

Anticoagulation Therapy for Prosthetic Valves

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INTRODUCTION

Various types of prosthetic valves are implanted at various positions in the heart for a variety of conditions, chronic rheumatic heart disease being the most common cause in this part of the world. The prosthetic valves are broadly categorised into 2 types the mechanical and the bioprosthetic prosthetic valves.

All the prosthetic valves especially the mechanical valves are made up of materials which are thrombogenic. Thus these patients are at a high risk of developing thromboembolic events. Patients with bioprosthetic valves too in the initial three months and especially when they are accompanied by complications like atrial fibrillation and left atrial thrombi are also at risk of developing thromboembolic events.

To prevent these thromboembolic events patients need to undergo careful and adequate anticoagulation with various drugs. Without anticoagulation the rate of embolism is 5-50%^{1,2} and with therapy it is reduced to 1-3%³. The dose of these drugs has to be carefully tailored for each patient and various parameters decide the level of anticoagulation that is required e.g. the type of valve mechanical or bioprosthetic, the subtype of the valve caged ball or tilting disc, the presence of associated conditions like atrial fibrillation, left atrial clot, pregnancy, left ventricular function etc⁴.

Also care is to be taken that over-anticoagulation does not occur as this leads to untoward side effects like hemorrhagic events which sometimes can be life threatening and lead to significant morbidity and death.

TYPES OF PROSTHETIC VALVES

The types of valves that are commonly implanted are as shown in the Table 1.

Table 1: Types of prosthetic valves

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|----|--|
| 1. | Mechanical |
| a. | Caged ball |
| b. | Tilting disc: <ol style="list-style-type: none"> i. Single leaflet ii. Bileaflet |
| 2. | Bioprosthetic |
| a. | Heterograft |
| b. | Homograft |

COMMON PROSTHETIC VALVES AND THEIR THROMBOGENECITY

Among these the mechanical valves are more thrombogenic than the others. The earlier versions of the mechanical valves like the Starr Edwards ball-in-cage type of valves are more thrombogenic while the newer third generation types of the mechanical valves like the bileaflet St. Jude valves are considerably less thrombogenic requiring less intense anticoagulation with INR range between 2.0 and 3.0³. Table 2 shows the relative thrombogenicity of the various types of valves that are currently implanted in patients.

The Bioprosthetic valves have much less thrombogenicity and require anticoagulation only during the initial 3-4 months of their implantation however they do require long-term anticoagulation if there are associated complications like atrial fibrillation or left atrial thrombus or very large left atrium and low cardiac output states.

FACTORS AFFECTING THE THROMBOGENICITY IN PATIENTS WITH PROSTHETIC VALVES

As discussed above in addition to the type of valve that is implanted, various other factors dictate the

Table 2: Common prosthetic valves and their thrombogenicity

Type of valve	Model	Thrombogenicity
Mechanical		
1. Caged Ball	Starr-Edwards	++++
2. Single Tilting Disc	Bjork-Shiley, Medtronic Hall	+++
3. Bileaflet	St. Jude Medical, Sorin Bicarbon, Carbomedics	++
Bioprosthetic		
4. Heterografts	Carpentier-Edwards, Tissue Med (Aspire), Hancock II	+ to ++
5. Homografts		+

From Goldsmith et al⁵

occurrence of thromboembolic events in these patients. Table 3 gives a partial list of various factors which can increase the thromboembolic events in such patients. Patients with advanced age, hypertension, diabetes mellitus, smoking, tobacco chewing, dyslipidemia, have more chances of thromboembolism. Also patients with associated conditions like atrial fibrillation, low cardiac output states, large left atrium on echo, have high chances of thromboembolic events. Similarly associated conditions like hepatic failure, coagulopathies, enhance the chances of thromboembolic events. Also the number of valves implanted in a patient, location of valves (mitral position more thrombogenic than aortic) also increase the chances of events. Thus careful evaluation of the patient, his associated conditions, primary disease, associated complications, other organ involvement, number of valves, type of valves, position of valves etc. all contribute in deciding the level of anticoagulation that is required to achieve an good balanced anticoagulation without any hemorrhagic complications. Also after stabilization of the therapy they need to be carefully monitored in the ensuing periods, at-least for 3-4 months in the bioprosthetic valves and lifelong in the mechanical valves.

AGENTS AVAILABLE FOR ANTICOAGULATION

1. Parenteral Intravenous and Subcutaneous Unfractionated Heparin:

- Excellent anticoagulant however requires parenteral administration
- Monitoring done by periodical estimation of APTT
- Because of parenteral use cannot be used for long term administration

Table 3: Factors affecting thrombogenicity in patients with prosthetic valves

1. Patient related
 - a. Age⁶
 - b. Smoking
 - c. Hypertension
 - d. Diabetes
 - e. Dyslipidaemia
2. Basic valve lesion
 - a. Type of lesion
 - b. Severity of lesion
3. Clinical conditions
 - a. Presence of atrial fibrillation⁷
 - b. Heart failure
 - c. Low cardiac output
 - d. Size of left atrium (more than 50 mm on echo)
 - e. Previous thromboembolism
 - f. Previous major bleeding
4. Other associated co morbid conditions like
 - a. hepatic failure
 - b. other coagulopathies
5. Types of prosthetic valves deployed
 - a. First generation Prosthetic valves like Starr Edwards have high thromboembolic rate⁸⁻¹⁰
 - b. single tilting disc have intermediate risk and
 - c. newer second and third generation bileaflet valves have low risk
6. Number prosthetic valves deployed
 - a. Double valve more than single valve
7. Location of prosthetic valve
 - a. Mitral valve thrombogenicity more than aortic valve¹¹⁻¹³
8. Coagulation intensity
 - a. Adequately anticoagulated - less thromboembolism¹⁴⁻¹⁶
 - b. Subnormal INR more chances of thromboembolism¹⁷

- Short half life: thus actions can be reverted easily and early
- Does not cross the placenta: hence can be used in early pregnancy
- Action can be reverted by IV protamine sulphate (1 mg = 100 u heparin)
- Not secreted in milk so can be used by breast-feeding females.

2. Subcutaneous: Low Molecular Weight Heparin:

- Does not require APTT monitoring
- Parenteral use only
- Not approved for patients with prosthetic valves and pregnancy.

3. Oral: Warfarin Sodium:

- Excellent oral anticoagulant activity.
- Monitoring done by periodically estimating prothrombin time and the INR.
- Crosses placenta and is foetotoxic, thus cannot be used during organogenesis in the fetal

development. Has to be replaced by unfractionated heparin for that period and during delivery

- Long half-life 18-36 hours difficult to revert
- Can be reverted by Vit. K, Factors II, IX, X, VII, or Fresh Frozen Plasma
- Not secreted in milk so can be used by breast-feeding females.

4. Antiplatelet Therapy:

- **Aspirin:** May be used in combination with warfarin, it may have a beneficial effect by reducing the platelet mediated activation of coagulation cascade. It has been shown that a low-dose aspirin (100 mg per day) in patients with a target INR of 3.0 to 4.5 reduces the annualized risk of death and major systemic thromboembolic events from 11.7 to 4.2%¹⁸. Although the risk of all hemorrhage increases in the group of patients receiving aspirin from 22 to 35%, the risk of major hemorrhagic events (cerebrovascular bleeding, gastrointestinal bleeding, and major bleeding requiring transfusion) appear to be similar in both groups (13% vs. 10%; 95% confidence interval—30 to 132%; $p = .43$)¹⁸. The reduction in death rate in the group of patients receiving aspirin may also be associated with the prevention of myocardial infarction in patients with coronary artery disease, which is present in at least 35% of the patients in this study. The additive benefit of aspirin is greater in patients who had experienced previous embolic events and were at higher risk for thromboembolism. High-dose aspirin (500 mg per day) may reduce the risk of thromboembolism in patients with a low INR (1.8 to 2.3), but it results in a higher incidence of gastrointestinal bleeding^{19,20}.
- **Dipyridamole and Ticlopidine:** The value of dipyridamole in preventing thromboembolism in patients with mechanical valves is controversial^{21,22}. A study by Hayashi and coauthors suggested that both dipyridamole and ticlopidine have beneficial effects similar to those of low-dose aspirin in combination with warfarin therapy²³. Because of the high cost and significant side effects of these drugs, their use should be reserved for high-risk patients who are intolerant to aspirin.

MONITORING OF ANTICOAGULANT THERAPY IN MECHANICAL VALVES

Patients with prosthetic valves on anticoagulation therapy to achieve a state where thromboembolic event

would be minimized need complete and full anticoagulation. Any alteration in the dose during the induction or maintenance phase would be detrimental. A lesser dose would lead to thromboembolic phenomenon and a higher dose in turn may lead to catastrophic events in the form of life threatening hemorrhages at various sites including the brain. Thus monitoring of these patients has to be carefully done.

Patients on warfarin sodium have to monitor their anticoagulant status by periodically estimating the prothrombin time and the INR. As discussed earlier various types of valves and their positions in the heart require different levels of anticoagulation and accordingly have to be maintained on corresponding different levels of INR. Table 4 shows the different levels of INR that have to be maintained for adequate anticoagulation in patients with mechanical valves depending on the type of valve, position of the valve and associated conditions.

Table 4: Antithrombotic therapy in mechanical heart valve replacement

	INR
Uncomplicated bileaflet aortic	2.0-3.0
Uncomplicated tilting disc aortic	2.0-3.0
Uncomplicated aortic, and atrial fibrillation	2.5-3.5 or 2.0-3.0 + Aspirin (80-100 mg. o.d.)
Uncomplicated bileaflet mitral	2.5-3.5
Uncomplicated tilting disc mitral	2.5-3.5
Additional risk factors	2.5-3.5 + Aspirin (80-100 mg.o.d.)
Systemic embolism	2.5-3.5 + Aspirin (80-100 mg.o.d.)
Caged ball valve or caged disc valve	2.5-3.5 + Aspirin (80-100 mg.o.d.)

From Stein et al³

Older versions of ball-in-cage type of Starr-Edwards valves require more intense anticoagulation and newer third generation valves like the bileaflet St. Jude Medical and Sorin Bicarbon require less intense anticoagulation and can be maintained on lower INRs thus having lesser chances of hemorrhagic complications.

MONITORING OF ANTICOAGULANT THERAPY IN BIOPROSTHETIC VALVES

Generally bioprosthetic valves do not require long-term anticoagulation. Table 5 shows the anticoagulant monitoring in patients with bioprosthetic valves. Heterografts are generally a little more thrombogenic

than the homografts. Patients with bioprosthetic valves require long-term anticoagulation when there are associated conditions like atrial fibrillation, left atrial thrombi and very low cardiac output states.

Table 5: Antithrombotic therapy in bioprosthetic heart valve replacement

	INR	Duration
Mitral	2.0-3.0	3 months
Aortic	2.0-3.0	3 months
Atrial fibrillation	2.0-3.0	Long-term
Left atrial thrombus	2.0-3.0	Long-term (duration uncertain)
Permanent Pacemaker	2.0-3.0	Optional
Systemic embolism	2.0-3.0	3-12 months
Normal sinus rhythm	Long term Aspirin (80 mg od)	

From Stein et al³

ANTICOAGULATION THERAPY IN PATIENTS WITH PROSTHETIC VALVES DURING PREGNANCY

As pregnancy causes relative hypercoagulability²⁴, rigorous anticoagulation therapy is required throughout gestation^{25,26} in patients with mechanical valve prostheses. Warfarin has teratogenic effects in the embryo and hence should be avoided between the sixth and ninth week of gestation²⁷. During this period it should be substituted with the unfractionated heparin. It can be used as continuous IV infusion or SC twice daily in dose of 17500 to 20000 units daily with a target of APTT two times the control. The risk of hemorrhagic complications in pregnant patients treated with heparin is approximately 2%. Then from the second trimester until the first half of third trimester warfarin appears to be safe. Again from 38th week until delivery heparin should be substituted for warfarin, because warfarin crosses the placenta and may cause fetal intracranial hemorrhage in the peripartum period^{26,28}. Heparin must be discontinued 24 hours before elective induction of labor.

Both heparin and warfarin can be used safely by nursing mothers, because they do not appear to be secreted into breast milk²⁹. Regarding low-molecular-weight heparins studies are needed, however, to determine whether are safe and effective during pregnancy in patients who have mechanical valves.

Low-dose aspirin has been shown to be safe when used in combination with heparin or warfarin in pregnant patients who have a high risk of thromboembolism³⁰. The ACCP recommends adjusted dose of UH or

LMWH from conception till 13th week. This is followed by warfarin till the middle of 3rd trimester and then again UH or LMWH until delivery³. Recent European thoracic society of cardiology recommendations do not recommend use of LMWH in pregnancy with MVR.

As shown in Table 6 a review of prospective and retrospective cohort studies compared maternal and foetal risks among three commonly used strategies: oral anticoagulants throughout pregnancy, UH throughout pregnancy, and UH from weeks 6 to 12, then oral anticoagulants³¹. Embryopathy occurred when oral anticoagulants were administered throughout pregnancy (6.4%) or when UH was administered from 6 to 12 weeks replacing oral anticoagulants (3.4%). Incidence of thromboembolic complications was impressively higher with UH administered throughout pregnancy (33%) than with UH used to replace warfarin for only a limited time (9.2%) and with oral anticoagulants throughout pregnancy (3.9%).

Table 6: Comparison of maternal and fetal risks among three commonly used strategies in patients with prosthetic valves

Strategies	Embryopathy	Thromboembolic complication
1. Oral anticoagulant throughout pregnancy	6.4%	3.9%
2. UH throughout pregnancy	3.4%	33%
3. UH from 6-12 weeks, then oral anticoagulant	3.4%	9.2%

It is thus suggested to encourage use of biological prosthetic valves instead of mechanical prosthesis in all women who would like to plan a pregnancy in future.

PREOPERATIVE MANAGEMENT IN PATIENTS WITH PROSTHETIC VALVES ON ANTICOAGULATION THERAPY

In patients undergoing minor surgical procedures with minimal blood loss discontinuation of anticoagulation therapy is not required. For major surgical procedures warfarin should be discontinued 3 days before surgery. In patients with high risks like mitral prostheses, ball-in-cage valves, atrial fibrillation, LV dysfunction, history of embolic events, warfarin should be substituted with intravenous heparin until 3 hours before the procedure and resumed postoperatively until adequate oral anticoagulation is resumed. In emergency situations, small parenteral doses of vitamin K or fresh-frozen plasma may be used to quickly reverse anticoagulation.

ANTICOAGULATION THERAPY IN PATIENTS WITH PROSTHETIC VALVES DURING PREGNANCY SUFFERING A STROKE

After a non-hemorrhagic stroke, if anticoagulant therapy is discontinued the risk of recurrent stroke is approximately 1% per day³². If anticoagulation is continued it reduces this risk to one-third, but carries an increased risk of hemorrhagic transformation of the cerebral infarct^{33,34}. Thus such therapy should be discontinued for 5 to 7 days in these patients. In patients with smaller cerebral infarcts, controlled blood pressure, anticoagulation therapy should be continued.

In patients with hemorrhagic strokes, it is recommended to discontinue the anticoagulation therapy for 1 to 2 weeks and resume when there is resolution of mass effect and no evidence of hemorrhage extension on repeated CT scan.

ANTICOAGULATION THERAPY IN PATIENTS WITH PROSTHETIC VALVES DEVELOPING PROSTHETIC ENDOCARDITIS

The risk of thromboembolism in patients with mechanical valve endocarditis who are not receiving anticoagulation therapy has been reported to be as high as 50% in different studies^{35,36}. Anticoagulation may reduce this risk to less than 10%, although such therapy may be associated with a 14% risk of cerebral hemorrhage. Heparin is preferred in such cases which can be withdrawn if necessary.

ANTICOAGULATION THERAPY IN PATIENTS WITH PROSTHETIC VALVES DEVELOPING PROSTHETIC VALVE THROMBOSIS

The incidence of prosthetic valve thrombosis is higher, approximately 6% per year, for patients with mechanical prostheses especially older models of Bjork-Shiley than with Starr-Edwards ball-and-cage, Medtronic Hall single-tilting-disc, and St. Jude's Medical bileaflet valves who are receiving suboptimal anticoagulation therapy^{37,38}. Patients with mechanical prostheses who are receiving adequate anticoagulation therapy, regardless of the type of valve, have a lower risk, 0.1% to 2.0% per 100 patient-years, similar to the risk among patients with bioprosthetic valves who are not receiving anticoagulation therapy³⁹. Valve thrombosis occurs more in the mitral position than the prostheses in the aortic position. For tricuspid valve prosthesis it is much higher (4% per year). The diagnosis is easily established by two-dimensional and Doppler echocardiography and transesophageal echocardiography may be required.

Small thrombi of less than 5 mm in diameter are treated with IV heparin if they are not obstructing and the occluding the valve mechanism⁴⁰. Large thrombi especially those obstructing the orifice require thrombolytic therapy or surgery.

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