

MECHANICAL AND BIOPROSTHETIC HEART VALVES: ANTICOAGULANT THERAPY



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OBJECTIVE:

To summarize evidence-based recommendations for the management of antithrombotic drugs in patients with surgical valve replacement (mechanical and bioprosthetic heart valves) and transaortic valve replacement (TAVR or TAVI).

BACKGROUND:

Surgical heart valve replacement (SAVR) can be done with either a bioprosthetic (tissue) or mechanical prosthesis. TAVI or TAVR is undertaken in a heart catheterization lab and the prosthetic aortic valve is deployed via catheter without an open-heart surgical sternotomy. Mitral valve replacement with a transcatheter approach is not currently available.

Bioprosthetic Valves

Long-term anticoagulation for patients with bioprosthetic valves is not indicated as the risk of thrombosis and thromboembolism is low (about 0.2%/year):

- In patients with a bioprosthetic mitral valve who are in sinus rhythm and have no other indications for anticoagulant therapy, 3 to 6 months of warfarin therapy (international normalized ratio [INR] target: 2.5) after valve replacement is suggested, to be followed by long-term acetylsalicylic acid (ASA) 81 mg daily.
- In patients with a bioprosthetic aortic valve who are in sinus rhythm and have no other indications for anticoagulant therapy long-term ASA 81 mg daily may be considered for patients with low bleeding risk after 3 to 6 months of warfarin therapy (INR target: 2.5).
- Patients with a bioprosthetic valve and atrial fibrillation should be considered for long-term anticoagulant therapy as outlined in the **Clinical Guide, Stroke Prevention in Atrial Fibrillation**.

Mechanical Valves

There are 3 basic types of mechanical valves:

1. Bileaflet (e.g. On-X, St. Judes, most frequently seen today)
2. Tilting disc (e.g. Bjork-Shiley, infrequently seen today)
3. 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 long-term anticoagulation. Even with anticoagulation, the risk of stroke/valve thrombosis is ~0.9%/year with mechanical mitral valves, ~0.5%/year for mechanical aortic valves, and ~1.2%/year in those with two mechanical valves.

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.

On-X aortic mechanical valve implant 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 this 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. In the 2017 Focused Update of the Valvular Heart Disease Guidelines, the American College of Cardiology made a weak (class IIb) recommendation based on a single moderate quality randomized clinical trial that a lower target INR range of 1.5 to 2.0 plus ASA 81 mg/day may be reasonable after 3 months of an INR target of 2.5 (2.0 to 3.0).

Transaortic Valves

TAVI or TAVR may be used as an alternative to surgical valve replacement 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 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.

Antithrombotic therapy after TAVI is not well established. It is based on expert consensus and on the original clinical trial protocols that examined indefinite low dose ASA 81 mg daily with an initial 1 to 6 months of a thienopyridine such as clopidogrel 75 mg daily. The addition of a thienopyridine was based on original studies showing that 7% to 40% of TAVI patients who receive antiplatelet therapy alone may develop valve thrombosis post procedure detected by computerized tomography. However, recent data suggest that there is less major or life-threatening bleeding with ASA alone, with no increase in thromboembolic events. As such, in the 2019 Position Statement for Transcatheter Aortic Valve Implantation, the Canadian Cardiovascular Society (CCS) suggests aspirin monotherapy after TAVI unless there is an indication for dual antiplatelet (i.e. recent percutaneous catheter intervention) (strong recommendation, medium quality evidence). 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**) in addition to ASA. The CCS caution against the use of triple therapy (ASA, antiplatelet agent, vitamin K antagonist (VKA), or direct oral anticoagulant (DOAC)) as triple therapy may render an excessively high bleeding risk in these patients. A recent study showed that among TAVI patients with an indication for long-term oral anticoagulation, oral anticoagulation with either VKA or DOAC alone compared with oral

anticoagulation (VKA, DOAC) plus 3 months of clopidogrel was associated with a lower risk of all bleeding (21.7% vs 34.6% respectively). However, concerns regarding the classification of bleeding and the reliability of secondary outcome analyses that addressed thromboembolic risk have been highlighted. There are currently several ongoing trials that are examining DOACs or VKA use in TAVI patients with or without a long-term indication for oral anticoagulation. It should be noted that a trial that examined rivaroxaban 10 mg daily (with ASA at a dose of 75 to 100 mg daily for the first 3 months) or ASA at a dose of 75 to 100 mg daily (with clopidogrel at a dose of 75 mg daily for the first 3 months) in TAVI patients without an indication for long-term oral anticoagulation was stopped prematurely because of excess mortality in the rivaroxaban group.

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 1** below for INR targets.

Patients requiring long-term warfarin therapy should be bridged with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) until a therapeutic INR has been attained. Maintenance of a therapeutic INR is important to reduce the risk of thrombosis. [See **Clinical Guides Warfarin** and **Warfarin: Management of Out-of-Range INRs**].

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. [See **Clinical Guide Acetylsalicylic Acid**]

Direct Oral Anticoagulants

The direct factor inhibitor anticoagulants, such as apixaban, dabigatran, edoxaban, and rivaroxaban, are contraindicated in patients with mechanical heart valves. A randomized trial demonstrated that dabigatran is associated with more thrombosis and bleeding compared with warfarin in patients with mechanical heart valves.

TABLE 1: ANTICOAGULANT DRUG MANAGEMENT IN PATIENTS WITH MECHANICAL HEART VALVES

Mechanical Valve Location	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. [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, so as 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:

- Acetylsalicylic Acid (ASA)
- Stroke Prevention in Atrial Fibrillation
- Warfarin
- Warfarin: Management of Out-of-Range INR
- Warfarin: Perioperative Management
- Warfarin: Point-of-Care INR Monitoring

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