Mechanical and Bioprosthetic Heart Valves: Anticoagulant Therapy

Thrombosis Canada
Thrombose Canada

Objective:

To summarize evidence-based recommendations for the management of antithrombotic medications in patients with surgical or transcatheter valve replacement or repair.

Background:

Surgical heart valve replacement can be done with either a bioprosthetic (tissue) or mechanical prosthesis and requires cardiopulmonary bypass, aortic cross-clamping, and sternotomy or thoracotomy. Transcatheter (bioprosthetic aortic, mitral, tricuspid or pulmonic) valve replacement is performed percutaneously, most commonly through the femoral vessels, and avoids the procedural risks involved with surgical valve replacement but is lacking longer-term (15-20+ years) outcome data. Valvular repairs can be performed using a surgical or transcatheter approach.

Antithrombotic Management in Surgical Bioprosthetic Valves

The reported rates of surgical bioprosthetic aortic valve thrombosis and thromboembolism in older studies prior to the use of antithrombotic therapy varies between 0.4-1.3% and 0.5-2.8% per patient year respectively with higher rates reported for surgical bioprosthetic mitral valves. These rates are likely underestimates. Recommendations for antithrombotic therapy in this population are derived from older, lower quality, observational data. Accordingly, professional society (American College of Chest Physicians, American Heart Association/American College of Cardiology and European Society of Cardiology) recommendations differ. Recommendations are summarized in **Table 1**.

Without another indication for anticoagulation:

- In patients with a bioprosthetic aortic valve who are in sinus rhythm and have no other indications for anticoagulant therapy, warfarin for 3-6 months (INR target 2.5) or aspirin (ASA) 81 mg daily may be used. Thereafter, long-term ASA 81 mg daily may be considered.
- In patients with a bioprosthetic mitral valve who are in sinus rhythm and have no other indications for anticoagulant therapy, warfarin for 3-6 months (INR target 2.5) or ASA 81 mg daily may be used. Thereafter, long-term ASA 81 mg daily may be considered.
- In patients with a bioprosthetic tricuspid valve, warfarin for 3 months (INR target 2.5) Is suggested.

With another indication for anticoagulation (e.g., atrial fibrillation)

Patients with a bioprosthetic valve and atrial fibrillation should receive long-term anticoagulant therapy as outlined in the **Clinical Guide, Stroke Prevention in Atrial Fibrillation.** While the RIVER and ENAVLE trials

have provided evidence for the non-inferiority of rivaroxaban and edoxaban compared to warfarin in patients with surgical bioprosthetic valve replacement or repair with or without AF, few patients were enrolled in the first three months after surgery. Additionally, concerning from a safety perspective was the increased rate of pericardial bleeding with dabigatran as compared to warfarin seen in the early post-operative cardiac surgery period in the RE-ALIGN trial. As such, although warfarin is still recommended in guidelines for the first three months after valve implantation, direct oral anticoagulants may be preferred in the longer term.

Antithrombotic Management in Transcatheter Aortic Valve Intervention/Replacement (TAVI/TAVR)

TAVI or TAVR may be used as an alternative to surgical valve replacement in older patients and/or when the risk of conventional open heart surgery is too high. There are currently 2 catheter-delivered valve systems in widespread clinical use to treat aortic stenosis. The SAPIEN valves (Edwards Lifesciences Inc., Irvine, CA) utilize a bovine pericardial valve mounted on a balloon-expandable stent which is placed entirely within the native diseased valve. The Evolut CoreValve ReValving System (Medtronic Inc, Minneapolis, MN) consists of a porcine pericardial valve mounted on a self-expanding stent which extends into the ascending aorta for stabilization.

Without another indication for anticoagulation

In patients without a separate indication for anticoagulation, previous guidelines have recommended the use of dual antiplatelet therapy (DAPT) for 3-6 months after TAVI based on protocols from the original clinical trials comparing TAVI to surgical aortic valve replacement which employed the use of 1-6 months of DAPT. The empiric use of DAPT in these trials was supported by observations that almost 75% of patients undergoing TAVI had evidence of embolic debris with fibrin or thrombotic material and DAPT was postulated to reduced peri-procedural and longer-term atherothrombotic events. More recent data including a patient-level meta-analysis of four randomized controlled trials, however, found an increased risk of bleeding with no reduction in clinical thrombosis in those receiving DAPT as compared to ASA. Furthermore, anticoagulation compared to antiplatelet therapy alone increased the risk of bleeding and death in TAVI patients without another indication for anticoagulation. Accordingly, recommendations in recent guidelines have shifted and now largely recommend single antiplatelet therapy. The 2020 American College of Cardiology/American Heart Association, which suggests consideration of DAPT for 3-6 months or warfarin (target INR 2.5) for 3 months in patients at low risk of bleeding, were published before these more recent data become available.

With another indication for anticoagulation (e.g., atrial fibrillation)

TAVI patients with another indication for anticoagulation, such as atrial fibrillation, should receive an oral anticoagulant as per guideline (See **Clinical Guide:** **Stroke Prevention in Atrial Fibrillation**). The ENVISAGE-TAVI trial provided evidence of comparable benefit with DOACs as compared to warfarin in TAVI patients. In this study, edoxaban was non-inferior to warfarin, but was associated with a higher risk of major bleeding, primarily gastrointestinal. The addition of antiplatelet therapy is not recommended in this population given the results of POPular TAVI trial which found that the addition of clopidogrel to anticoagulation therapy increased bleeding risk without benefit.

Non-Aortic Transcatheter Valve Replacement

Non-aortic transcatheter valve replacements of mitral, tricuspid and pulmonary valves, are becoming increasingly common. Transcatheter mitral valves may have a higher thromboembolic risk as compared to

aortic valves due to their larger size and higher incidence of post procedural atrial fibrillation. Transcatheter tricuspid valves may be associated with even higher thrombotic risk as a result of the lower pressure circulation in the right heart. There is, however, a paucity of data to guide antithrombotic therapy in non-aortic transcatheter valve replacement patients and European and American guidelines make no recommendations on this topic. Available registry data in transcatheter mitral valve replacement patients suggests anticoagulant therapy may reduce the risk of valve thrombosis as compared to antiplatelet therapy. Until additional data are available, in patients without a separate indication for anticoagulation, it may be reasonable to extrapolate antithrombotic therapy guideline recommendations from surgical bioprosthetic valves to transcatheter mitral and tricuspid valves (warfarin for 3 months).

Valvular Repair

Surgical Repair

In patients without a separate indication for anticoagulation, guidelines recommend ASA for at least 3 months after aortic valve repair, ASA or warfarin for 3 months after mitral valve repair and warfarin for 3 months after tricuspid valve repair.

Transcatheter Repair

Guidelines provide no recommendations with respect to antithrombotic therapy in this population. Until additional comparative data are available, it may be reasonable in patients without a separate indication for anticoagulation to use single or dual antiplatelet therapy for1-6 months, followed by single antiplatelet therapy for transcatheter mitral valve repairs as employed in the clinical trials assessing efficacy of these devices. With respect to transcatheter tricuspid valve repairs, it may be reasonable to extrapolate guideline recommendations for surgical tricuspid valve repair and use warfarin for 3 months.

Table 1: Antithrombotic Management in Patients with Bioprosthetic Heart Valves in the absence of other indication for anticoagulation

Bioprosthetic Valve Location/Type	Antithrombotic Recommendation
Surgical aortic valve	Warfarin or ASA x 3-6 months, then consider ASA lifelong
Surgical mitral valve	Warfarin or ASA x 3-6 months, then consider ASA lifelong
Surgical tricuspid valve	Warfarin x 3 months
Transcatheter aortic valve	ASA lifelong

Subclinical Valve Thrombosis

The entity of subclinical valve thrombosis, characterized by hypoattenuated valve leaflet thickening on CT with reduced leaflet motion in the absence of clinical symptoms, initially identified in TAVI patients, is associated with an increased risk of stroke. More recently, it has also been recognized in surgical aortic valve replacement patients. A number of trials (GALILEO, ATLANTIS and ADAPT-TAVR) have examined DOAC use in TAVI patients with or without a long-term indication for anticoagulation. Overall, it appears that anticoagulation reduces the risk of subclinical valve thrombosis as compared to DAPT, however, GALILEO was stopped early due to excess mortality in the rivaroxaban group, with a similar trend seen in ATLANTIS. The value of screening for subclinical valve thrombosis and anticoagulation for its prevention and/or treatment requires further study and cannot be routinely recommended at this time.

Mechanical Valves

There are 3 basic types of mechanical valves:

- Bileaflet (e.g. On-X, St. Judes, most frequently seen today)
- Tilting disc (e.g. Bjork-Shiley, infrequently seen today)
- Ball-cage (e.g. Starr-Edwards, rarely seen today)

Patients with mechanical heart valves are at increased risk for embolic stroke and thrombosis of the valve itself and, therefore, require lifelong anticoagulation. Even with anticoagulation, the risk of stroke/valve thrombosis is ~0.5%/year for mechanical aortic valves, ~0.9%/year with mechanical mitral valves, and ~1.2%/year in those with both aortic and mitral mechanical valves. Mechanical mitral valves are hypothesized to be more thrombogenic than mechanical aortic valves because they are exposed to passive blood flow from the left atrium to the left ventricle; thus they require more intensive anticoagulation compared to mechanical aortic valves. Mechanical valves are rarely used in the tricuspid position, in part because they are at very high risk of thrombosis due to passive and low-pressure blood flow from the right atrium to the right ventricle.

In selecting the optimal anticoagulation for patients with a mechanical heart valve, it is also important to consider the risk of bleeding, the different INR targets depending on valve type and location, and the need for bridging anticoagulant therapy for surgical procedures.

The On-X aortic mechanical valve has design features and construction materials thought to reduce thrombogenicity and flow turbulence compared to other valve designs; theoretically allowing a lower intensity INR target range to protect from valve thrombosis that could result in a lower rate of anticoagulant associated major bleeding. The safety of a lower target range INR (1.5 to 2.0) compared to the traditional target range INR (2.0 to 3.0) following placement of the On-X aortic valve implant was evaluated in the PROACT study. Patients with at least one additional risk factor for stroke were randomized after 3 months of warfarin anticoagulation with an INR target of 2.5 to either the lower INR target range or to continue with the traditional INR target range. All subjects received concurrent low dose ASA 81 mg/day. Follow up was planned for 5 to 8 yrs. Interim results of this trial published in 2014 with an average follow up of 3.8 years reported that the subjects in the lower INR target range group had a significantly lower rate of major bleeding compared to those in the traditional INR target range group (1.48% per year vs 3.26 % per year). There was no difference between the groups on the endpoints of stroke, transient ischemic attack, total neurological events and all-cause mortality. Conversely, the recently published PROACT mitral valve trial in patients with On-X mitral mechanical valve at least 3 months after valve replacement which compared lower target INR range of 2.0-2.5 with standard range of 2.5-3.5 was stopped early due to failure of lower target

INR range to meet non-inferiority with respect to the primary outcome thromboembolism, valve thrombosis, and bleeding events.

Antithrombotic Agents and Dosing for Patients with Mechanical Valves:

Warfarin

Long-term warfarin therapy is indicated in all patients with mechanical heart valves. The target INR is dependent on the valve type and manufacturer (e.g. bileaflet or tilting disc, St. Jude or On-X) and location (e.g. aortic or mitral). See **Table 2** below for INR targets.

Aspirin

It is recommended that patients with a mechanical aortic or mitral valve who are at low risk of bleeding should receive ASA 81 mg daily in addition to the warfarin therapy. Caution should be used in patients with an increased bleeding risk, especially with a history of gastrointestinal bleeding.

Direct Oral Anticoagulants

The direct oral anticoagulants, including dabigatran, apixaban, rivaroxaban and edoxaban, are contraindicated in patients with mechanical heart valves. Randomized trials (RE-ALIGN and PROACT-Xa) demonstrated that dabigatran and apixaban are associated with more thrombosis (RE-ALIGN and PROACT-Xa) and bleeding (RE-ALIGN) compared with warfarin in patients with mechanical heart valves.

Table 2: Anticoagulant Drug Management in Patients with Mechanical Heart Valves

Mechanical Valve Location/Type	INR Target and Range	Recommendation for ASA (81 mg daily)‡
Aortic (St. Jude)	2.5 (range 2.0-3.0)†	Yes
Aortic (On-X) First 3 months	2.5 (range 2.0-3.0)	Yes
Aortic (On-X) After 3 months	1.8 (range 1.5-2.0) ++	Yes
Mitral (any manufacturer)	3.0 (range 2.5-3.5)	Yes
Combined aortic and mitral	3.0 (range 2.5-3.5)	Yes
Pulmonic	2.5 (range 2.0-3.0)	No
Tricuspid	3.0 (range 2.5-3.5)	No
Combined pulmonic and tricuspid	3.0 (range 2.5-3.5)	No

† Higher-intensity INR (target: 3.0) can be considered in selected patients with additional risk factors for stroke and in patients with ball-cage valves (e.g. Starr-Edwards).
++Higher-intensity INR (target 2.5) should be continued beyond 3 months for On-X aortic valves in patients who also have atrial fibrillation or additional risk factors for stroke.
‡ Co-administration of ASA should be considered in selected patients at low risk for bleeding.

Special Considerations:

Periprocedural Management

In patients with a mechanical heart valve who need an elective surgery or procedure, bridging with UFH or LMWH is indicated prior to the surgery or procedure, but may not be required post procedure (PERI-OP 2). [See **Clinical Guide,** Warfarin: Perioperative Management]. Interruption of warfarin in patients with mechanical heart valves is not recommended for minor procedures, such as cataract removal, dental procedures and skin biopsies.

Pregnancy in Women with Mechanical Heart Valves

Pregnant women with mechanical heart valves are at especially high risk of developing thrombotic complications; however, relatively little evidence is available to guide recommendations. These women should be managed by multidisciplinary teams experienced in the care of these patients. Women of childbearing age who have mechanical heart valves should receive preconception counseling regarding risks associated with prosthetic valves and the risks and benefits of antithrombotic therapy.

Therapeutic anticoagulation should continue throughout the pregnancy for all women with mechanical valves. Warfarin is effective in preventing thrombotic complications in pregnant women with mechanical valves, but is associated with risks of teratogenicity, mostly with use during the first trimester, fetal loss and, if used close to term, neonatal hemorrhage. It has been reported that warfarin at low doses is less likely to be associated with adverse fetal outcomes and current guidelines suggest that in women requiring 5 mg per day or less of warfarin, warfarin may be continued throughout the pregnancy while in those who require more than 5 mg per day, twice-daily LMWH monitored with regular anti-Xa testing and dose adjustment or intravenous unfractionated heparin can be considered instead of warfarin for the first trimester. It is important to note that warfarin embryopathy, miscarriage, and stillbirth have been reported in women taking less than 5 mg of warfarin per day. Therefore, in well-informed women who place a relatively higher value on avoiding teratogenic effects, monitored twice-daily LMWH may be considered throughout pregnancy. ASA 81 mg daily can be added during the second and third trimesters to further reduce the thrombotic risk. All pregnant women with mechanical valves should have planned deliveries and should be switched to unfractionated heparin prior to delivery to minimize the time off anticoagulants in the peri-delivery period.

Pediatrics

There are few studies and no randomized controlled trials on the safety and efficacy of antithrombotic therapy post-heart valve placement in children. Children should be managed post-valve placement by a cardiologist and adult recommendations for management should be followed.

Other Relevant Thrombosis Canada Clinical Guides:

- Acetyl Salicylic Acid (ASA)
- Stroke Prevention in Atrial Fibrillation
- Warfarin
- Warfarin: Management of Out-of-Range INRs
- Warfarin: Peri-Operative Management
- Warfarin: Point-of-Care INR Monitoring

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