Review Article

Antithrombotic Therapy Considerations in Mechanical and Bioprosthetic Cardiac Valves

by Yi Kan Leung, PharmD

Valvular heart disease is a leading cause of cardiovascular morbidity and mortality worldwide.[1,2] The prevalence is high, at about 25% of the general population, and projected to increase in the coming decades.[1,2] There are four valves in the heart: the tricuspid, pulmonic, mitral, and aortic valves. Blood from the body flows into the right atrium, passes through the tricuspid valve into the right ventricle, then is sent through the pulmonary valve into the lungs for gas exchange. After being oxygenated through the lungs, the blood then returns to the left atrium, passes through the mitral valve into the left ventricle, and is pushed through the aortic valve to the whole body. The cardiac valves prevent back-flow between the heart chambers and maintain the pressure gradients necessary for hemodynamic circulation.

Globally, the most prevalent valve pathologies include rheumatic heart disease, aortic valve stenotic disease, mitral regurgitation, and aortic regurgitation.[1] In developing countries, rheumatic heart disease is the most common valvular heart disease, affecting about 41 million people with prevalence continuing to increase. Prognosis for rheumatic heart disease without treatment is poor, with a 5-year mortality rate of up to 94% for patients who are unable to tolerate surgical or transcatheter intervention. In developed countries, aortic valve stenotic disease is the most common valvular heart disease, accounting for 61% of all valvular heart disease deaths. About 75% of patients with severe aortic stenosis are symptomatic.[3]

Aortic valve replacement (AVR) is the treatment of choice for patients with symptomatic aortic stenosis and those with left ventricular dysfunction. Aortic regurgitation is associated with diastolic hypertension and is also rising in prevalence in developed countries.[1] Etiologies responsible for chronic aortic regurgitation can be extensive, including rheumatic heart disease, age-related aorta dilation, congenital valve abnormalities, infective endocarditis, and others. Valvular surgery is necessary for moderate to severe cases of aortic regurgitation. Mitral valve disease, which accounts for 15% of all valvular heart disease deaths in developed countries, includes mitral regurgitation, mitral stenosis, and mitral valve prolapse. Mitral regurgitation accounts for the majority of mitral valve disease cases, affecting more than 10% of the population over 75 years old.[4] Surgical intervention is the recommended treatment for mitral regurgitation, while pharmacological treatment improves symptoms but does not improve survival. There are other clinical settings in which the native cardiac valves are beyond repair and need to be replaced. Prosthetic valves used in replacement surgeries include both mechanical and bioprosthetic (tissue) valves, which have different thromboembolism risks and anticoagulation requirements, which will be discussed later.

Cardiac valve replacement can be performed either as a traditional open-chest surgery that can last for hours, or via a transcatheter procedure in which the valve is inserted into a blood vessel from the chest or groin area with imaging guidance.[5-7] Transcatheter implantation is considered minimally invasive because only a small puncture is needed for temporary catheter access during the procedure, which reduces the risks for surgical blood loss and infection.[5] Transcatheter implantation also greatly shortens the length of operation and surgical site healing time. Therefore, transcatheter methods have largely replaced traditional open-chest surgery for cardiac valve replacement.

Patients with valvular heart disease are at high risk for thrombosis, which can lead to transient ischemic attack and stroke.[4] Factors that influence the risk of thrombosis in patients with valve replacements include the implanted valve material and design, location of the implant (high versus low pressure gradient), and time since valve placement (before or after the 3-month mark) (Table 1).

Thromboembolic risk relative to valve position is related to the intracardiac pressure of the valve. Tricuspid, pulmonic, and mitral valves have a higher risk due to possessing a lower pressure gradient, which results in slower blood flow and thus an increased thromboembolic risk. The aortic valve has a higher blood pressure gradient; thus, blood flow is faster and less likely to form clots. Additionally, mechanical valves are more thrombogenic than bioprosthetic valves. This is because when blood is exposed to an artificial (non-tissue) surface, it causes more significant disruptions in blood flow and prompts clot formation.[2] However, patients who undergo valve replacement surgeries are at high risk for both thrombosis and hemorrhage.

TABLE 1. Risk Factors for Thrombosis in Patients with Valve Replacement[2]

Characteristic	*Higher Thromboembolism Risk*	*Lower Thromboembolism Risk*
Material	Mechanical	Bioprosthetic
Design	Caged-ball, tilting disc	Bi-leaflet
Position	Mitral, tricuspid	Aortic
Side of the heart	Right	Left
Time since valve placement	0-3 months	>3 months

Balancing the risk between thrombosis and hemorrhage is a delicate art, as there are numerous patient characteristics that need to be taken into consideration (e.g. advanced age, comorbidities, mobility) as well as commonly prescribed medications post-surgery that impact hemostasis (e.g. antiplatelets, NSAIDs).

Patients with mechanical valves require life-long anticoagulation, while those with bioprosthetic valves may stop after a specific period of time. Aspirin and vitamin-K antagonist (VKA; e.g., warfarin) are the common medications used in this setting. Numerous trials have established that warfarin is superior to aspirin in reducing thromboembolic risk in patients with mechanical valves.[8-10] It is notable that patients with bioprosthetic valves and not on any antithrombotic therapies have even lower thromboembolic risk compared to those with mechanical valves on warfarin.[8-10] Moreover, patients with bioprosthetic valves may use direct oral anticoagulants (DOAC) for anticoagulation, which require far less monitoring compared to warfarin. This treatment strategy has increased the utilization of bioprosthetic valves over mechanical valves.

The 2020 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Management of Patients with Valvular Heart Disease published recommendations on anticoagulation and antiplatelet therapies based on valve type, implant position, and patient-specific risk factors for thrombosis (Table 2).[6] Risk factors in consideration include prior thromboembolism (TE), atrial fibrillation (AF), rheumatic mitral stenosis (any degree), and left ventricular ejection fraction (LVEF) < 35%.

TABLE 2. Antithrombotic Strategies by ACC/AHA Guidelines[6]

Type	Position	Risk Factors	Warfarin	Antiplatelet Therapy
Mechanical	Mitral	Any mitral valve (include On-X®)	INR 2.5-3.5	ASA 75-100 mg if otherwise indicated AND low risk of bleeding
	Aortic	AF, previous TE, LV dysfunction, hypercoagulable state		
	Aortic	No additional risk factors	INR 2-3	
On-X® Mechanical	Aortic	No additional risk factors	INR 2-3 x 90 days, then INR 1.5-2.0	ASA 75-100 mg daily
Bioprosthetic	Aortic / Mitral	Low risk of bleeding	INR 2-3 x 3-6 months (OR use DOAC)	ASA 75-100 mg if no other oral anticoagulant indication

Note: INR – international normalized ratio, DOAC – direct oral anticoagulants, ASA – aspirin, AF – atrial fibrillation, TE – thromboembolism, LV – left ventricle

TABLE 3. Thromboembolism (TE) Risk Categories Per 2022 CHEST Guideline[17]

High TE Risk (>10%/yr risk of ATE)	Moderate TE Risk (4-10%/yr risk of ATE)	Low TE Risk (<4%/yr risk of ATE)
MVR with Risk factors AVR with caged ball / tilting-disc devices	MVR without Risk factors AVR with Risk factors	AVR without Risk factors

Note: TE – thromboembolism, ATE – arterial thromboembolim, MVR – mitral valve replacement, AVR – aortic valve replacement

Mechanical Valves

There are three types of mechanical valve designs, which include bi-leaflet (e.g., St. Jude, CarbomedicsTM, On-X®), single-tilting disc (e.g., Medtronic-Hall), and caged-ball (e.g., Starr-Edwards). Earlier tilting-disc valve types (e.g., Omniscience, Lillehei-Kaster, Björk–Shiley) are associated with a greater risk of complications. Caged-ball valves have unfavorable hemodynamic qualities, which pose a higher risk of TE; therefore, these earlier designs are considered retired and no longer implanted.

As mentioned above, thromboembolic risk varies with time since implantation, valve position, and valve type. Mechanical valves are known for their strength and durability, as they can easily last over 20 years. However, they are also notorious for having frequent complications with thromboembolism and prosthetic valve thrombosis. Even with therapeutic anticoagulation, these patients have the highest risk of TE during the first three to six months post-implantation, especially in the first 30 days.[11] Therefore, patients with mechanical valves require anticoagulation, which typically includes early bridging with heparin overlapping with long-term VKA therapy (i.e., lifelong warfarin). The addition of aspirin is generally not required unless there is a concurrent indication, except for patients with aortic On-X® valves, who should be on aspirin even with no additional risk factors. Adding an antiplatelet agent to anticoagulation decreases thromboembolic risk but also increases the risk of major bleeding.[12] Prescribers should discuss both risks and benefits with patients considering mechanical valves and concurrent indications for an antiplatelet agent.

Typically, the INR goal range is 2.5-3.5 for mechanical mitral valves and mechanical aortic valves with concurrent risk factors due to high thromboembolic risk. A lower INR goal range of 2-3 can be pursued for mechanical aortic valves with no additional risk factors and for first three months post-implant of aortic On-X® valves.[6,13] After three months of On-X® aortic valve implantation, the INR goal range is further reduced to 1.5-2.[6,13] This recommendation was based on the result from the PROACT trial comparing goal INR 1.5-2.0 versus INR 2-3 in patients with aortic On-X® valves.[13] The mean INR was 1.89 ± 0.49 versus 2.50 ± 0.63 (p<0.0001), with significantly less major bleeding in the lower INR group (1.48 %/year versus 3.31 %/year, p=0.032) but no difference in ischemic stroke, all TE, and composite outcome (major bleeding, TE).[13]

Although DOACs are more convenient and require less monitoring than VKA, DOACs should not be used in patients with mechanical valves. They have been shown to be inferior to VKA in randomized trials.[14,15] The PROACT Xa study investigated the possibility of using DOACs instead of

warfarin for anticoagulation in patients with On-X® aortic valves.[14] The trial enrolled 863 patients who were at least three months post-On-X® AVR procedure. All participants received aspirin 81 mg daily in addition to either apixaban 5 mg twice daily or warfarin (goal INR 2-3). This trial found apixaban to be a less effective anticoagulation option than warfarin in patients with On-X® aortic valve as the apixaban group showed significantly more valve thrombosis and valve-related TE events (difference in primary composite end-point rates 2.9, 95% CI 0.8-5.0).

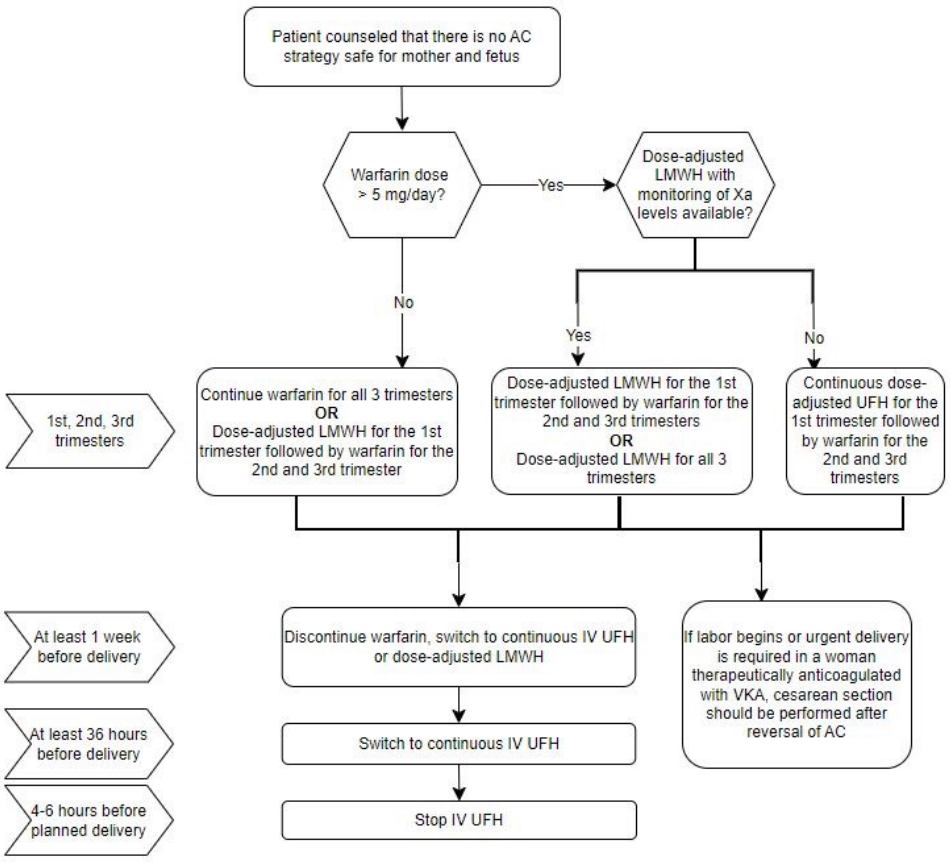
Additionally, dabigatran is contraindicated in these patients based on the results from the RE-ALIGN trial, which demonstrated that dabigatran use was associated with higher risk of thromboembolic events and bleeding compared to warfarin in patients with mechanical AVR or mitral valve replacement (MVR).[15] The trial was terminated early due to excess negative outcomes in the dabigatran group.

Mechanical Valves & Pregnancy

While warfarin is effective in preventing valve thrombosis, it is also teratogenic and increases the risk of serious fetal complications including stillbirth.[16] ACC/AHA acknowledge the challenges associated with antithrombotic management in pregnant patients with mechanical valves. The published 2020 ACC/AHA guideline included a flow chart (Figure 1) for recommendations on anticoagulation pertaining to pregnancy and mechanical valves.[6]

Figure 1 shows that warfarin should be replaced by dose-adjusted low molecular weight heparin (LMWH), such as enoxaparin, at least for the first trimester, except for daily warfarin dose of 5 mg or less, in which case warfarin may be continued after a discussion of risks versus benefits with a patient.[6] Warfarin may be resumed for the second and third trimester. At least one week prior to expected delivery, warfarin should be stopped and switched to heparin or LMWH. In case labor begins prior to expected dates and urgent delivery is required, anticoagulation should be reversed before performing a cesarean section.

FIGURE 1. ACC/AHA Guideline on Pregnancy and Mechanical Valves[6]



Warfarin Peri-operative Management with Mechanical Valves

Due to its half-life, warfarin typically needs to be held for five days prior to procedures with high bleeding risk. Whether the patient should be bridged with heparin/LMWH post-op remains a point of debate and confusion. The CHEST 2022 guidelines listed three categories of TE risk (Table 3).[17] Risk factors in consideration include AF, prior stroke or transient ischemic attack (TIA), prior valve thrombosis, rheumatic heart disease, hypertension (HTN), diabetes, congested heart failure (CHF), and age ≥ 75. The CHEST 2022 guideline recommends heparin bridging in patients on VKA for mechanical valve only if they fall into the "High TE Risk" category. For low- to moderate-risk patients, the guidelines suggest against heparin bridging, although there may be select moderate-risk patients within this classification grouping in whom heparin bridging could be considered after weighing risks vs. benefits.

Bioprosthetic Valves

Bioprosthetic valve options include pericardial and xenograft valves, typically created from porcine aortic valves or bovine pericardium.[5] Other options include aortic homografts (from a human donor) and the Ross procedure (pulmonary autograft to aorta + pulmonary homograft to replace pulmonary valves). Bioprosthetic valves are less thrombogenic compared to mechanical valves; therefore, anticoagulation may be stopped after three to six months per provider discretion.[5-7] Generally, bioprosthetic valves are durable and can last for 10-20 years. The 2020 ACC/AHA guideline recommends three to six months of anticoagulation therapy with warfarin or DOAC after bioprosthetic AVR/MVR procedures (Table 2).[6]

Transcatheter Aortic Valve Replacement (TAVR)

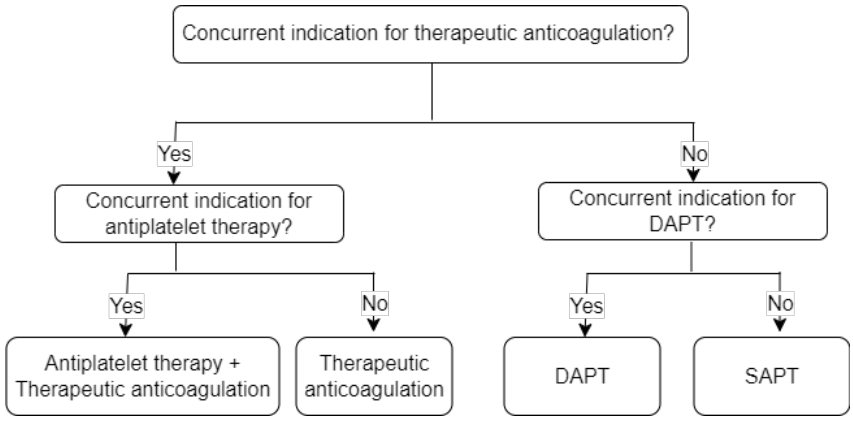
Transcatheter aortic valve replacement/insertion (TAVR/TAVI) is the transcatheter insertion of the replacement aortic valve. Common brand names for these

bioprosthetic valves include CoreValve, SAPIEN, etc. It is common practice to start antiplatelet therapy after TAVR. A meta-analysis with three randomized trials compared dual antiplatelet therapy (DAPT) versus single antiplatelet therapy (SAPT) in post-TAVR patients and revealed no significant difference between the two groups in the occurrence of the 30-day combined endpoint (death, major or life-threatening bleeding, major vascular complications) (DAPT 17.6% versus SAPT 10.9%, OR 1.73, 95% CI 1.00-2.98), all ischemic events (3.8% versus 3.8%, OR 1.00, 95% CI 0.37-2.71), and all-cause death (5.2% versus 3.8%, OR 1.40, 95% CI 0.56-3.51).[18] However, significantly more major bleeding events were reported in the DAPT group (11.4% versus 5.2%, OR 2.24, 95% CI 1.12-4.46).[18]

The Galileo trial investigated DOAC versus aspirin to prevent thromboembolic events post-TAVR.[19] The DOAC group received rivaroxaban 10 mg + aspirin 81 mg for first three months post-TAVR, then continued with rivaroxaban 10 mg daily. The aspirin group received DAPT for the first three months, then continued with aspirin 81 mg daily. After a median follow-up period of 17 months, the DOAC group had significantly higher occurrence of the combined endpoint (death, stroke, myocardial infarction, valve thrombosis, venous TE, systemic embolism) compared to the aspirin group (HR 1.35, 95% CI 1.01-1.81). There was no difference in major bleeding occurrence between the two groups (HR 1.50, 95% 0.95-2.37). Therefore, aspirin is the preferred option over a DOAC when there are no other indications for anticoagulation.

It is important to note that the Galileo trial excluded patients with AF or venous TE.[19] For patients with TAVR and concurrent indication for anticoagulation (e.g. AF, venous TE), per data review of the Society of Thoracic Surgeons and ACC Transcatheter Valve Therapy Registry 2013-2018, DOACs are preferable to warfarin due to lower cumulative incidence for intracerebral hemorrhage (0.33% versus 0.59%, HR 0.54, 95% CI 0.33-0.87), bleeding (11.9% versus 15%, HR 0.81, 95% CI 0.75-0.89), and all-cause mortality (15.8% versus 18.2%, HR 0.92, 95% CI 0.85-1.00).20 In short, DOACs should not regularly be used for TAVR alone, but they are safe and preferred options for concurrent indications in patients with TAVR (Figure 2).

FIGURE 2. Post-TAVR Antithrombotic Strategies



Transcatheter Mitral Valve Replacement (TMVR)

Transcatheter mitral valve repair (TMVR) is like TAVR but operates on the mitral valve instead of the aortic valve. It is a safe and effective treatment for mitral regurgitation, especially for patients who cannot tolerate conventional surgery and/or are at high risk for one. Although both 2020 ACC/AHA guidelines and 2017 European Society of Cardiology guidelines recommend TMVR as treatment option, there is no standard consensus on antithrombotic strategy post-TMVR.[6,7] A meta-analysis with five observational cohort studies compared therapeutic anticoagulation for at least four weeks following TMVR versus no anticoagulation.[4] This study found significantly reduced rates of stroke in the anticoagulation group (RR 0.14, 95% CI 0.0-0.77, p=0.02) but no differences between groups in rates of bleeding, combined endpoints, and all-cause death. Therefore, it may be beneficial for physicians to discuss anticoagulation options and risks versus benefits with post-TMVR patients.

Conclusion

Cardiac valve replacement patients remain a significant population in which pharmacists can provide benefit by ensuring safe and appropriate medication therapy and monitoring following these procedures. Despite advances in medical technology and pharmaceutical development, it remains a delicate art to balance thromboembolism risk and hemorrhage risk in patients with prosthetic cardiac valves. Insufficient anticoagulation leads to thrombosis, which subsequently can cause stroke/TIA. However, anticoagulated patients have an increased bleeding risk even when anticoagulants are taken appropriately and are in therapeutic range. Valve-related thrombotic risks are related to the valve location, valve type and material, and patient comorbidities. For mechanical valves, warfarin is the best and only appropriate choice for antithrombotic regimens, with selective use of aspirin based on valve type and concurrent indications. For bioprosthetic valves including TAVR, patients should be on short-term anticoagulation for the first three to six months, then transition to SAPT. Important perioperative considerations for patients taking warfarin with mechanical valves are reflected in the newest CHEST guideline updates, stating most patients will not need to bridge unless they are considered at high risk of TE. Overall, it is important to evaluate risks versus benefits in anticoagulation strategies and individualize treatment plans based on the patient's specific condition and history.

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