Anticoagulation Management in Patients with Valve Replacement

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Abstract

Background: Prosthetic valve implantation requires postoperative prophylactic anticoagulation to preclude thrombotic events. The aim of this review is to assess the role of anticoagulation therapy in the management of valve replacement patients.

Methodology: Literature from PubMed, Embase, Medline and Google Scholar were searched using the terms “valvular heart disease”, “anticoagulant”, “mechanical heart valve”, “bioprosthesis”, “bridging”, “Vitamin K antagonist (VKA)”, and “acenocoumarol”. A committee comprising leading cardiothoracic surgeons from India was convened to review the literature and suggest key practice points.

Results: Prosthetic valve implantation requires postoperative prophylactic anticoagulation to preclude thrombotic events. A paramount risk of thromboembolic events is observed during the first three months after surgery for both mechanical and bioprosthetic devices. The VKA therapy with individualized target international normalized ratio (INR) is recommended in patients after prosthetic valve replacement. Therapies for the management of prosthetic valve complications should be based on the type of complications. Special care is mandated in distinguished individuals and those with various co-morbidities.

Conclusion: In patients with prosthetic valve replacement, anticoagulant therapy with VKA seems to be an effective option. The role for non-VKA oral anticoagulants in the setting of prosthetic valve replacement has yet to be established. Furthermore, whether the novel oral anticoagulants are safe and efficacious in patients after placement of a bioprosthetic valve remains unanswered.

Introduction

Valvular heart disease (VHD) is one of the common causes of cardiac morbidity and mortality. 1 The burden of VHD is growing worldwide due to the high incidence of rheumatic heart disease (RHD), especially in developing countries and the increase in degenerative etiologies in industrialized nations. 2,3 In industrialized countries, the prevalence of VHD is estimated at 2.5% (2). Data on the burden of RHD in India comes from hospital data (20-50%), population based studies (2.2-1.6%) and school surveys (0.67-4.54%). 4 The pattern of valve involvement is mitral (54.4%), aortic (11.1%), mitral and aortic (18.0%), tricuspid (10.7%) or pulmonary (0.04%). Overall, RHD contributed 63.4% to the prevalence of VHD. 3 This pattern of VHD in India is in contrast to the developed countries, where the most frequently involved valve type is aortic with degenerative etiology. 6,7 Surgical repair using either a mechanical or bioprosthetic valve is a common solution practiced globally. The worldwide annual rate of valve replacement is projected around 275,000 to 370,000; of which 55% are mechanical heart valves (MHVs) and 45% are bioprostheses heart valves. In India this number is estimated to be in excess of 10000. 8 Globally, the prosthetic valve implantations are increasing at a rate of 5-7% per year. 9-12 An ideal prosthetic valve with excellent...
Bioprosthetic valves are increasingly used in younger patients. Their longevity and hemodynamic performance and long-term durability without enhanced thromboembolic risk or the requirement for long-term anticoagulation therapy does not exist. Choice of operation and the prosthesis used for those patients undergoing valve replacement is important for each individual patient and ideally should be made together by the patient, cardiologist, and surgeon.

Prosthetic valve implantation requires postoperative prophylactic anticoagulation to preclude thrombotic events; which are the common cause of morbidity and mortality after surgery for VHD. A paramount risk of thromboembolic events is observed during the first three months after surgery for both mechanical and bioprosthetic devices. Nevertheless, mechanical valves exhibit life time thrombotic risk. Atrial fibrillation (AF), which is a common arrhythmia in VHD, necessitates lifelong anticoagulation in the majority of patients; especially if it involves mitral valve. Therefore, patients on anticoagulants are at risk of thrombosis and bleeding, if the target INR levels are not maintained. Restrictions on certain physical activities are advised subsequently after surgery to reduce chances of bleeding accidents and these compromises the lifestyle of the young patients. These considerations emphasize the importance of addressing proper anticoagulation techniques to minimize postoperative thrombotic complications, while maintaining acceptable levels of risk related to bleeding.

**Anticoagulation in Prosthesis**

<table>
<thead>
<tr>
<th>Type of valve</th>
<th>Aortic position</th>
<th>Mitral position</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uncomplicated/ without risk factors</td>
<td>With risk factors*</td>
</tr>
<tr>
<td>Mechanical Valve*</td>
<td>2.0–3.0</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Bileaflet</td>
<td>2.0–3.0</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Tilting disc</td>
<td>2.0–3.0</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Caged ball</td>
<td>2.5–3.5</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Caged disc valve</td>
<td>2.5–3.5</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Bioprosthetic**</td>
<td>2.0–3.0</td>
<td>2.0–3.0</td>
</tr>
</tbody>
</table>

*AF: previous thromboembolism, LV dysfunction, or hypercoagulable conditions; **VKA plus aspirin, class I indication by ACC (75-100 mg o.d.), ACCP (50-100mg o.d.) recommends aspirin only in high risk patients; **VKA for 3 months in all except uncomplicated aortic valve replacement where ACCP recommends aspirin over VKA and it should be continued if there is no other indication of anticoagulation. Postoperative aspirin (80-100mg o.d.) is recommended for all by ACC, while ACCP recommend aspirin 3 months after replacement.

Based on the current evidence, the American College of Chest Physicians (ACCP) and the American College of Cardiology (ACC)/American Heart Association (AHA) provide recommendations regarding the use of anticoagulation and target INR in patients with mechanical prosthesis, which are comparable in both guidelines and summary of which is presented in Table 1.

Studies revealed, VKA therapy being superior to aspirin therapy alone for total thromboembolism risk and currently there is no evidence to support its replacement by antiplatelet agents (APA) as demonstrated in CAPTA trial. The patients with mechanical aortic valve were randomized to Coumadin vs aspirin/clopidogrel in this trial. The trial was stopped after valve thrombosis events reported in 22 patients in the APA group. Succeeding studies have shown that the addition of aspirin to VKA therapy in patients with mechanical valves leads to reduction in risk of thromboembolism and mortality when compared to VKA therapy alone (65% observed risk reduction in major systemic embolism or death in the aspirin plus VKA group). The addition of at least 50 to 75 mg/day of aspirin is, therefore, recommended in the current ACC/AHA and ACCP guidelines in all patients with mechanical valves, though care must be taken to an individual patient’s bleeding risk.

**Anticoagulants in bioprosthesis**

Thromboembolic events with
bioprosthetic valves have been reported to range from 0.2% to 3.3% per year. The risk is higher in the mitral position compared to valves in the aortic position. Studies have demonstrated that bioprosthetic devices have an increased risk for thromboembolic events during the first three months after the procedure but less than that associated with mechanical valves.

Several large cohort studies have addressed the need of VKA anticoagulation with and without APA after bioprosthetic valve replacement. Numerous Indian studies have demonstrated the benefits of adding APA to anticoagulants. The optimal antithrombotic regimen and its duration after placement of a bioprosthetic device are less clear across these studies. The optimal antithrombotic regimen and its duration after placement of a bioprosthetic device are less clear across these studies.

The variation in an optimal antithrombotic regimen and its duration after valve replacement in the literature have made the recommendations given by guidelines for bioprostheses to be dissimilar compared with the mechanical prosthesis. The ACCP currently recommends VKA therapy with target INR 2.5 (range 2.0 to 3.0) for the first three months after bioprosthetic mitral valve replacement. For aortic valve replacement with a bioprosthetic device, the ACCP recommends aspirin (50 to 100 mg/day) over VKA therapy for the first three months after surgery, for patients in whom there is no other indication for anticoagulation (i.e., atrial dysrhythmias, history of thromboembolism, etc.). If the patient remains without a definitive indication for anticoagulation therapy without VKA therapy beyond the initial three-month postoperative period in all patients with a bioprosthesis. In the 2014 ACC/AHA guidelines, class I recommendations supporting the use of VKA therapy in patients with bioprosthetic valves are not available. The ACC/AHA does, however, offer a class IIa recommendation supporting VKA therapy for the first three months after bioprosthetic valve replacement at the mitral position and a class IIb recommendation supporting VKA therapy for the first three months after bioprosthetic valve replacement at the aortic position. Aspirin therapy at a dose of 75 to 100 mg/day is recommended in patients regardless of whether anticoagulation is employed in all bioprosthetic valve patients. Moreover, there are no specific recommendations offered in regards to duration of aspirin therapy in this population. Recommendations from the ACC/AHA largely leave the choice of the antithrombotic regimen in the setting of bioprosthetic valve replacement up to individual clinicians. Several factors that may influence a clinician’s decision include institutionally-specific outcomes, the likelihood for patient adherence to medication regimen, prior personal experience, regional convention, and personal preference. The duration and intensity of treatment with aspirin are also left up to the individual clinician’s discretion. These recommendations have been summarized in Table 1.

**Anticoagulants in TAVR**

Transcatheter aortic valve replacement (TAVR) has become established as a treatment option for patients with symptomatic aortic stenosis. In comparison with surgical aortic valve replacement, TAVR offers superior quality of life with similar mortality rates among patients at very high surgical risk. However, thromboembolic complications from TAVR are significant, and stroke, in particular is a concern. While the immediate procedural risk relates to valvular debris embolization, 50% of strokes develop after the first day and may relate to non-procedural events. The incidence of cerebrovascular events after TAVR remains raised for ≤60 days. This implies that the prothrombotic environment of the bioprosthesis...
itself may be implicated in distal thromboembolism, and therefore antiplatelet or antithrombotic treatment should play an important role in stroke prevention.39

Various combinations of antithrombotic regimens (single-antiplatelet, dual-antiplatelet, or VKAs) have been used, but evidence-based guidance remains lacking. A number of randomized and non-randomized studies evaluated the risk of embolization, optimal antithrombotic regimen and duration thereof after TAVI.36-41 The evidence on anticoagulation after TAVI from India is limited to only a few case reports.42-43

Antithrombotic recommendations for TAVI from various guidelines are illustrated in Figure 1.

**Key points**

**Anticoagulants in mechanical prosthesis**
- VKA therapy with a target INR range of 2.0 to 3.0 is recommended in patients with mechanical aortic valve replacement without risk factors.
- VKA therapy with a target INR range of 2.5 to 3.5 is recommended in patients with mechanical aortic valve replacement with risk factors- AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions.
- In mechanical mitral valve replacement, VKA therapy with a target INR range of 2.5 to 3.5 is recommended in patients with and without additional thromboembolic risk factors.
- With mechanical valves in both the aortic and mitral position, a target INR range of 2.5 to 3.5 is recommended.
- VKA therapy in combination with antiplatelet therapy (aspirin 75-100mg) is recommended for long-term management over no antiplatelet therapy with mechanical valve prosthesis.

**Anticoagulants in bioprosthesis**
- VKA therapy is recommended in bioprosthetic aortic valve and mitral valve replacement, with a target INR range of 2.0 to 3.0 over no VKA therapy for 3 months.
- In patients with dual valve replacement (aortic, mitral) VKA therapy is recommended with a target INR range of 2.5 to 3.5.
- After bioprosthetic aortic or mitral valve replacement, antiplatelet therapy at a dose of 75 to 100 mg/day is recommended.

**Anticoagulants in TAVR**
- Anticoagulants are recommended pretreatment and during treatment.
- Life-long aspirin 75-100 mg/day along with clopidogrel 75 mg daily is recommended for 3-6 months.

**Bridging Anticoagulation**

The perioperative management of patients who are receiving VKAs or antiplatelet drugs and require a surgical or invasive procedure presents a dilemma for practicing clinicians. Several factors such as type, location and number of heart valve prosthesis and type of procedure and risk factors should be taken into account while managing patients with mechanical heart valves in whom interruption of anticoagulation therapy is needed for diagnostic or surgical procedures. To minimize the delay in achieving therapeutic anticoagulation, a “bridging” anticoagulant is prescribed. The “bridge” is administered parenterally (short acting anticoagulant as UFH or LMWH), thereby providing an immediate anticoagulant effect. However, the use of low molecular weight heparin (LMWH) or unfractionated heparin (UFH) as perioperative bridging is an off-label use because their use is not approved by regulatory authorities or drug manufacturers in this clinical setting as a bridging agent. There is a relative paucity of well-designed clinical trials to enlighten best practices. There are a disproportionately large number of methodologically weak observational studies.

Large number of studies have evaluated, and proposed an interval of 1-3 days preoperatively and 7 days postoperatively for VKA interruption.44 However, VKA interruption may not be required in minor procedures like dental procedures,45-50 minor dermatological procedures51-53 and cataract surgery.54 Furthermore, no well standardized studies were performed regarding the use of LMWH and UFH. However, a study showed no significant difference in thromboembolic and major bleeding between patients bridged with LMWH and those bridged with UFH.55 Most studies assessing the use of LMWH as bridging anticoagulation have used therapeutic dose regimens; for detailed information refer Douketis et al.56 Two studies have used low dose LMWH (including patients with mitral valve prosthesis),57,58 however, whether the dose utilized is sufficient is not known clearly as it can be argued that higher doses of LMWH are needed for the prevention of arterial thrombosis. The latter, however, is also not established.

On account of the current evidence, ACC and ACCP recommend uninterrupted VKA with local hemostasis optimizing agents in procedures with minimal bleeding, such as surgeries on the skin (excision of basal and squamous cell skin cancers, actinic keratosis, and premalignant or cancerous skin nevi), cataracts, glaucoma and dental cleaning or simple treatment for dental caries. For tooth extractions and endodontic procedures, ACCP recommends stopping for 2 to 3 days (partial reversal). However, both guidelines recommend interruption of VKA with bridging anticoagulation in patients with any mitral valve prosthesis, caged-ball, tilting disc aortic valve prosthesis, bileaflet AVRs with additional risk factors such as the recent (within 6 months) stroke or transient ischemic attack, prior thromboembolism during the temporary interruption of VKAs. In such cases when the interruption is required, ACC recommends stopping for 2-4 days while ACCP recommends not less than 5 days before the procedure. Both recommend restarting approximately 12 to 24 hours after surgery when there is adequate hemostasis instead of later resumption of VKAs. Moreover, the reversal of VKA required during emergency surgery or invasive procedures can be achieved by administration of fresh frozen plasma (FFP) or intravenous prothrombin complex concentrate (PCC).
Key points
- It is not recommended to interrupt VKA therapy during minor dental procedures (cleaning), dermatological procedures and cataract surgery due to minimal bleeding.
- In patients with low thrombotic risk (bileaflet AVR without any risk factors) it is recommended to interrupt VKA without bridging.
- Bridging anticoagulation is recommended in patients with any mitral valve prosthesis, any caged-ball or tilting disc aortic valve prosthesis, bileaflet AVR with additional risk factors, patients with recent (within 6 months) stroke or transient ischemic attack, patients with prior thromboembolism during temporary interruption of VKAs.
- When interruption of VKA therapy is required, it is recommended to stop 2-4 or not more than 5 days before the procedure. The VKA should be restarted after 12-24 hours after surgery.
- The reversal of VKA therapy during emergency surgeries can be achieved by administration of FFP or PCC. Low dose vitamin K may be administered with caution to sustain effects with FFP as rebound is known with vitamin K.
- Interruption of VKA therapy with bridging anticoagulants is recommended for not more than 2 days in case of major surgeries.

Point of Care INR Testing

The subtherapeutic target INR increases the risk of thromboembolic events, on the other side, above the therapeutic INR presents the patient to bleeding risk. Apart from the assistance in deciding the appropriate dosage regimen, monitoring helps in avoiding over coagulation. Routine monitoring can help detect dangerous situations well in time, allowing dose adjustment, as well as actions can be taken to prevent recurrence of such situations. The prothrombin time (PT) test is the most common test used to monitor anticoagulation therapy that is expressed as the INR. Further, the time in therapeutic range (TTR) is a good overall measure of the quality of antithrombotic treatment with VKAs in patients with valvular heart disease.

The gold standard for monitoring INR is the lab testing of blood obtained by venipuncture, in the hospital. The point of care (POC) INR systems can be an alternative to older laboratory testing of INR. POC testing involves putting a single drop of blood from a finger stick, onto a test strip. POC is aimed at convenience for the patient, faster test results to a healthcare provider, faster decision making, improved clinical outcome and reduced healthcare resources. However, these devices are economical as they reduce the cost of visiting the healthcare facility. This is of great importance in India, as most of INR facilities are available far from the urban or semi urban area. These POC devices have shown to be cost-effective for patients on long term anticoagulants. Studies have found a statistically significant advantage of self-management methods for achieving better INR control in patients with mechanical valves. Furthermore, ACC/AHA recommends the practice of self-management of patients over outdoor INR monitoring for VKA anticoagulation, in patients who are motivated, and can demonstrate competency in self-management strategies.

Key points
- Practice of self-management is recommended in patients who are living in urban and semi-urban areas, who are competent of doing the same.
- Use of POC devices can be alternated with the conventional laboratory testing to reduce hospital visits and the cost of the treatment.

Management of Prosthetic Valve Complications

Thromboembolic events

The annual risk of thromboembolic events in patients with a mechanical heart valve is 1% to 2% versus 0.7% with a bioprosthetic valve, even with appropriate antithrombotic therapy. Transesophageal echocardiogram (TEE) is the first step in the evaluation of suspected prosthetic valve thromboembolism to evaluate valve hemodynamics. However, transesophageal echocardiography (TEE) is needed often, particularly for mitral prosthetic valves. It is also useful to assess the kinetics of the mobile part of a mechanical prosthesis. However, ACC recommends TTE in patients with suspected prosthetic valve
**Thrombosis** to assess hemodynamic severity and resolution of valve dysfunction, and if the thrombus is detected, TEE to assess thrombus size and valve motion. The left-sided prosthetic heart valve thrombosis can be treated either with fibrinolytics or surgical intervention. When treating left-sided PVT, the risks associated with re-operative surgery must be weighed against the risks of embolic complications and bleeding associated with the use of fibrinolytic therapy. Factors that identify patients at risk for adverse outcomes of fibrinolytic therapy include active internal bleeding, history of hemorrhagic stroke, recent cranial trauma or neoplasm, diabetic hemorrhagic retinopathy, large thrombi, mobile thrombi, systemic hypertension (>200 mm Hg/120 mm Hg), hypotension or shock, and New York Heart Association (NYHA) class III to IV symptoms. The degree of risk is directly related to thrombus size. Thrombus area (2D TEE) >0.8 cm² and thrombus diameter 1.0 cm is associated with increased embolic risk. Rate of complications increases 2.4-fold, per 1.0 cm² increase in size, which makes surgery better option. In patients with recent hemorrhagic stroke, surgery is a better choice because of the bleeding risks associated with fibrinolysis. Although RCTs have not been performed, the weight of the evidence favors surgical intervention for left-sided prosthetic valve thrombosis unless the patient is asymptomatic and the thrombus burden is small.

However, fibrinolysis of right-sided valve thrombosis appears better option with the resulting small pulmonary emboli seem to be well tolerated and systemic emboli are uncommon.

ACC and ACCP recommend fibrinolytics or surgical intervention for management of PVT; the clinical judgment should be based on the position of the valve (left or right) and thrombus burden as assessed by echocardiography.

**Bleeding complications**

The incidence of major bleeding complications in patients with a mechanical valve and taking oral anticoagulants varies from 0.34% to 1.32% per patient-year. The prominent feature of anticoagulant overdose is bleeding, which may be manifested as nasal bleeds, haematemesis, haemoptysis, gastrointestinal bleeding, vaginal bleeding, haematuria, cutaneous haemorrhages, gingival bleeding, haematoma, and bleeding into joints or menorrhagia. Numerous risk scores have been developed to help predict bleeding events, considering the other comorbidities such as previous gastrointestinal bleeding, chronic kidney disease, previous stroke or myocardial infarction, and anemia (Table 2). Furthermore, excessive anticoagulation (INR ≥ 5) greatly increases the risk of hemorrhage. Discontinuation of anticoagulation for 1-2 weeks had a low probability of thromboembolic events in patients with high embolic risk.

In the presence of major bleeding (active bleeding) with VKA, four factor prothrombin complex concentrate (FFPCC) or FFP should be given for reversal of anticoagulation. However, ACCP recommends additional use of Vitamin K (5-10 mg IV inj.) along with coagulation factors and shows a preference for FFPCC over FFP.

**Key points**

**Thromboembolic events**

- TTE is recommended for diagnosis of thromboembolic events.
- Treatment with tPA and heparin is recommended to patients with stroke; other vascular occlusions should be managed by surgery.
- Daily aspirin (75-80 mg) is recommended in anticoagulated patients with thromboembolic events with increase in the target INR range (mechanical AVR: 2.5-3, mechanical MVR: 3-4).
- In patients with bioprosthetic valve, who are already on aspirin, addition of VKA can be considered.
- Measures to increase patient compliance (patient education) are recommended in all patients with thromboembolic events.

**Thrombosis of prosthetic valves**

- It is recommended to address adequacy of anticoagulation (low INR), and exclusion of other causes of high gradients like anemia, tachycardia, fever.
- TTE is recommended in patients with suspected prosthetic valve thrombosis to assess hemodynamic severity and resolution of valve dysfunction.

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**Table 2: Bleeding risk prediction scores**

<table>
<thead>
<tr>
<th>Risk score</th>
<th>Bleeding risk factors</th>
<th>Risk classification points</th>
<th>Annual rate of major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient bleeding risk index</td>
<td>Age ≥ 65 years, history of stroke, history of gastrointestinal bleeding, recent MI or, Hct&lt;30% or SCr&gt;1.5 mg/dl or diabetes; 1 point each</td>
<td>Low: 0</td>
<td>Low: 3</td>
</tr>
<tr>
<td>Contemporary bleeding risk model</td>
<td>(0.49 x age ≥70 years) + (0.32 x female sex) + (0.58 x remote bleed) + (0.62 x recent bleed) + (0.71 x alcohol/drug abuse) + (0.27 x diabetes) + (0.82 x anemia) + (0.32 x antiplatelet therapy)</td>
<td>Intermediate: 1-2</td>
<td>Intermediate: 12</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td>Hypertension (SBP&gt;160mmHg), abnormal renal/liver function, stroke, history of bleeding, labile INR, age ≥65 years), drugs (antiplatelet/NSAIDs/alcohol); 1 point each</td>
<td>Low: ≤0.07</td>
<td>Low: 0.9</td>
</tr>
<tr>
<td>HEMORR\HAGES</td>
<td>Hepatic or renal disease, ethanol abuse, malignancy, older age (&gt;75 years) reduced platelet function, re-bleeding, uncontrolled hypertension, anemia, genetic factors (CYP2C9 SNP), excessive fall risk, stroke; 1 point each</td>
<td>Intermediate: 1.07-2.18</td>
<td>Intermediate: 2.0</td>
</tr>
</tbody>
</table>

MI= myocardial infarction; SBP= systolic blood pressure; NSAIDs= non-steroidal anti-inflammatory drugs
Factors Affecting VKA Therapy

Pharmacogenetics
Growing evidence indicates that up to 60% of the individual pharmacological response to warfarin might be due to genetic variables and affected by polymorphisms in the genes mainly, vitamin K epoxide reductase complex subunit 1 (VKORC1), the target enzyme of warfarin and cytochrome P450 2C9 (CYP2C9), the main enzyme involved in warfarin metabolism. Similarly, many Indian studies have earlier shown that around 75-80% of the Indian population carries VKORC1-1639GG (rs9923231) genotype, which is associated with the high dose requirement.

Recently, FDA has recommended pharmacogenetics testing before initiating warfarin. However, ACCP remains against the routine use of pharmacogenetics testing for guiding doses of VKA in patients initiating VKA therapy.

Anticoagulant interactions

Drug-drug interaction
As VKAs are metabolized mainly by cytochrome P-450 (CYP) 2C9, the inhibition of CYP 2C9 results in a decreased catabolism of VKAs and a stronger anticoagulant effect, whereas its induction enhances their catabolism and leads to a lower anticoagulant effect. Drugs such as amiodarone, fluconazole, fluvoxamine, isoniazid, lovastatin, miconazole, metronidazole, trimethoprim-sulfamethoxazole, phenylbutazone are known inhibitors of CYP 2C9, thus potentiating VKAs effect. Antibiotics, which cause decreased production of vitamin K by the intestinal microbiota result in an increased sensitivity to VKAs. Barbiturates (carbamazepine, rifampicin) are inducers of CYP 2C9. Over the counter medications, i.e. paracetamol and other nonsteroidal anti-inflammatory drugs (NSAIDs) were shown to enhance the anticoagulant effect of warfarin, thus patients receiving warfarin must monitor their INR more frequently when taking these medications especially, paracetamol at doses exceeding 2g/day. However, acenocoumarol compared to warfarin may elicit lower drug interactions due to less sensitive to metabolic enzymes (CYP2C9) and easy clearance from the body.

Drug-Herbs interaction
The interaction of VKAs with herbs is well reported in literature. These includes the interaction with Panax ginseng, Hypericum perforatum, Salvia miltiorriza, Gingko biloba, Serenorepens, Angelica sinensis, Vaccinium species, Allium sativum, Zingiberofficinalae, Tanacetumparthenium, Luchiumbarbarum, Matricariachamomila, Boswelliaserrata and Camellia sinensis have been estimated.

Drug-food interaction
Indians with their different dietary habits compared to their western counterparts are more prone for VKAs-food interactions. An average Indian consumes more of dietary green leafy vegetables, which would prevent the achievement of target INR in patients with warfarin/acenocoumarol and cause variability in INR values. The interaction between the dietary vitamin K and VKAs is well known. Evidence has demonstrated that anti-coagulated patients should maintain a steady intake of vitamin K once INR stability has been achieved. Patients should be educated not to avoid Vitamin K rich foods; however, they should be advised to maintain the vitamin K content of diet constant. The best way to achieve this is by avoiding changes to normal eating patterns. ACCP suggests against routine use of vitamin K supplementation for patients on VKA.

Key points

Drug-drug interaction
- It is recommended to avoid drugs metabolized by cytochrome P450 enhancing or inhibiting VKAs effect during the therapy.
- It is recommended to educate patients on drug interaction with over the counter drugs and antibiotics; and need for frequent monitoring INR when they are used.

Drug-food interaction
- Patients are advised to maintain constant Vit K composition in the diet to avoid fluctuation of VKA therapy.
- Food inhibiting (Cabbage, spinach, brussels, sprouts) and potentiating (Mango, grapefruit, cranberry) the efficacy of VKAs should be taken in moderation while maintaining regularity.

Anticoagulation in Special Patient Populations

Pregnancy
Pregnancy is a hypercoagulable state, due to increase in fibrinogen,
factors VII, VIII and X, von Willebrand factor, and a relative decrease in protein S activity, stasis, and venous hypertension.\textsuperscript{104} The increase in total blood volume affects the distribution of anticoagulants during pregnancy contributing to unpredictable changes in the amount of medication required.\textsuperscript{105,106} This state of hypercoagulability extends into the postpartum period too, and requires a persistently higher maintenance dose of warfarin.\textsuperscript{105} Thus, optimal anticoagulation therapy is considered essential, but the appropriate choice of agent among the options available (VKAs, heparin or LMWH) is highly debatable.\textsuperscript{107}

The low molecular weight of warfarin enables it to cross the placental barrier and cause embryopathy. The embryopathy actions are dose dependent; reduced adverse events are seen with dose <5mg.\textsuperscript{108-110} However, warfarin can be replaced with LMWH since they do not cross the placenta. The use of heparin is associated with reported incidence of 12-24% of the increased risk of maternal thromboembolic events.\textsuperscript{111} Henceforth, women of childbearing age should be warned about the teratogenic and harmful effects of VKAs, especially in early pregnancy. They should be advised to use secure methods of contraception while on VKAs. If pregnancy is suspected, early pregnancy test 5 weeks from last menstrual period must be offered. Hence, if patients are not prior Educated about the teratogenic and harmful effects of VKAs, are recommended in elderly patients considering them as high risk patients for developing hemorrhagic complications.

Renal impairment

As VKAs are metabolized in the liver, no dosage adjustments are required in patients with chronic renal impairment. Pharmacokinetic studies have shown that anti-Xa activity is prolonged in patients with severe renal impairment (creatinine clearance <30 mL/min) and, to a lesser extent, in patients with moderate dysfunction (30-50 mL/minute).\textsuperscript{119} The prevalence of AF is reported to be higher in patients with renal impairment. Also, the risk of AF development increases with worsening of renal function.\textsuperscript{120} Heparin derivatives depend largely on renal excretion; dosage adjustment is necessary in order to avoid accumulation and hence over-anticoagulation.\textsuperscript{115} Dosage adjustment for factor Xa inhibitors in patients with renal insufficiency is recommended by ACCP.\textsuperscript{121}

Before 36 weeks of gestation

- Oral VKA therapy is recommended throughout pregnancy in patients with daily warfarin dose requirement of ≤5mg (or equivalent acenocoumarol dose) with target INR of 3.
- It is recommended to replace VKAs by LMWH if warfarin dose>5mg (or equivalent acenocoumarol dose) is required for achieving therapeutic INR.
- Low dose (75-100 mg) aspirin is recommended in second and third trimester (only in high risk patients or all patients or in stable to reduce INR by 0.5 and reduce dose of VKAs).

At 36 weeks of gestation

- At 36 weeks of gestation, VKA should be discontinued and iv UFH or LMWH should be initiated and continued till 36 hours before delivery.
- If vaginal delivery is expected VKA should be discontinued at 34 weeks and LMWH should be administered with monitoring of factor X assays.
- If labor starts unexpectedly, 2-4 mg IV vitamin K and FFP should be administered to reduce risk of fetal injury.
- When hemostasis is adequate, VKA therapy should be restarted on day 1-2 as maintenance dose.

Elderly population

- Frequent renal tests and observation for adverse effects with concomitant medications, are recommended in elderly patients considering them as high risk patients for developing hemorrhagic complications.

Renal impairment

- Monitoring of anticoagulation therapy in renal insufficiency patients is recommended to avoid the risk of over-anticoagulation

Concomitant Cardiac Disease

Heart failure

Prosthetic valve patients are at high risk of congestive cardiac failure due to significant cardiac compromise. Cardiac medicines like angiotensin converting enzyme inhibitors, diuretics, and digoxin should be given as per the standard heart failure management guidelines.\textsuperscript{122}

CAD

The concurrent use of dual antiplatelet agents with VKAs has been a major issue in percutaneous coronary intervention (PCI) patients in an era of widespread use of drug-eluting stents (DES),
Table 3: Recommendations on management of anticoagulation in pregnancy

<table>
<thead>
<tr>
<th>ACC/AHA(^21)</th>
<th>ACCP(^113)</th>
<th>ESC(^114)</th>
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<td><strong>Before 36 gestational weeks</strong></td>
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| Oral (VKA) | Can be used throughout pregnancy (class IIa) with substitution by UFH/LMWH during weeks 6-12 of gestation if | Can be used throughout pregnancy in high risk\(^*\) patients with UFH or LMWH before delivery (grade 1A) | If warfarin daily dose is <5mg, oral anticoagulation is the safest regimen with 3% embryopathy throughout the pregnancy
  - preferred by the patient | | |
  - dose of warfarin required to achieve target INR >5mg (class IIa) | | |
  - just before planned delivery has to be replaced by UFH or LMWH (class I) | | |
  - strongly recommended in MPV in 2nd and 3rd trimesters | | |
| Heparin derivatives | | |
  - Recommendations on 1) s.c use of LMWH and UFH throughout pregnancy 2) s.c UFH in the 1st trimester completely removed in current 2014 guidelines. | | |
  - The patients who prefer: **LMWH administered twice daily and the dose should be adjusted to attain peak anti-factor Xa levels: 0.8–1.2 U/mL approx. 4–6 hours after the injection. | | |
  - Alternatively, continuous IV UFH (with aPTT at least twice that of the control) during the 1st trimester is permissible if the dose of warfarin is <5 mg/day | | |
  - IV UFH in the first trimester is difficult from a practical standpoint, as a three-month hospital admission is required. | | |
| | | |
| All of the above guidelines agree that LMWH should be given twice daily and that it is harmful to administer LMWH without regularly monitoring the patient’s anti-factor Xa levels | | |
| Aspirin | Low dose (75-100mg/day) given in second and third trimesters (class I) | Low dose given in addition to anticoagulation in high risk patients (grade 2C) | Not recommended |
| Target INR | 3 for all prosthetic valve patients | 2-3 for patients with bileaflet aortic valves w/o high risk factors* | No target recommendation |
| **After 36 gestational weeks** | | |
| | | |
| The ACC/AHA guidelines suggest stopping warfarin at 36 weeks and starting continuous IV UFH with aPTT monitoring, which should be continued until approximately 2–3 weeks before the planned delivery. | | |
| Additionally, they recommend that UFH be discontinued 4–6 hours before the planned delivery and restarted 4–6 hours after delivery. | | |
| In the absence of significant bleeding, oral warfarin should then be initiated 24 hours after the birth. | | |
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| | | |
| Approximately 5% of patients requiring PCI also present with an indication for oral anticoagulation therapy. In such cases, the type of stent selected; the use of oral anticoagulants, antiplatelet, or their combinations; the target INR; and the duration of treatment is essential considerations in relation to the risk of thrombosis/thromboembolic events and bleeding risk. Whenever possible, shorter durations of triple therapy are favored in preference to longer durations of triple therapy.\(^{123}\) The WOEST (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial is the first published study to address the question of optimal antiplatelet therapy in patients taking oral anticoagulant medication. Patients randomized to single antiplatelet treatment with clopidogrel had significantly fewer bleeding complications and no increase in thrombotic events compared with those randomized to DAPT with aspirin and clopidogrel.\(^{124}\) The ACC/AHA recommends in patients with non ST segment elevation acute coronary syndrome (NSTE-ACS) who require oral anticoagulation for AF, mechanical heart valve, deep venous thrombosis, or other conditions, a bare-metal stent may offer the advantages of lower bleeding risk over a DES because of the potentially shorter duration of triple antithrombotic therapy.\(^{125}\) However, these recommendations do not specify the optimal treatment
Atrial Fibrillation

Overall, it is estimated that the incidence of post-operative atrial fibrillation is approximately 30% after pure coronary artery bypass grafting (CABG) surgery, 40% following valve replacements or repair, and increases to approximately 50% after combined CABG/valvular procedures. In a large prospective trial, the Prophylactic Oral Amiodarone for the Prevention of Arrhythmias That Begin Early After Revascularization, Valve Replacement, or Repair (PAPABEAR), amiodarone was compared with placebo. Oral amiodarone prophylaxis of atrial tachyarrhythmia after cardiac surgery was effective and safe. Furthermore, a meta-analysis of 19 trials comparing amiodarone with placebo has demonstrated a significant reduction in AF (reduced by 50% in the amiodarone group), ventricular tachyarrhythmia, strokes, and hospital stay. Prophylactic amiodarone should be implemented as a routine therapy for high-risk patients undergoing cardiac surgery. The addition of beta-blockers can also help in reducing sympathetic triggers of AF post-operatively. The European Society of Cardiothoracic Surgery recommends the perioperative use of beta blockers as the first choice in all patients undergoing cardiac surgery, unless otherwise contraindicated.

Cardiac catheterization in patients with prosthetic valves

The first postoperative workup is isolation ablation (PVI). Patients in patients undergoing ablation of cardiac implantable electronic devices should be operated on VKA unless they are at very low risk for a thromboembolic event. In this particular case, it recommends interrupting VKA without bridging with heparin. The ACC recommends only slight modification in VKA dosing for procedures with a low bleeding risk, such as coronary angiography from the radial approach. With interventional procedures at higher risk, stopping VKA anticoagulation and using bridging therapy as is done for other surgical procedures has been recommended.

Follow up cardiac evaluation

Doppler echocardiography at baseline (before discharge) serves as a reference for subsequent examinations. The measurements should include regional and global left and right ventricular systolic function and size, diastolic LV function (not assessable with mitral valve prosthesis), atrial size, function of the native valves, estimates of pulmonary artery pressure, pressure gradient across the newly implanted prosthesis, effective valvar orifice area, presence of paravalvular leaks. The first postoperative workup should include echocardiography along with all other physical and blood tests. Ideally, all patients who have undergone valve surgery should continue to be followed-up at a cardiac center in order to detect deterioration in prosthetic function, recurrence of regurgitation following valve repair, or progression of disease at another valve site at an early stage. The frequency of future follow-up should be determined by the patient’s progress and availability of local facilities. The frequency of echocardiography during follow-up should be determined by the results of previous echocardiography, symptomatic status, the type of surgery, and the existence of other pathology. However, ESC recommends the first post-operative visit to a hospital or a cardiac specialist within 6 weeks of discharge if there has been no period of inpatient rehabilitation or within 12 weeks if a rehabilitation program has been completed. The current 2014 ACC VHD guideline recommends annual follow up for cardiac history and physical examination in an asymptomatic uncomplicated patient. It also recommends an echocardiographic examination at 6 weeks to 3 months after valve implantation, while AS-Echo guideline recommends a baseline TTE at discharge or 2-4 weeks after hospital discharge; as an essential component of the first post-operative visit. Both guidelines recommend further follow up by TTE and/or TEE if clinical symptoms or signs suggestive of prosthetic valve dysfunction or other cardiac pathology persist; with preference to TTE for initial examination. ACC and As-Echo recommend no further echocardiographic testing after the initial postoperative evaluation in stable mechanical valve patients and who have no symptoms or clinical evidence of prosthetic valve or ventricular dysfunction or dysfunction of other heart valves. ACC recommend TTE after the first 10 years, while AS-Echo recommends annual echocardiography after the first 5 years in bioprosthetic valve patients; even in the absence of a change in clinical status. CT and MRI scan-Post valve implantation

Prosthetic cardiac valves are generally made up of metals, polymers, and carbons. However, there is a hypothetical probability of electromagnetic interaction with metal in valves that may cause interruption of opening and closing of valves (referred to as the Lenz effect). Nevertheless, no such cases have been reported in clinical practice. Consequently, these patients are unlikely to be at risk for valve dehiscence and the
heating due to MR was reported to be minor.\(^{138-141}\) Consequently, prosthetic heart valves, as well as metal sternal sutures and mediastinal clips, should not be considered as contraindications for an MRI at 3 T or less any time after implantation.\(^{142,143}\)

According to AHA scientific statement, the presence of a prosthetic heart valve or annuloplasty ring that has been formerly evaluated for MR safety should not be considered a contraindication to an MR examination at 3 T or less (and possibly even 4.7 T in some cases) any time after implantation. MR examination of patients with sternal wires is generally considered to be safe and patients with endocarditis and risk of valve dehiscence cannot undergo MRI.\(^{144}\)

**Prosthetic Valve -Endocarditis**

Prosthetic Valve Endocarditis (PVE) is a serious complication of cardiac valve replacement and is an important cause of morbidity and mortality. Echocardiography should be performed in all cases in which there is a medium or high clinical suspicion or when the patient is severely ill, after excluding other common causes of fever.\(^{145}\) The diagnostic strategy proposed by Durack and colleagues (the Duke criteria) combines echocardiographic findings with clinical and microbiological data. Three echocardiographic findings were considered to be major criteria for the diagnosis of endocarditis: (1) presence of vegetation defined as mobile echo dense masses implanted in a valve or mural endocardium in the trajectory of a regurgitant jet or implanted in prosthetic material with no alternative anatomical explanation; (2) presence of abscesses; or (3) presence of a new dehiscence of a valvular prosthesis.\(^{146}\)

The reported sensitivity and specificity for the diagnosis of perivalvular abscesses with TTE are 28% and 98%, respectively, and with TEE, 87% and 95%, respectively.\(^{147-150}\) Bioprosthetic valve leaflets may become infected with secondary destruction of leaflet tissue. The distinction between wear-and-tear degeneration of tissue valves and endocarditis is often difficult. TEE also led to an improved diagnostic accuracy in the diagnosis of endocarditis on bioprosthetic valves.\(^{151}\) TEE is therefore necessary in cases in which infective endocarditis is strongly suspected, even when no significant findings are seen on TTE.\(^{152}\) Further, multiple TEE planes combined with TTE views must be exploited to minimize the risk of missing a significant finding when images are technically difficult to obtain. When both TEE and TTE studies are negative, there is a 95% negative predictive value.\(^{153,154}\)

Antimicrobial therapy remains the mainstay of therapy; however, most patients require surgical removal and replacement of infected prosthesis. The delay in embolization prevention is associated with stroke within 3 days of diagnosis.\(^{155}\) The risk of embolism is related to the size, and mobility of vegetation, the risk is increased in large (>10 mm) vegetation and particularly high with very mobile and large (>15 mm) vegetation. The risk of new embolism is highest during the first days following initiation of antibiotic therapy and decreases after 2 weeks.\(^{68}\)

In a case-control study, Agarwal et al identified the risk factors for prosthetic valve endocarditis in Indian population.\(^{156}\) These risk factors were functional class III or IV (New York Heart Association), alcohol consumption, prior history of endocarditis, fever in the intensive care unit, and gastrointestinal bleeding. Functional class III or IV and complications of the surgical wound were independent predictors of early infective endocarditis, whereas fever in the intensive care unit and gastrointestinal bleeding were predictors of prosthetic valve endocarditis late after the operation.\(^{156}\) However, there are no randomized studies assessing the impact of antithrombotic therapy on PVE. The results of observational studies suggest that the risk of continuing anticoagulation outweighs the benefits.\(^{155,157-160}\)

In patients on VKA for a prosthetic valve who develop IE, ACCP suggest VKA be discontinued at the time of initial presentation until it is clear that invasive procedures will not be required and the patient has stabilized without signs of CNS involvement. When the patient is deemed stable without contraindications or neurologic complications, reinstitution of VKA therapy is recommended.\(^{19}\)

**Key points**

- Concomitant heart failure should be managed as per standard heart failure management guidelines.
- In patients with non ST segment elevation acute coronary syndrome (NSTE-ACS) who are on anticoagulation, bare metal stent is preferred over drug eluting stent that offers the advantages of lower bleeding risk because of the potentially shorter duration of triple antithrombotic therapy.
- Beta blockers should be used for management of perioperative atrial fibrillation, unless otherwise contraindicated.
- Un-interrupted VKA can be offered in patients undergoing alation procedures like PVI.
- Interruption of VKA should not be performed during implantation of cardiac implantable electronic devices unless patients are at very low risk of thromboembolic events. However, if required can be interrupted without bridging.
- Low bleeding risk procedures like coronary angiography by radial approach can be performed with slight modification in VKA dose. However, interventional procedures with high risk of bleeding should be performed with interruption of VKA and bridging as with other surgeries.

**Follow up cardiac evaluation**

- The first postoperative workup should include echocardiography along with all other physical and blood tests.
- The frequency of future follow-up should be determined by the patient’s progress and availability of local facilities.

**CT and MRI scan-Post valve implantation**

- Patients with prosthetic valve which is formerly evaluated for MR safety can undergo MR examination at 3T or less any time after implantation. However, patients at risk of valve dehiscence should not undergo MR examination.

**Prosthetic Valve -Endocarditis**

**Diagnosis**

- TTE in recommended in suspected IE, in case of negative TTE in suspected PVE, TEE is recommended. If initial examinations are negative, repetition of TTE/TEE is recommended within 7-10
days in patients with high suspicion of IE. Modified Duke Criteria should be used in evaluating a patient with suspected IE.

Prophylaxis
- Antibiotic prophylaxis is recommended in dental procedures (gingival tissue, perforation of oral mucosa), invasive respiratory tract procedures and skin tissue treatment procedures.

Antithrombotic
- It is recommended to discontinue VKA, in patients on VKA for a prosthetic valve who develop IE, until it is clear that invasive procedures will not be required and the patient has stabilized without signs of CNS involvement. When the patient is deemed stable without contraindications or neurologic complications, reinitiation of VKA therapy is recommended.

Future Anticoagulants

In the current era of expanding strategies for anticoagulation, investigators have yet to establish the role for non-VKA oral anticoagulants in the setting of prosthetic valve replacement. To date, there are no large randomized clinical trials enrolling to answer this question. New anticoagulants that are direct thrombin inhibitors or factor Xa inhibitors (dabigatran, apixaban, and rivaroxaban) have been approved by U.S. Food and Drug Administration for anticoagulant prophylaxis in patients with AF not caused by VHD. There was no evidence of thrombosis of valve despite dabigatran use. There are reports of thrombosis of valve despite dabigatran use.

Following this report, Food and Drug Administration (FDA) announced a statement to contraindicate dabigatran for mechanical heart valves. A question is unanswered, whether the novel oral anticoagulants are safe and efficacious in the patients early following placement of a bioprosthetic valve. Dedicated studies in this setting are unfortunately likely to be years away, thus leaving some degree of uncertainty regarding optimal antithrombotic therapy for the near future.

Disclaimer
This publication was funded by Abbott Healthcare Pvt Ltd. Dr. Vikrama Raja, Medical Affairs has authored this publication in the capacity of employee of Abbott Healthcare Pvt Ltd., Dr. Devendra Saksena, Dr. S. Muralidharan, Dr. Bipin Bihari Mohanty, Dr. C.P. Srivastava, Dr. Jagdish Mange, Dr. Manish Puranik, Dr. Manoj P Nair, Dr. Pankaj Goel, Dr. Pankaj Srivastava, Dr. RM Krishnan, Dr. Sathyaki Nambala, Dr. Vivek Kanhere, Dr.Yugal K Mishra have co-authored this publication. The authors have declared and confirmed that there is no conflict of interest with respect to this authored publication.

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can be considered as an indicator of patients' adherence and persistence: focus on anticoagulants for the treatment and prevention of thromboembolism. Patient Prefer Adherence 2010; 4:51-60.


