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# Antithrombotic Therapy in Patients with Prosthetic Heart Valves

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**Abstract:** Patients with mechanical valve prostheses require a lifelong anticoagulant treatment. The combined use of Warfarin and low-dose aspirin appears to reduce the risk of valve thrombosis and systemic embolism at a low risk of bleeding. The management of women with prosthetic heart valves during pregnancy poses a particular challenge, as there are no available controlled clinical trials to provide guidelines for effective antithrombotic therapy. Oral anticoagulants, such as Warfarin, cause foetal embryopathy; unfractionated heparin and low-molecular-weight heparin have been reported to be ineffective in preventing thromboembolic complications. This article discusses the available data and the most recent guidelines in the antithrombotic management of patients with prosthetic valves, and antithrombotic therapy in various clinical situations such as pregnant women with prosthetic heart valves, and patients with prosthetic heart valves undergoing noncardiac surgery.

Key words: *Anticoagulation, Valve disease, Valve prosthesis*

## Introduction

Patients with mechanical valve prosthesis, require long-term anticoagulation and aspirin administration because of the risk of thromboembolism, which is often greatest in the first postoperative year. Without anticoagulants and aspirin, the incidence of thromboembolism is three-to six-fold higher than when proper doses of these medications are administered [1].

Abnormal flow conditions imposed by the prosthetic heart valves increase risk of thrombosis and embolism. The abnormal flow conditions caused by prosthetic valves are of two types: relative stagnation and high-velocity disturbed flow causing high shear stress [2]. Aortic valve prostheses are associated with high-velocity flow, high shear stress and relatively little stagnation. In contrast, mitral valve prostheses are associated with much more stagnation because the velocity of forward flow is much lower, and they are situated facing into the left atrium, which is an area of relative stagnation. These fundamental differences result in a higher incidence of both valve thrombosis and embolism after mitral valve replacement (MVR) than after aortic valve replacement (AVR) [2].

Despite design changes and modifications that have been made to improve the longevity, hemodynamics, and thrombogenicity of newer generation mechanical valves, thromboembolism and anticoagulant-related bleeding continue to account for 75% of all complications after mechanical valve replacement [3].

## Antithrombotic management following valve replacement

Current practice suggests that Warfarin therapy should begin about 2 days after prosthetic valve placement [3,5].

After mechanical AVR, the goal of antithrombotic therapy is usually to achieve an International Normalized Ratio (INR) of 2.5 to 3.5 for the first 3 months after surgery and 2.0 to 3.0 beyond that time [4]. Low-dose aspirin (75 to 100 mg per day) is also indicated in addition to Warfarin [6]. At that level of anticoagulation, the risk of significant haemorrhage appears to be 1% to 2% per year.

Thrombosis and thromboembolism risks are greater with any mechanical valves in the mitral than the aortic position, and, therefore, higher INR levels (2.5 to 3.5) are generally recommended for mechanical mitral valve prostheses.

Homografts and most bioprosthetic valves in the aortic position do not require long-term anticoagulation, providing that the patient is in sinus rhythm and has adequate left ventricular systolic function. However, there is evidence that anticoagulant therapy for the first 3 months, until the sewing ring is endothelialized, reduces the higher incidence of embolism at this time. After 3 months, the tissue valve can be treated like native valve, and Warfarin can be discontinued in more than two thirds of patients with biological valves. In the remaining patients, who have risk factors for thromboembolism (table 1), lifelong Warfarin therapy, to achieve an INR of 2.0 to 3.0, is indicated [5,7,8].

Antiplatelet agents without anticoagulants do not provide adequate protection to patients with mechanical valve prosthesis. However, the addition of aspirin, 80 to 160 mg daily, together with Warfarin may reduce the risk of thromboembolism and should be given to all patients with mechanical prosthetic valves [4,8].

Aspirin alone has been recommended as long-term prophylaxis for patients with bioprostheses to minimize platelet adhesion.

Clopidogrel (Plavix) may be considered for those who cannot take aspirin [4].

Risk factors for thrombosis (Table 1), and underlying causes of hypercoagulability should be corrected if possible. Atrial fibrillation is associated with a fivefold increase in the risk of stroke and, therefore, it is important to try to restore sinus rhythm. Hypertension, obesity, and hyperlipidemia should be treated, cigarette smoking stopped, and advice is given about diet, exercise and the avoidance of potentially thrombogenic drugs. Correcting these factors will substantially reduce the risk of thrombosis.

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**Table 1** Risk Factors for Prosthetic Valve Thrombosis

| |
|---|
| 1- Atrial fibrillation. |
| 2- Previous thromboembolism. |
| 3- Left ventricular dysfunction (LVEF < 30%). |
| 4- Mechanical mitral or tricuspid prosthesis. |
| 5- Older-generation thrombogenic valves (e.g. Starr-Edwards, and mechanical disc valves). |
| 6-Those with demonstrated thrombotic problems when previously off Warfarin therapy. |
| 7- More than one mechanical valves. |
| 8- Hypercoagulable state. |

**Table 2** Potential Advantages of LMWHs over UFH during pregnancy

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|---|
| 1- Cause less heparin-induced thrombocytopenia; |
| 2- Have a longer plasma half-life & a more predictable dose response; |
| 3- Easier to administer, with lack of need for laboratory monitoring; |
| 4- Associated with a lower risk of heparin-induced osteoporosis; |
| 5- Appear to have a low risk of bleeding complications. |

**Table 3** Recommended therapeutic interventions in patients with prosthetic valves who suffered an embolic event while receiving adequate antithrombotic therapy.

| Current Therapy | Current INR range | Intervention to prevent further embolic events |
|---|---|---|
| Warfarin | 2.0-3.0 | Increase Warfarin dose to achieve INR of 2.5-3.5 |
| Warfarin | 2.5-3.5 | Increase Warfarin dose to achieve INR of 3.5-4.5 |
| Not taking ASA | | Add ASA 75 to 100 mg per day. |
| Warfarin plus ASA 75-100 mg/day | | Increase ASA to 325 mg daily. |
| Aspirin alone | | Increase ASA to 325 mg/day, add Clopidogrel 75 mg/day and/or add Warfarin. |

In the patient who has a definite embolic episode while undergoing adequate antithrombotic therapy, the dosage of antithrombotic therapy should be increased, when clinically safe (Table 3) [4].

In patients with mechanical valve prostheses who have experienced repeated systemic embolization despite optimal anticoagulation therapy, the incidence of embolization might be reduced by replacement with a tissue (bioprosthetic) valve.

The risk of thrombosis of mechanical prostheses in the tricuspid valve position is quite high and, therefore, bioprostheses are preferred at this site [9].

It must be recognized that the administration of Warfarin carries its own mortality and morbidity, i.e., serious haemorrhage.

**Interruption of Warfarin therapy for invasive procedures or noncardiac surgery**

Anticoagulation interruption in a patient with a prosthetic valve is potentially hazardous and may result in prosthetic valve thrombosis and thromboembolism. The risk is much higher for patients with mitral prostheses, for patients with congestive heart failure, and for patients with more thrombogenic prostheses.

The risk of increased bleeding during a procedure performed with a patient receiving antithrombotic therapy has to be weighed against the increased risk of thromboembolism caused by stopping the therapy.

In patients at low risk of thrombosis, defined as those with a bileaflet mechanical AVR with no risk factors, it is recommended that Warfarin be stopped 48 to 72 hours before the procedure (so the INR falls to less than 1.5) and restarted within 24 hours after the procedure. Heparin is usually unnecessary [4,10].

Bridging anticoagulant therapy is recommended for the higher- risk individuals including those with a mechanical mitral or tricuspid prosthesis or those with a mechanical aortic prosthesis who have risk factors (table 1). The recommended bridging therapy is intravenous unfractionated heparin (UFH). Subcutaneous doses of UFH or low-molecular weight heparin LMWH) may also be considered [4,10].

The decision to provide bridging therapy requires careful consideration of the relative risks of thromboembolism and bleeding in each patient.

The ACC/AHA guidelines recommend bridging therapy in patients with mechanical valves who require interruption of Warfarin therapy, as follows:

1- In patients at high risk of thrombosis, defined as those with any mechanical MV replacement or a mechanical AVR with any risk factor (table 1), therapeutic doses of intravenous UFH should be started when the INR falls below 2.0 (typically 48 hours before surgery), stopped 4 to 6 hours before the procedure, restarted as early after surgery as bleeding stability allows, and continued until the INR is again therapeutic with Warfarin therapy.

2- In patients at high risk of thrombosis (table 1), therapeutic doses of subcutaneous UFH (15 000 U every 12 hours) or LMWH (100 U per kg every 12 hours) may be considered during the period of a subtherapeutic INR. LMWH is attractive because it is more easily used outside the hospital.

**Anticoagulation during pregnancy**

The majority of women with bioprosthetic valves do not require anticoagulation during pregnancy. All pregnant patients with mechanical prosthetic valves must receive continuous therapeutic anticoagulation. In women with mechanical valves, a detailed discussion of the advantages and disadvantages of the three anticoagulant options (Warfarin, UFH and LMWH) is indicated.

Warfarin (vitamin K antagonist therapy) is an effective antithrombotic agent in women during pregnancy. Warfarin crosses the placenta and has been associated with an increased incidence of spontaneous abortion, prematurity, and stillbirth when the dose is > 5 mg/day [11].

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Warfarin is probably safe during the first 6 weeks of gestation, but there is a risk of embryopathy if Warfarin is taken between 6 and 12 weeks of gestation. Warfarin is also relatively safe during the second and third trimesters of pregnancy but must be discontinued and switched to a heparin compound several weeks before delivery.

Several studies suggest that UFH or LMWH therapy is safe for the foetus [9-13]. Heparin does not cross the placenta and does not have the potential to cause foetal bleeding or teratogenicity. Thus, heparin is generally considered safer than Warfarin during pregnancy in terms of the development of embryopathy [14]. However, many experts questioned the efficacy of heparin in prevention of thromboembolic complications during pregnancy. Numerous case series and patient registries attest to a high incidence of thromboembolic complications (12% to 24%), including fatal valve thrombosis, in high-risk pregnant women managed with subcutaneous UFH or LMWH [13-16].

Low-molecular-weight heparin (LMWH) is considered a recommended anticoagulation option in pregnant women with prosthetic heart valves [17]. It has potential advantages over UFH during pregnancy (table 2).

Pregnant patients with mechanical prosthetic valves who elect to stop Warfarin between weeks 6 and 12 of gestation should receive continuous intravenous UFH, dose-adjusted UFH (to maintain aPTT at least twice control), or dose-adjusted subcutaneous LMWH (to maintain the anti-Xa level between 0.7 and 1.2 units per ml, 4 hours after administration). In pregnant patients with mechanical prosthetic valves who receive Warfarin, the INR goal should be 3.0 (range 2.5 to 3.5). In pregnant women with mechanical prosthetic valves, Warfarin should be discontinued 2-3 weeks before planned delivery, and replaced with either a continuous intravenous UFH or a dose-adjusted LMWH [4].

The American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy [18] concluded that it is reasonable to use one of the following 3 regimens:

1- Either LMWH or UFH between 6 and 12 weeks and close to term only, with Warfarin used at other times;

2- Aggressive dose-adjusted UFH throughout pregnancy; or

3- Aggressive adjusted-dose LMWH throughout pregnancy.

Neither Warfarin nor heparin is contraindicated in postpartum mothers who breast-feed.

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