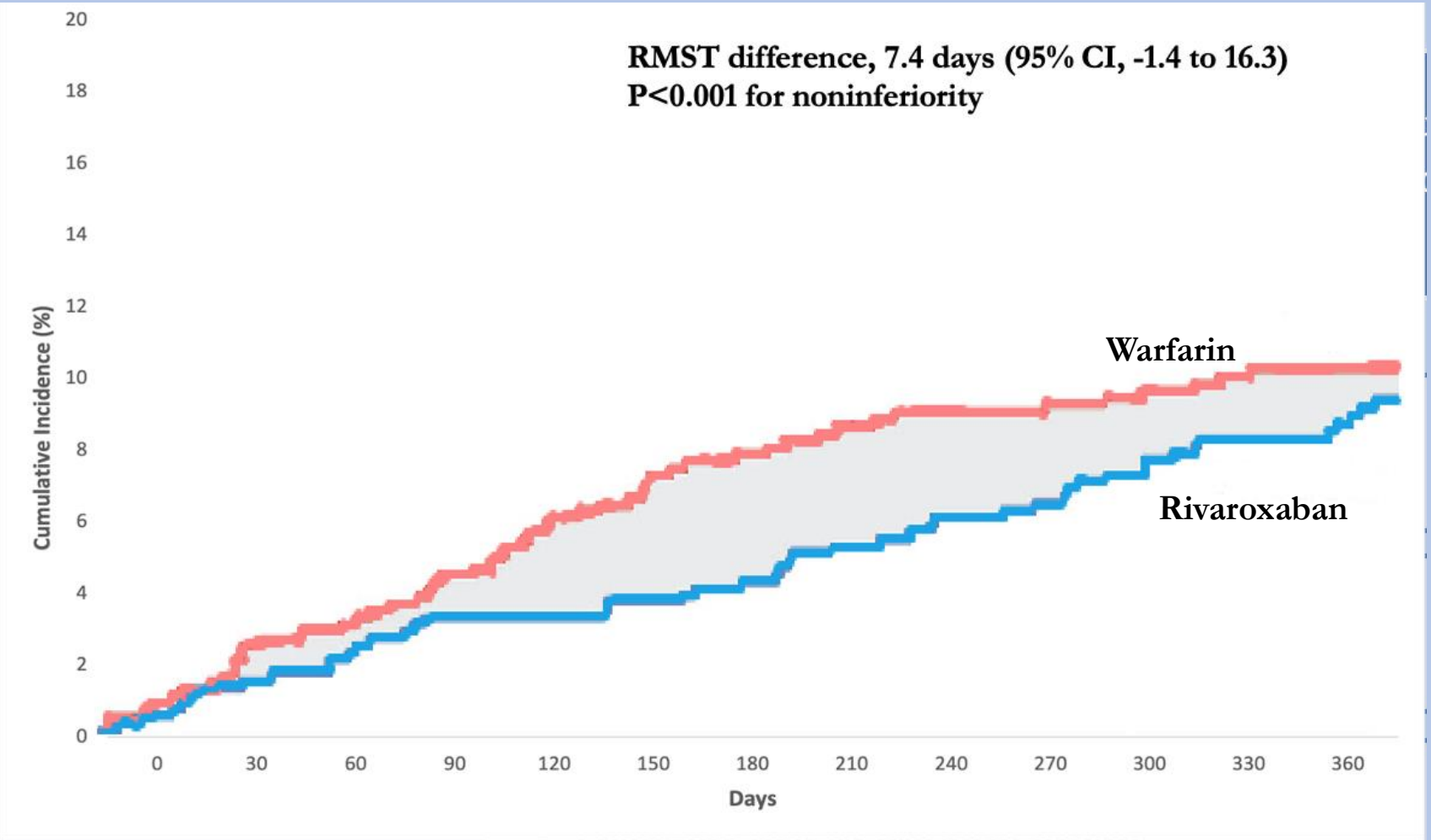
Randomized Mean Survival Time (RMST) difference of 7.4 days

95% CI: -1.4 to 16.3; P<0.001

Death from cardiovascular / thromboembolic causes	• 17 patients (3.4%) rivaroxaban group • 26 patients (5.1%) warfarin group
Stroke	• 3 patients (0.6%) rivaroxaban group • 12 patients (2.4%) warfarin group
Valve thrombosis	• 5 patients (1.0%) rivaroxaban group • 3 patients (0.6%) warfarin group

Source(s): N Engl J Med. 2020 Nov 26;383(22):2117-2126.

River Trial: Efficacy Outcomes



Source(s): N Engl J Med. 2020 Nov 26;383(22):2117-2126.

River Trial: Safety Outcomes

Bleeding Event no. (%)	Rivaroxaban (N = 500)	Warfarin (N = 505)
Any bleeding	65 (13.0)	78 (15.4)
Major bleeding	7 (1.4)	13 (2.6)
Intracranial bleeding	0 (0)	0 (0)
Fatal bleeding	0 (0)	0 (0)
Clinically relevant nonmajor bleeding	24 (4.8)	23 (4.6)
Minor bleeding	37 (7.4)	49 (9.7)

Bleeding events not statistically significant

Other serious adverse events occurred at similar rates between both groups

Source(s): N Engl J Med. 2020 Nov 26;383(22):2117-2126.

River Trial: Conclusion

In patients with atrial fibrillation and a bioprosthetic mitral valve, rivaroxaban was noninferior to warfarin with respect to:

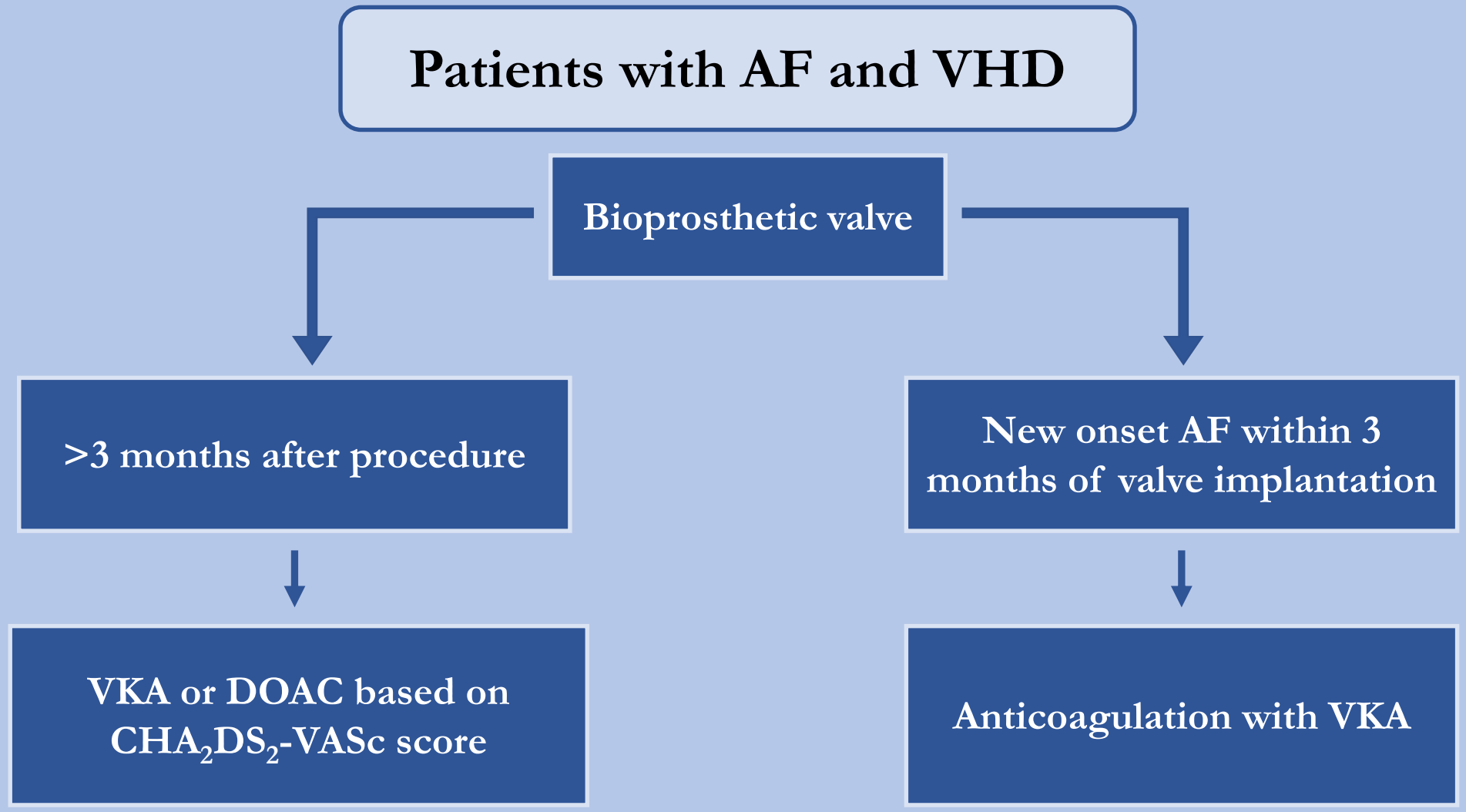
✓ Mean time to primary outcome of death
✓ Major cardiovascular events
✓ Major bleeding at 12 months

Source(s): N Engl J Med. 2020 Nov 26;383(22):2117-2126.

Atrial Fibrillation and Valvular Heart Disease

Source(s): N Engl J Med. 2020 Nov 26;383(22):2117-2126.

Antithrombotic Therapy for AF in VHD



Source(s): Circulation. 2021 Feb 2;143(5):e35-e71.

Assessment Question

A 55-year-old male with PMH of CAD s/p CABG x1, HTN, T2DM, and CKD stage III presents with worsening SOB on exertion and LE edema. The patient was discovered to have severe aortic stenosis and underwent aortic valve replacement with a porcine valve.

Which antithrombotic regimen is most appropriate for the patient?

A. Warfarin (INR goal 2.5-3.5) + ASA long term

B. Warfarin (INR goal 2-3) + ASA for 3-6 months then long term ASA

C. Warfarin (INR goal 2-3) monotherapy for 3-6 months followed by ASA long term

D. ASA + clopidogrel for 3-6 months then ASA long term

Assessment Question: Correct Response

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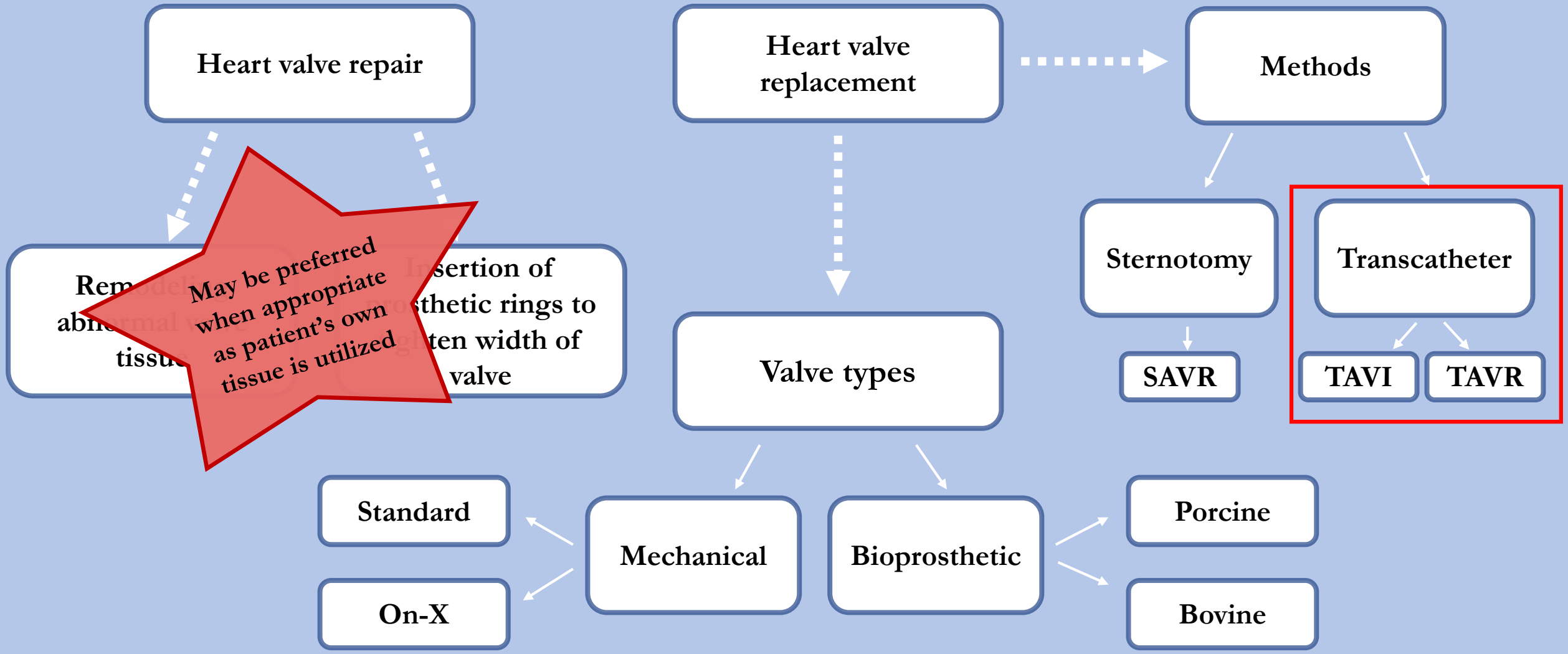
Key Points

Antiplatelet agents are mainstay therapy for patients with bioprosthetic valves

Long-term therapy with warfarin does not appear to provide additional thromboembolic protection and may increase risk of bleeding

The role of DOAC agents in patients with bioprosthetic valves is promising, but further research is indicated to clarify the risks and benefits

Intervention



Source(s): Exp Ther Med. 2016 Apr;11(4):1184-1188.

Transcatheter Aortic Valve Implantation/Replacement (TAVI/TAVR)

Mechanical or bioprosthetic?

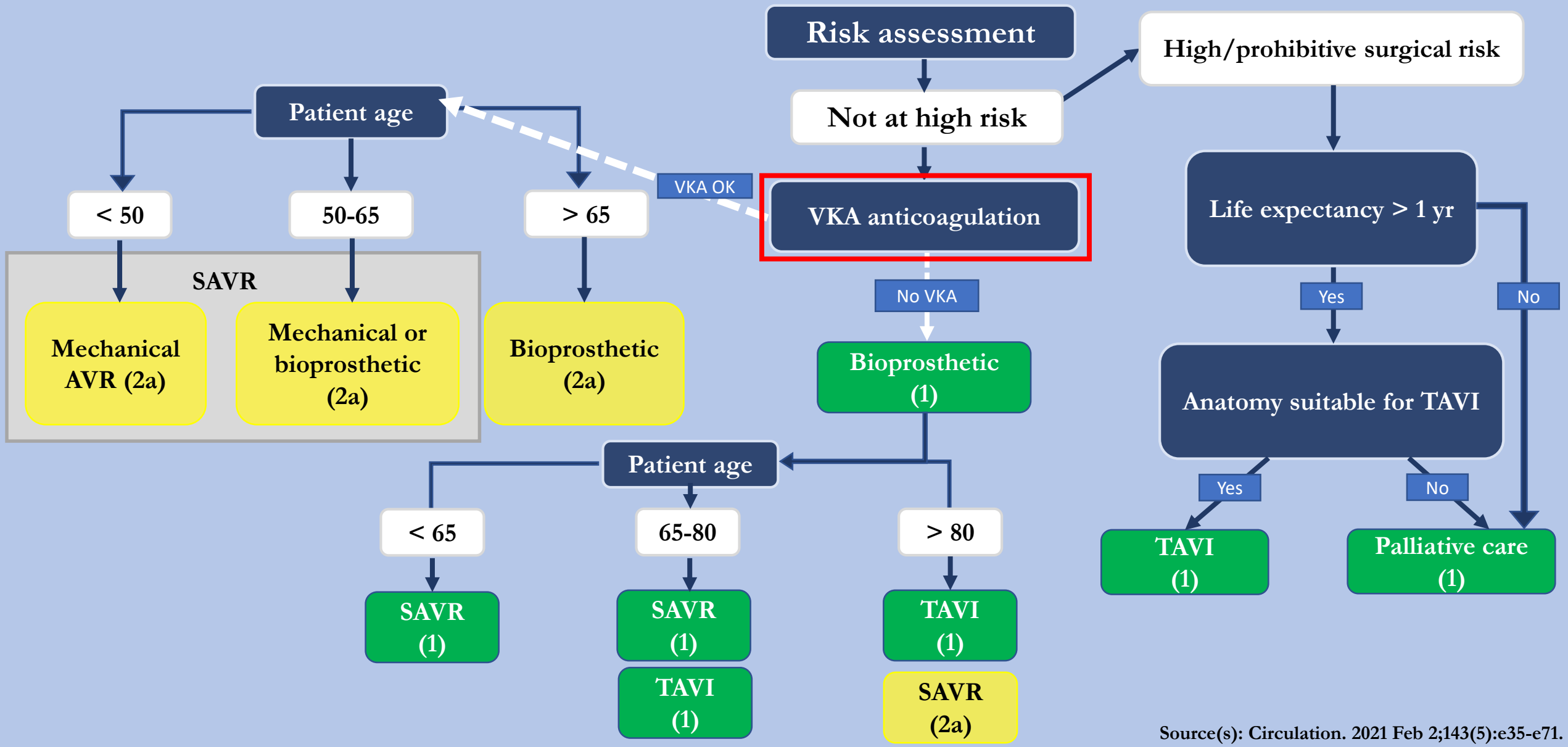
- Structurally similar to bioprosthetic valve
- Recovery time similar to coronary angiogram
- Research suggests valve lifespan of ~10 years

How does it differ from traditional valve replacements?

- Minimally invasive procedure vs sternotomy
- Valve inserted through a catheter
  - New valve placed inside diseased valve (TAVI)
  - New valve replaces diseased valve (TAVR)

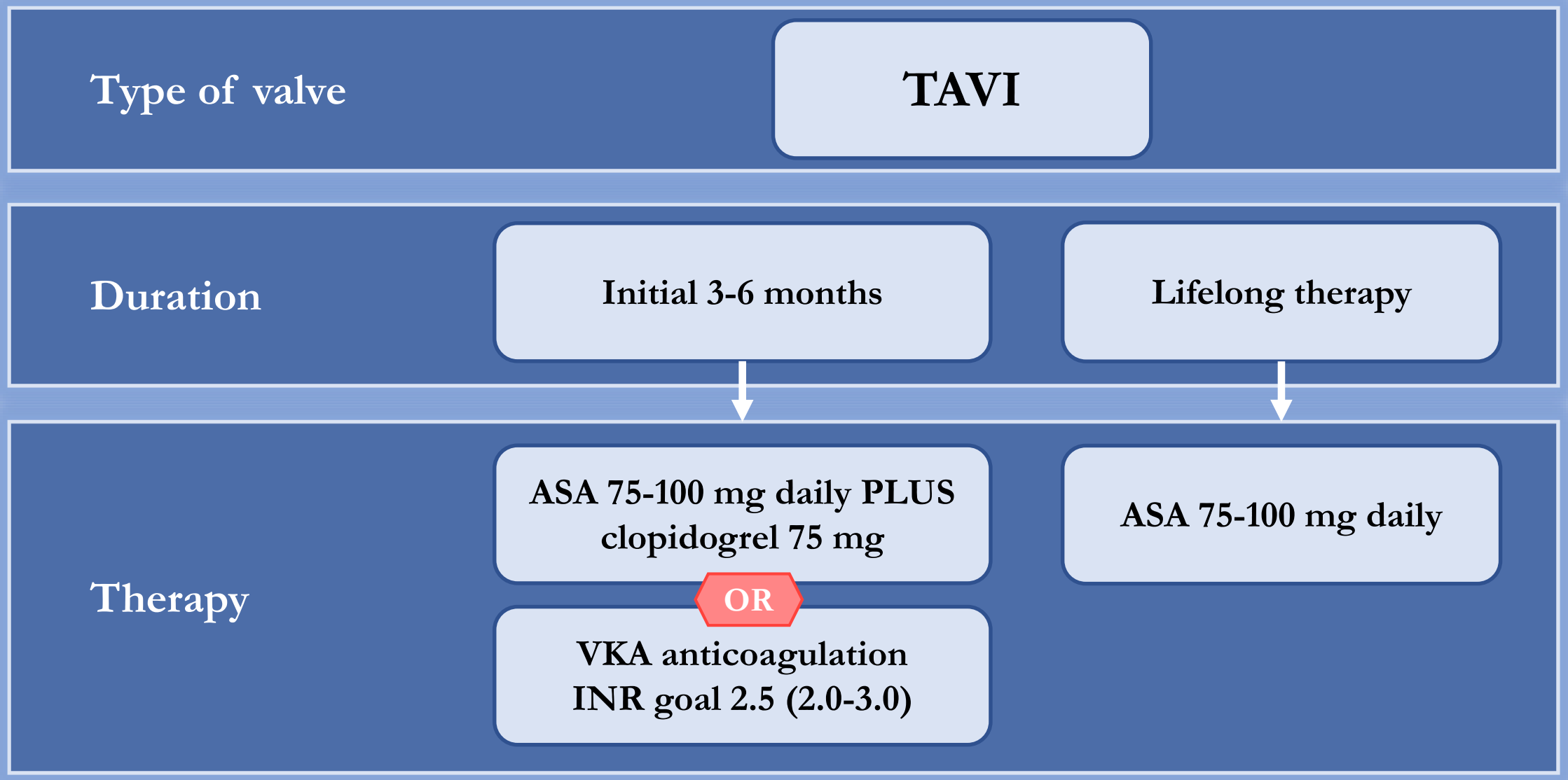
Source(s): J Interv Cardiol. 2020 Dec 24;2020:2582938.

TAVI vs. SAVR



Source(s): Circulation. 2021 Feb 2;143(5):e35-e71.

Antithrombotic Therapy after TAVI



Source(s): Circulation. 2021 Feb 2;143(5):e35-e71.

ATLANTIS Trial – Stratum 2: Intervention

International, randomized, superiority trial

Patients with TAVI + no indication for anticoagulation

Apixaban 5 mg BID	vs.	ASA + clopidogrel
2.5 mg BID if CrCl 15-29 mL/min or receiving APT		Dose adjusted per provider
749 patients		751 patients
391 (74.3%) apixaban alone 116 (22.05%) apixaban + SAPT 19 (3.6%) triple therapy**		412 (78.8%) ASA and clopidogrel 109 (20.8%) ASA OR clopidogrel 2 (0.4%) VKA and SAPT

**oral anticoagulation with ASA + clopidogrel

Source(s): Eur Heart J. 2022 Aug 1;43(29):2783-2797.

ATLANTIS Trial: Endpoints

✓ Efficacy

- Primary at 1 yr: composite of death, MI, stroke, TIA, systemic embolism, VTE, intracardiac or valve thrombosis
- Secondary: death, MI, or any stroke/TIA

Safety

- Primary: Bleeding events (major, minor, minimal, fatal)

Source(s): Eur Heart J. 2022 Aug 1;43(29):2783-2797.

ATLANTIS Trial: Outcomes

Efficacy

Outcome	Apixaban – no. (%) N = 749	APT – no. (%) N = 751	HR (95% CI)
Primary	89 (16.9)	101 (19.3)	0.88 (0.66-1.17)
Death Cardiovascular Non-cardiovascular	31 (5.9) 17 (3.2) 14 (2.7)	18 (3.4) 13 (2.5) 5 (0.96)	1.86 (1.04-3.34) 1.42 (0.69-2.95) 2.99 (1.07-8.36)
Valve thrombosis	6 (1.1)	32 (6.1)	0.19 (0.08-0.46)

Safety

Primary	41 (7.8)	38 (7.3)	1.09 (0.70-1.69)
Minor bleeding	49 (9.3)	51 (9.8)	0.96 (0.65-1.43)
Any bleeding	115 (21.9)	112 (21.4)	1.05 (0.81-1.36)

Source(s): Eur Heart J. 2022 Aug 1;43(29):2783-2797.

ATLANTIS Trial: Conclusion

Conclusion

Apixaban compared to "standard of care":

- Similar in antithrombotic events
- Similar in bleeding events
- May be associated with increased risk of death

Superior? No

Non-inferior? Yes

Source(s): Eur Heart J. 2022 Aug 1;43(29):2783-2797.

GALILEO Trial: Intervention

S/p successful TAVR + no indication for anticoagulation

Rivaroxaban 20 mg daily if patient developed AF

VKA daily if patient developed AF (INR goal 2-3)

Rivaroxaban 10 mg daily + ASA 75-100 mg daily x3 months

vs.

ASA 75-100 mg daily + Clopidogrel 75 mg daily x3 months

826 patients

818 patients

Median time from TAVR to randomization: 2.0 days

Patient population: ~81 years old ~51% female

Source(s): N Engl J Med. 2020 Jan 9;382(2):120-129.

GALILEO Trial: Endpoints

✓ Efficacy

- Primary: Composite of death from any cause
  - Thromboembolic events (stroke, MI, valve thrombosis, etc.)
- Secondary: Death from cardiovascular causes

Safety

- Primary: Composite of life-threatening, disabling, or major bleeding

Source(s): N Engl J Med. 2020 Jan 9;382(2):120-129.

GALILEO Trial: Efficacy Outcomes

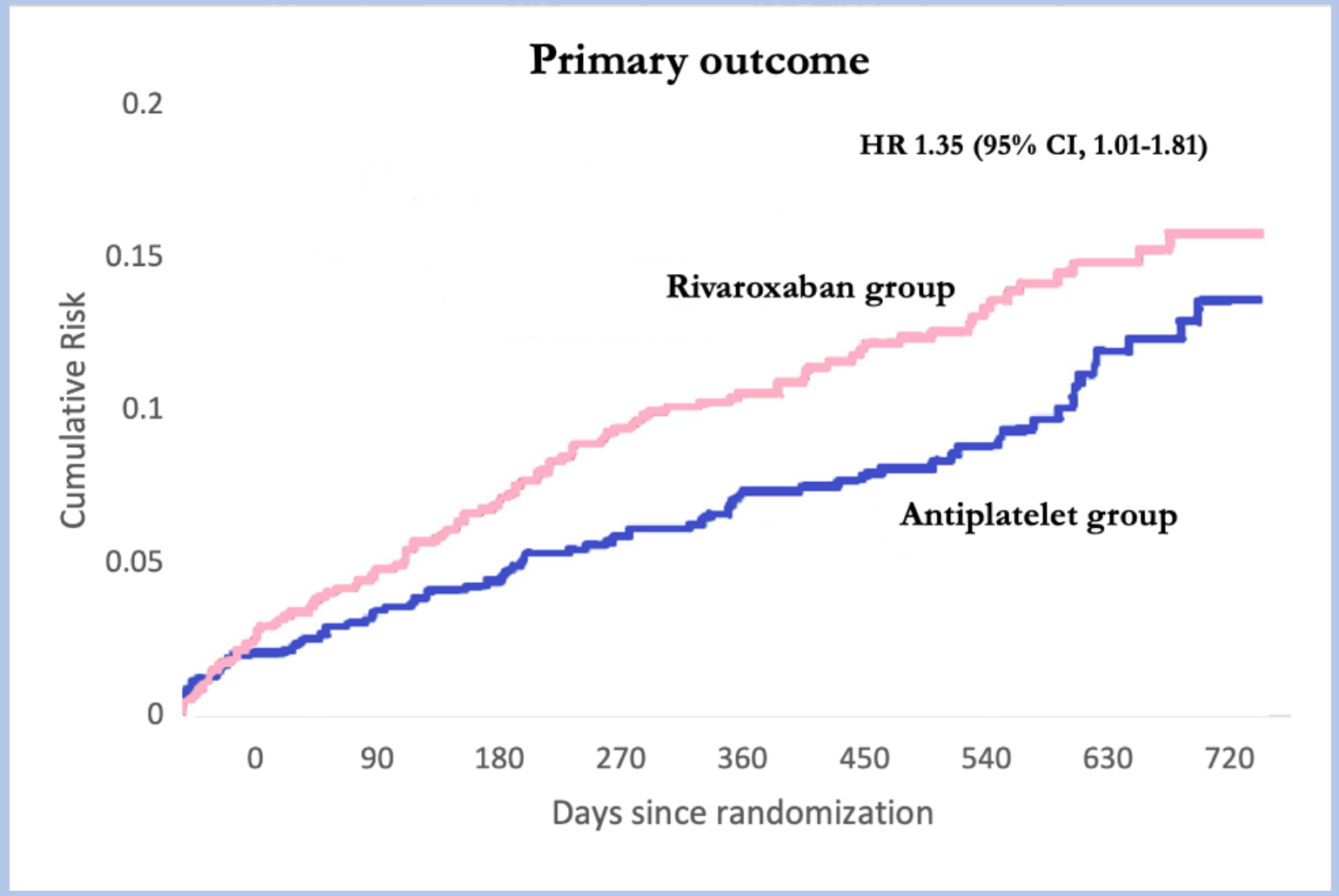
Death from any cause/first thromboembolic event	• 105 patients (12.7%) rivaroxaban group • 78 patients (9.5%) antiplatelet group
Death from cardiovascular causes	• 83 patients (10.0%) rivaroxaban group • 68 patients (8.3%) antiplatelet group
Valve thrombosis	• 3 patients (0.4%) rivaroxaban group • 7 patients (0.9%) antiplatelet group

<u>Total deaths</u> Rivaroxaban group: 64 Antiplatelet group: 38	HR 1.69 (95% CI 1.13-2.53)

Safety outcome:
No significant between-group difference in rate of life-threatening or disabling bleeding

Source(s): N Engl J Med. 2020 Jan 9;382(2):120-129.

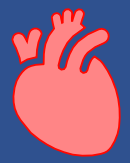
GALILEO Trial: Efficacy Outcomes



Source(s): N Engl J Med. 2020 Jan 9;382(2):120-129.

GALILEO Trial: Conclusion

Rivaroxaban compared to antiplatelet therapy



Higher rates of death or thromboembolic complications

Higher risk of bleeding

Unanswered question:

Would lower dose of rivaroxaban (2.5 mg) have better risk-benefit profile?

Source(s): N Engl J Med. 2020 Jan 9;382(2):120-129.

POPULAR-TAVI Trial: Intervention

All patients receiving anticoagulation before randomization

Patients undergoing TAVI on anticoagulation with appropriate indication

Oral anticoagulation	vs.	Oral anticoagulation + clopidogrel x 3 months
157 patients		156 patients

Baseline anticoagulant:
VKA: 75.2%
DOAC: 23.6%

Patients:
~81 yr
45.4% women
~94-95% AF

Source(s): N Engl J Med. 2020 Apr 30;382(18):1696-1707.

GALILEO Trial: Endpoints

✓ Efficacy

- Primary: All bleeding + non-procedural related bleeding
- Secondary: CV death, non-procedure bleeds, stroke from any cause, or MI

Safety

- Primary: Composite of life-threatening, disabling, or major bleeding

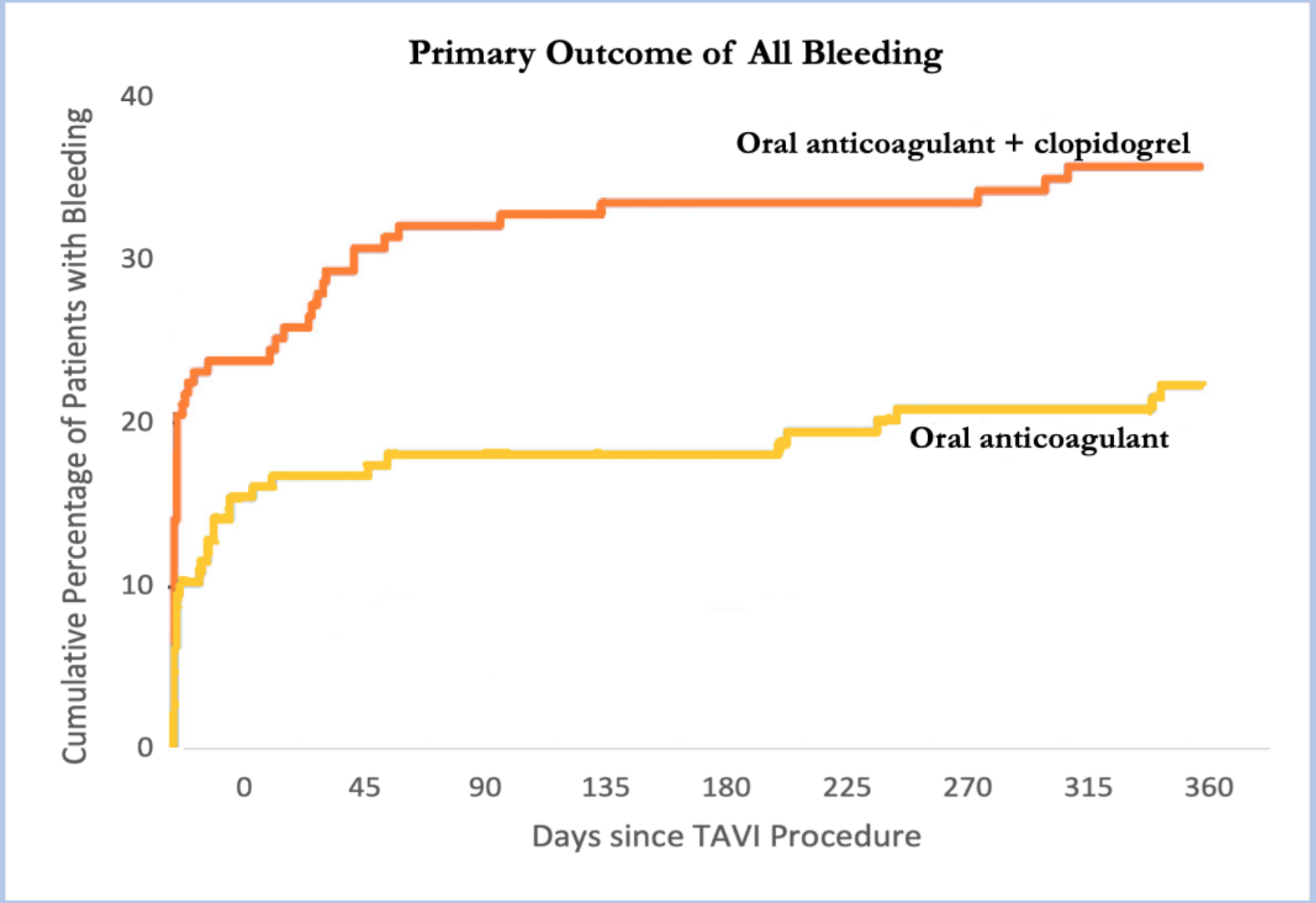
Source(s): N Engl J Med. 2020 Jan 9;382(2):120-129.

POPULAR-TAVI Trial: Efficacy Outcomes

Outcome	Oral anticoagulation	Oral anticoagulation PLUS clopidogrel	Risk ratio (95% CI)
All bleeding	34 (21.7%)	54 (34.6%)	0.63 (0.43 to 0.90)
Non-procedure-related bleeding	34 (21.7%)	53 (34.0%)	0.64 (0.44 to 0.92)
CV death, non-procedure bleeds, any stroke, MI	49 (31.2%)	71 (45.5%)	0.69 (0.51 to 0.92)

Source(s): N Engl J Med. 2020 Apr 30;382(18):1696-1707.

POPULAR-TAVI Trial: Efficacy Outcomes



Source(s): N Engl J Med. 2020 Apr 30;382(18):1696-1707.

POPULAR-TAVI Trial: Conclusion

Incidence of serious bleeding over 1 year:

Lower with oral anticoagulation alone than oral anticoagulation with clopidogrel

Source(s): N Engl J Med. 2020 Apr 30;382(18):1696-1707.

Assessment Question

Based on existing evidence, which antithrombotic regimen for a patient post-TAVI without an indication for anticoagulation is most appropriate?

A. Patient with h/o PAD discharged on rivaroxaban 10 mg BID + ASA 81 mg daily x 3 months

B. Patient with chronic AF discharged on baseline apixaban 5 mg BID

C. Patient with no other PMH discharged on DAPT x 3-6 months followed by ASA 81 mg long term

D. Patient with chronic AF discharged on baseline warfarin x3 months + ASA 81 mg daily lifelong

Assessment Question: Correct Response

Based on existing evidence, which antithrombotic regimen for a patient post-TAVI without an indication for anticoagulation is most appropriate?

A. Patient with h/o PAD discharged on rivaroxaban 10 mg BID + ASA 81 mg daily x 3 months

B. Patient with chronic AF discharged on baseline apixaban 5 mg BID

C. Patient with no other PMH discharged on DAPT x 3-6 months followed by ASA 81 mg long term

D. Patient with chronic AF discharged on baseline warfarin x3 months + ASA 81 mg daily lifelong

Key Points

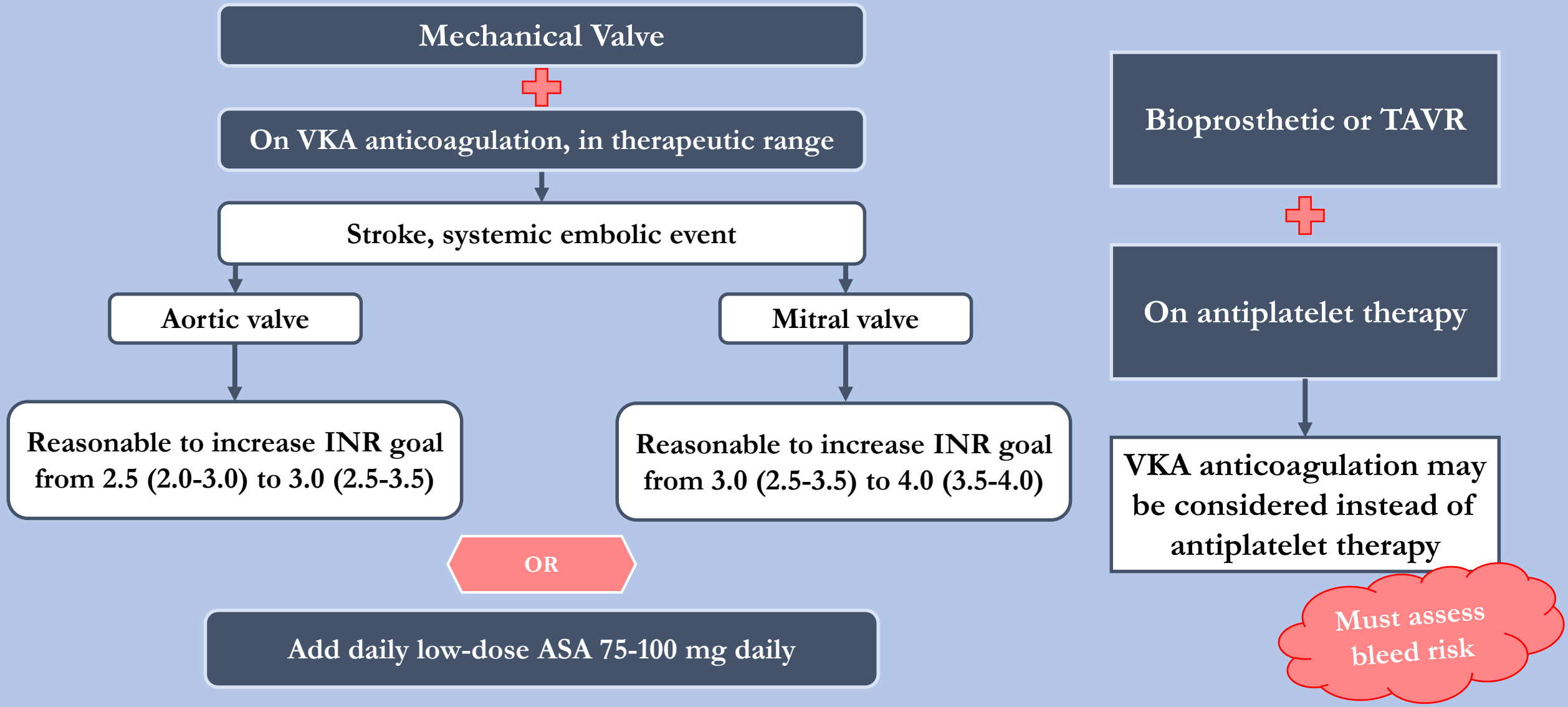
If no other antithrombotic needs besides TAVR indication:

- **Use SAPT vs DAPT, anticoagulation**

If anticoagulation needed for other indications:

- **Use oral anticoagulant (no significant difference in VKA vs DOAC according to literature)**
- **Avoid additional antiplatelet therapy unless strong indication**

Thromboembolic Events with Prosthetic Valves

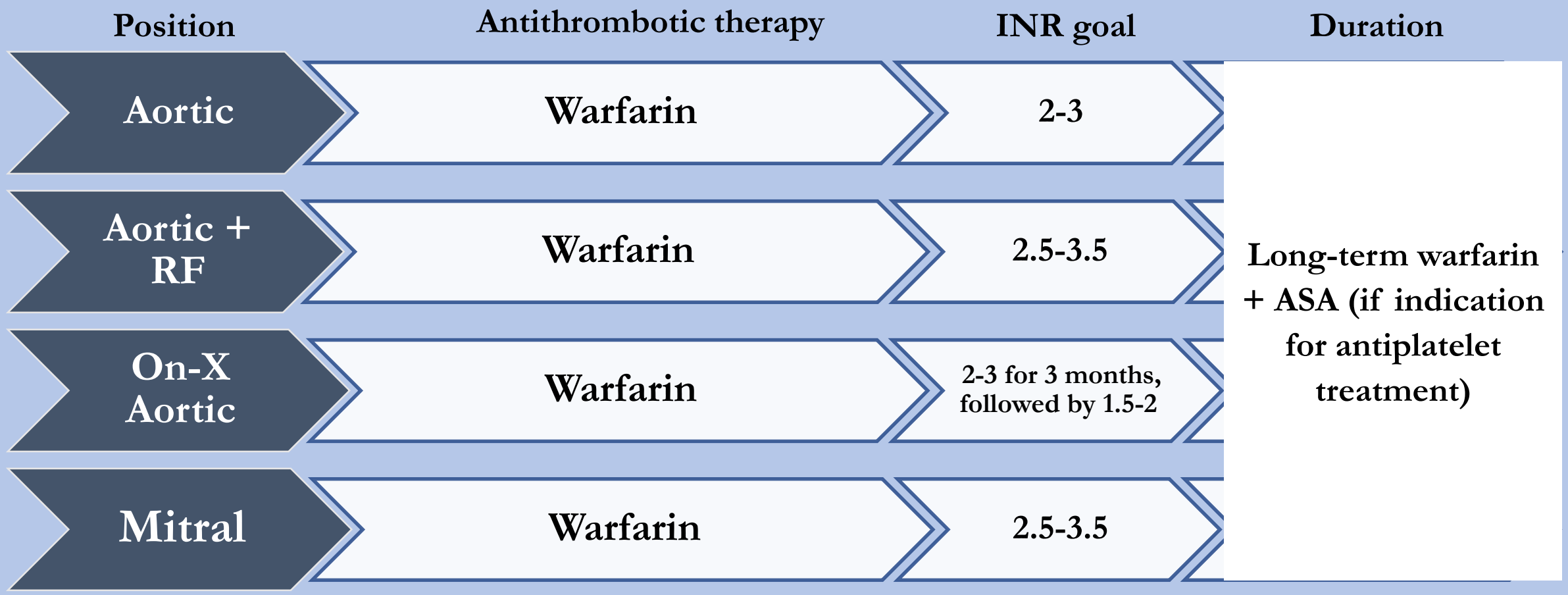


Source(s): Circulation. 2021 Feb 2;143(5):e35-e71.

Summary – Bioprosthetic valves

Position	Antithrombotic therapy	INR goal	Duration
TAVR	ASA 81 mg + clopidogrel 75 mg (or warfarin if alternative OAC indication)	2-3 if warfarin is utilized	3-6 months, followed by long-term ASA
Aortic	ASA 81 mg ± warfarin (based on bleeding risk)	2-3	Warfarin 3-6 months (if selected) + long-term ASA
Mitral	ASA 81 mg + warfarin	2-3	Warfarin 3-6 months + long-term ASA

Summary – Mechanical valves



RF: Risk factors (history of VTE, LV dysfunction, hypercoagulable state

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Thank you!

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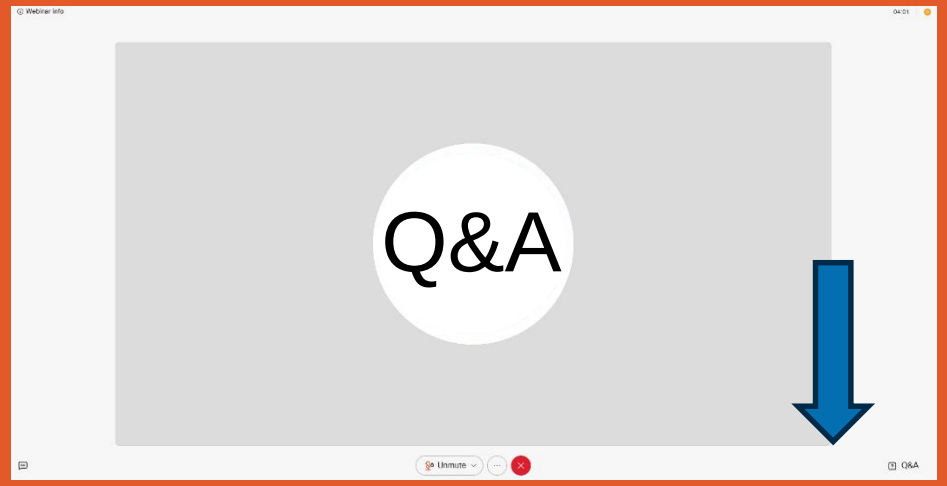
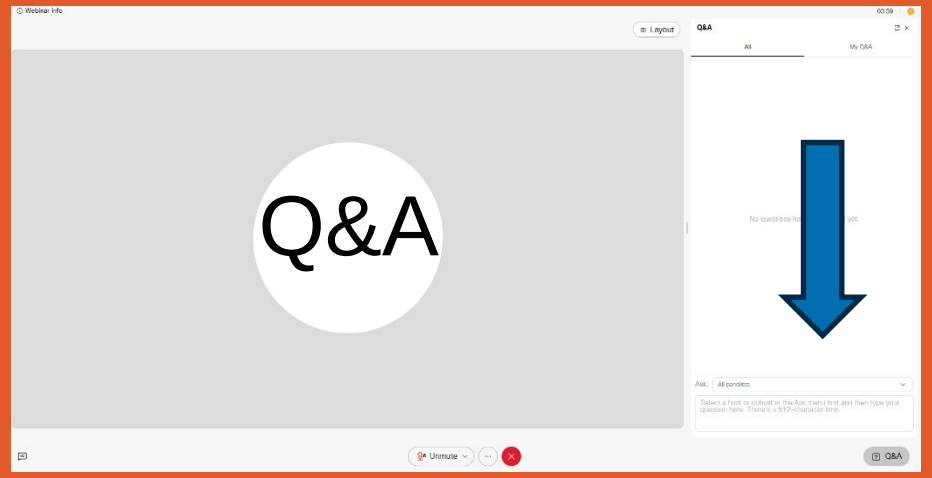
Questions?





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