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CSI consensus statement on prosthetic valve follow up

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1. The process

The mandate to prepare Guidelines was given by the Executive Members of the CSI at its Governing Body Meeting in December 2010. The Expert Panel was to be representative and include members from diverse backgrounds. Inclusion of Indian data was emphasized. The Guidelines on prosthetic valve follow up were to be constructed by Rajiv Bajaj, Dr Nakul Sinha, Dr Yash Lokhandwala, and 10 or more other experts, including non-CSI members wherever additional expertise was thought necessary. The first and second drafts were circulated to the Expert Panel in August and October 2011. The Expert Panel met in December 2011 during the Annual Meeting in Mumbai, and the third draft was presented to CSI in an academic session the next day, with over 3 h of discussion, and their recommendations were incorporated.

[v] Members of Task Force/Writing Committee.
[w] Late.

0019-4832/$ – see front matter
http://dx.doi.org/10.1016/j.ihj.2012.11.001

2. Prosthetic valve follow up

Approximately ten thousand patients undergo valve replacement in India every year. Patients with prosthetic valves require lifelong follow up and anticoagulant therapy. Unfortunately, a sizeable number of these patients are poor, or hail from remote locations. Shortcomings in follow up care can lead to life threatening mechanical, haemorrhagic and thrombotic complications.

To help reduce morbidity and mortality in these patients, The Cardiological Society of India has developed Guidelines for Follow up care of patients with prosthetic valves. The Expert Committee has attempted to provide guidelines suited to Indian circumstances and resources. Extensive reviews are already available on related topics,[1–4] although data from India is limited. Sufficient knowledge exists to frame guidelines, and randomized control trials are available on many aspects where this methodology is suitable. Consensus views are presented where data from randomized controlled trials is lacking.

3. Major issues

The following are the most important issues in the management of prosthetic valve patients:

3.1. *Choice of prosthesis*

Oral anticoagulant therapy, including PT/INR and Coumadin dosages, home INR kits, genetic profiling of Coumadin sensitivity.
Additional anti-thrombotic drugs.
Additional cardiac medications.
Follow up cardiac investigations.
Management of thrombosis and bleeding.
Management during pregnancy, inter-current illnesses, and during non-cardiac surgery.
Evaluation of unexplained fever.
Diet, exercise, vocational advice.

4. Choice of prosthesis

Both metallic and bio-prosthetic valves are widely used, and valved-conduits with metallic or bioprosthetic valve are used for reconstruction of aorta or pulmonary artery.[5] Current bioprosthetic valves have a durability of about ten years, slightly less in mitral position, the young and in child bearing women. To avoid fetal and maternal complications of oral anticoagulant therapy, women in child bearing age may be offered bioprosthesis, provided the need for reoperation is understood. Old patients too are at greater risk of bleeding, and patients over 65 should be offered bio-prosthesis. Some differences exist in the thrombotic risk of different metallic prosthetic valves, with non-metallic (carbon, plastic, etc.) leaflets or discs carrying the lowest risk. Ball and cage valves are no longer implanted, they have inferior hemodynamics, but lower risk of obstructive thrombosis. Disc prosthesis have a high thrombosis rate in the tricuspid position, and bioprosthesis are durable in tricuspid position. Social factors, emotional lability, which is commoner in the young. Remote location and poor access to reliable INRs are additional factors when present, enhance the risks of oral anticoagulant therapy, and are a relative contra-indication for metallic prosthetic valves.

5. Anti-vitamin K therapy ('Coumadin Therapy')

Vitamin K antagonists[6] remain the recommended therapy for patients with metallic prosthetic valves, and for the first 3 months in patients receiving bioprosthesis in sinus rhythm.[7] Warfarin and acenocoumarol are available, and have comparable costs. A single late evening dose is recommended. Warfarin has a lower potency per milligram (50% approximately), and a longer half-life (96 h vs. 24 h). Onset and offset of acenocoumarol are therefore faster, and genetic variability may be less compared to warfarin. Longer half-life of warfarin may be of some advantage in patients who occasionally miss doses.

5.1. *Thrombotic risk*

Patients requiring life-long OACT for metallic prosthetic valves should be categorized into lower, high and very high risk groups Table 1. Low risk patients have annual risks of near 1% per year, and high risk patients up to 15%, especially in the first year. Presence of adverse social factors increases risks of thrombosis substantially.

5.2. *Hemorrhagic risk*

Hemorrhagic risk may be less important than thrombotic risk, especially in younger rheumatics with prosthetic valves.[9–11] Menorrhagia, bruising, minor respiratory system bleeds are the most common. For older patients, (eg. degenerative aortic stenosis), the HAS-BLED score may be used to assess risk. For younger rheumatics with few co-morbidities, the hemorrhagic risk may be assessed as follows.

Table 1 – Thrombotic risk-profiling of prosthetic valve patients.

Lower thrombotic risk group (target INR 2.5, range 2.0–3.0)
Aortic metallic valve in sinus rhythm, no history of thrombosis when on adequate treatment, absence of marked chamber dilatation, or CHF
High thrombotic risk group (target INR 3.0, range 2.5–3.5)
A) Initial 3 months of bioprosthesis implant
B) Metallic prosthesis less than one year since implant
C) Mitral metallic prosthesis
D) Aortic metallic prosthesis with atrial fibrillation
E) CHF
F) Severe chamber dilatation
Very high risk group (target 3.5, range 3.0–4.0)
A) History of recurrent thrombosis while on adequate treatment with range INR 2.5–3.5
B) Patients recovering from recent prosthetic valve thrombosis[8]

5.2.1. *Low risk*
Males and non-menstruating females aged between 18 and 65, with no history of significant hemorrhage on adequate anti-coagulant doses, and no potential bleeding sources in CNS, GI or GU systems.

5.2.2. *High risk*
All others including elderly, patients with liver or renal dysfunction, alcohol abuse, concomitant use of interfering drugs, previous history of bleedings on OACT, or presence of potential bleeding sites like old cerebral infarcts, proliferative retinopathy etc.[12]

6. Laboratory facilities for INR and biochemical measurements

The Prothrombin time/INR test (PT/INR) is used for monitoring oral anti-coagulant therapy (OACT). Reliable testing requires high quality laboratory services, as each step in the process is critical.[13] It is strongly recommended that INR and biochemical measurements should be done in facilities that are NABL accredited. The laboratory should process sample onsite, and the analysis must be completed within 4 h of drawing of blood. Collection-centre/central lab model is therefore not recommended. When INR is ordered from uncertified laboratories, ensure accuracy in each step of the process. Common sources of error are given in Box 1. A reliable INR facility should be available to the patient within 4 h travel-time. Metallic prosthetic valves are not recommended when a reliable facility is unavailable to the patient (located more than 6 h away). In such patients mechanical valves should be used only with home INR kits.[14]

Box 1 Quality control in INR test

Sample collection

Use light or no tourniquet; use vacutainers (before expiry date) for accurate ratio of sample and citrate. Sample/citrate volume should be adjusted when severe anemia or polycythemia exists.

Processing

Early centrifuging of sample at 4000 rpm for 15 min; confirmation of platelet count <10,000 in plasma; early processing of sample. On sight laboratory facilities are recommended; if sample is collected at remote location, it should be centrifuged, and transported at room temperature (20–24°). Analysis must be completed within 4 h of venesection.

Thromboplastin reagent

There is variability between reagents. WHO introduced International Normalized Ratio for standardization of prothrombin test. Lyophilized and liquid stable thromboplastin reagents from internationally renowned manufacturers are easily available in India. Locally prepared reagents are not recommended. Sensitive reagents with International Sensitivity Index (ISI) close to 1.0 should be used. Thromboplastin with ISI value specific for that thromboplastin, instrument and model is preferable. These reagents require a 'cold chain', and procurement from reliable suppliers is essential. Grade I pure water should be used for reconstituting lyophilized thromboplastin. Once reconstituted, store and preserve it as per the manufacturer's instructions to maintain stability. Expired reagents must be discarded. In India, supply of quality reagents, control plasma, certified plasma, coagulometer and other accessory are available from reliable manufacturers and distributors including Siemens Diagnostics (previously Dade Behring), Germany; Stago of France, and Instrumentation Laboratory (HemosiL) of USA & Italy. It is strongly recommended that only highly sensitive reagents (high ISI) from very reliable manufacturers should be used.

Analysis

Automated coagulation analyzer is recommended. In case of manual or semi automated instruments, temperature (37°), accurate pre-warming of reagent and blood sample and accurate pipetting are crucial.

Standardization

Use Mean Normal Prothrombin Time (MNPT), single control PT is unreliable. Standardization is required each time a brand of thromboplastin or a new lot is used, or the method is modified, or coagulometer is changed or a major repair has taken place or blood collection system has changed, including change of new brand of vacutainers. INR value should be reported to the nearest tenth of a unit.

7. INR monitoring schedule

Immediately after valve replacement Coumadin is usually started after hemostasis is secure, at 48 h. Daily INR monitoring is required. Loading doses have significant disadvantages, they cause rapid prolongation of INR, but do not provide adequate protection from events. Starting OACT with maintenance doses is recommended. Treatment may be initiated with previously effective dose, or with 2 mgms of acenocoumarol, or 5 mgms of warfarin, with some adjustment for body size and liver congestion when necessary. The initial dose should be administered as a stat dose, and continued every evening. In high risk cases, bridging therapy with heparin is required till therapeutic INR is achieved on consecutive days (INR >2.0). Following discharge from hospital the recommended schedule for monitoring is given in Table 2.

After major intercurrent illnesses including severe hepatitis, the full schedule should be re-initiated till stabilization of INR and complete recovery from the illness.

Patients requiring antiepileptics, antitubercular drug rifampicin, amiodarone and similar interfering medications[15] should have fortnightly INR monitoring for 2 months after starting the interfering drug. The same 2 weekly monitoring is required for 2 months after discontinuation of the drug (for 4 months for amiodarone).

Table 2 – INR monitoring schedules.

Till 14th post-operative day: every 3 days
From 3rd to 6th weeks: weekly
From 6th to 12th weeks: 2 weekly
3–18 months: monthly
18 months and later: 2 monthly for low risk patients in the first 3 years, and 3 monthly subsequently, 1–2 monthly for high risk patients.

Beyond the first 3 months, INR measurements are pre phoned whenever INRs are deranged. Pre phoning is generally to half the scheduled time or earlier. Eg: at one month on a patient on 2 monthly measurements. With severe derangements, in high risk patients, weekly or even more frequent INRs may be needed during dose adjustments.

8. Dosage adjustments

Therapeutic range and acceptable range are defined in Table 3. Frequent dose titrations may be required in the initial 3 months after valve replacement. In asymptomatic patients beyond the first year of operation, usual treatment is continued if the INR is within 30% of accepted range. Thus when target INR is 3.0, any value between 2.1 and 3.9 is accepted. Adjustments of dose are indicated when 2 indications exist (when 2 consecutive readings are high, or low, or the patient has bruising or bleeding and high INR, or embolism occurs with low INR). If the INR is within 40% of target range, and no cause for fluctuation is apparent, the same dose may be continued, with pre phoning of the next INR measurement. Any INR above >5.2, or <1.8 requires reconfirmation of the value and adjustment of dose within 48 h. For patients with high thrombotic risks reconfirmation should be done when the INR is <2.0 or >5.2.

In most asymptomatic fluctuations, dose adjustment should be approximately 10%. The weekly or monthly dose should be calculated, and adjusted upwards or downwards by 10% (Box 2).

Box 2 Examples of dose titrations

Eg. 1, weekly dose calculation: Two consecutive below target range INR values while patient on 2 mg daily: present dose 14/mg/week. Change to 16 mg/week. 2 mg daily, except Wednesday and Saturday, take 3 mg on these 2 days every week. A catch up dose of 2 mg stat should be given in addition to the above change. Monthly dose calculation: present dose 2 mg/day = 60 mg/month. Change by 10%–54/month if INR high, 66/month if low. The daily dose remains 2 mg per day. Every fifth day the dose is less/more by 1 mg. A catch up dose or a 'cool down' dose can be used by advising double dose or skip dose for one day.

Eg. 2, Two consecutive high INRs on 5 mg–>/day: present weekly dose 35. Reduce by 3–4 mg/week. Today 'cool down' dose 1 mg; and maintenance doses 5 mg/4 mg alternate days. Monthly method: present dose 150 mg/month. Decrease by 15 mg/month. Alternate day 5, and alternate day 4. Skip dose for today to 'cool down'.

Table 3 – Therapeutic range of INR.

Therapeutic range: an INR value within 15% of the target INR
Acceptable range: an INR upto 30% of target value is 'acceptable range' in stable patients, and upto 20% in high risk patients
Moderately deranged INR: 20–30% of target range in high risk and 30–40% in low risk patients
Severely deranged INR: above 5.2, or below 1.8 (below 2.0 in patients at high thrombotic risk

9. Home INR kits

These are now available from many manufacturers,[14] and a reputed one should be used (eg: Coaguchek, Roche). The performance of these is sufficiently accurate, and these should be offered to patients as an additional resource to be used in conjunction with conventional testing. Home monitoring may be used for spot tests during bleeding. They can also be alternated with conventional tests to reduce the number of visits to the laboratory. This may be instituted after an initial period of familiarization; when initial readings correlating well with conventional assay. It is strongly recommended that physicians caring for prosthetic valve patients should make these available wherever INR measurements are unreliable.

10. Genetic profiling of Coumadin sensitivity

Dose of Coumadin varies 15 fold between individuals. Even larger variations occur when enzyme inducing medications are co-prescribed. Affordable tests are now available for determining the presence of genetic phenotypes that markedly alter Coumadin dose.[16] Although these tests correlate with maintenance dose, titration of dose is still required in every individual, and these tests, as employed presently, are not recommended in management.

11. Additional antithrombotics

Patients with biological prosthetic valves can discontinue Coumadin after 3 months (unless additional indication like atrial fibrillation present). They must be treated with aspirin long term, starting soon after surgery.[17] The risks of embolism are 5% in the first 3 months after bioprosthetic valve placement and closely monitored oral anticoagulant therapy is recommended for this period.

Aspirin should be prescribed in the first year[18] for most high thrombotic risk patients, 75–150 mg/day. It should be continued long term in very high risk patients: metallic tricuspid prosthesis and patients with history of valve thrombosis/symptomatic embolic episode despite adequate Coumadin therapy. Clopidogrel (75 mg od) and dipyramidole (25 mg bid) are alternatives to aspirin. Dual antiplatelets may be prescribed for a few weeks/months in all patients recovering from obstructive valve thrombosis.

Orally active antithrombins are now being developed as an alternative to Anti-vitamin K therapy (AVKT/OACT). These

drugs may offer significant advantages over OACT, but currently they are not recommended for patients with metallic prosthesis. Randomized controlled trials are urgently needed, as occasional patients are very intolerant to OACT therapy.

11.1. *Bridging therapy*

'Bridging therapy' with heparin or low molecular weight heparins may be required when Anti-vitamin K therapy is temporarily discontinued for elective surgery, when patient is kept nil orally for any intercurrent illness, etc. It can be omitted in stable patients at low risk of thrombosis. Pre-op, acenocoumarol should be stopped 60 h before the operation. An INR value of <1.5–1.9 on the morning of operation is acceptable. Very high risk cases should receive heparin, or low molecular heparin from 36 h after the last acenocoumarol dose. Warfarin should be stopped 5–7 days before surgery, and daily INRs and treatment with bridging therapy are required after the initial 60 h. Post-operation, Half dose heparin may be started after 12 h or whenever hemostasis is secure, and full dose heparin can be given from the next day. Anti-vitamin K therapy is restarted on post op day 1 or 2 or whenever oral medication is allowed. Bridging therapy with heparin or low molecular heparin is continued till therapeutic INR is achieved on 2 consecutive days (INR ratio >2).

12. Additional cardiac medicines

12.1. *Congestive heart failure*

Prosthetic valve patients have significant cardiac compromise and should be assumed to be high risk for congestive heart failure. Cardiac medicines like diuretics, ACE inhibitors, and digoxin are often prescribed at the time of discharge from hospital. The ACC/AHA staging of heart failure is useful for prosthetic valve patients. Stage A and B of heart failure are preclinical stages. Valve patients frequently have overt congestive heart failure before surgery, stage C or D. Post-op, the most patients should be treated as stage B or C.

Stage A: Young patients with minimal structural heart disease undergoing aortic valve surgery after endocarditis or dissection; those undergoing very timely surgery for congenital aortic stenosis; isolated tricuspid valve replacements. Stage A patients may be treated with anti-thrombotics alone; although addition of ACE inhibitors and beta blockers is recommended specially after age 40.

Stage B and C: patients undergoing mitral valve replacement for predominant mitral stenosis; aortic stenosis with timely valve replacement corresponds to stage B. The vast majority of patients with left sided prosthetic valve should be assumed to be stage C, even when doing well after surgery, especially when aged over 40. The treatment of stage B and C patients includes moderate doses of ACE and beta blockers; with additional spirinolactone and digoxin if congestive failure supervenes despite regular medications.

Stage D CHF: refractory CHF eventually supervenes in many prosthetic valve patients, especially those who had chronic regurgitant lesions, and were operated late. Correctable factors like peri-valvar leak should be excluded. Some patients have received cardiac transplant for end stage disease.

12.2. *Coronary artery disease*

Coronary artery disease may co-exist, most commonly in patients with calcific aortic stenosis, ischemic papillary muscle rupture, in men aged above 40, and women above 45. Diabetes frequently develops during follow up in prosthetic valve patients. Usual care, including aspirin, should be advised. Anti-coagulated patients requiring coronary stents may be at high risk for bleeding on dual antiplatelet therapy. Non-medicated stents requiring shorter periods of dual antiplatelet therapy may be preferred when bleeding risk is high, or additional operations are anticipated.

12.3. *Arrhythmias*

Atrial fibrillation is a frequent problem in valve patients, especially in mitral valve disease. For patients who were in sinus rhythm at any time in 6 months preceding surgery, the cardiologist should try to achieve sinus rhythm before discharge, and closely monitor the rhythm after discharge.

Transient peri-op AF should be treated with amiodarone 100–200 mg for 3 months. Addition of beta-blockers can help in the post-operative period by reducing sympathetic triggers of AF.

Patients who have atrial fibrillation may be managed with rate control or rhythm control. Patients below age 30 and with reasonable atrial size (<5 cm), and patients below age 45 and left atrial size less than 4.0 should be considered for rhythm control with amiodarone. 200 mg daily can achieve sinus rhythm in 1/3 of the cases in 2 weeks. DC cardioversion should be attempted after 2 weeks, and amiodarone continued. Transient bradycardias are common in the first few minutes after return to sinus rhythm, but bradycardia persisting beyond the first few hours suggests co-existing sick sinus syndrome.

Rhythm control should be with 100–200 mg of amiodarone daily. The dose is titrated upwards during breakthroughs, and downwards by 50 mg 6–12 monthly if in sinus rhythm. Rhythm control should be abandoned if a dose of 200 mg is ineffective, with recurrent breakthrough AF requiring cardioversion; or if patient desires to avoid cardioversions. Approximately 2–3 years in sinus rhythm can be expected by this approach before permanent AF supervenes.[19]

Atypical atrial flutters, usually left sided, are very common in mitral valve patients, especially in those on rhythm control with amiodarone. The atrial rate varies from 150 to 250. Episodes of atypical flutter are treated as breakthrough of AF.

Prosthetic valve patients are at higher risk of many other arrhythmias including isthmus dependent 'typical' flutter; sinus node dysfunction, VT, LBBB with CHF, and are at increased risk of sudden death. These require standard care as in other cardiac patients.

13. Follow up cardiac investigations

Prosthetic valve patients require monitoring for overt and occult bleeding. Patients with audible paravalvular leaks are

prone to hemolysis, and may require folate supplement or closure of leak.

Anemia, diabetes, hypertension and renal dysfunction may supervene. All patients require 3 monthly hemoglobin, sugar and creatinine estimations if they are stage D, 6 monthly when stage B or C, annually if stage A. Serum sodium and potassium should be done alongside if the patient is on diuretics or ACE-I/ARB.

An echocardiogram should be done after recovery from operation, either before discharge, or in sicker patients, after 8–12 weeks of recovery. Baseline LV dimensions, gradients, pulmonary pressures, and baseline abnoramalities like peri-prosthetic leak should be recorded at this time.

The patient should undergo an echocardiogram for a) unexplained cardiac symptoms, b) annually in patients with CHF, c) once in 2 years even if doing well. Echocardiography is indicated whenever there is an episode of thromboembolism.[16]

13.1. *Thrombosis*

Thrombosis may be obstructive (prosthetic valve thrombosis) or non-obstructive (embolism). Significant embolism and obstruction occur equally frequently with metallic disc valves.[10,11] In ball and cage valves thrombosis is less frequent, most episodes are embolic. Embolism should be classified as minor, major, and massive. Minor embolisms are TIA, and mildly symptomatic embolism to spleen, kidney, and limbs. These should be treated with dose adjustments if INR is low. Raising the target INR by 0.5 and addition of aspirin is indicated if the event occurs when INR is within range. Disabling strokes, occlusion of brachial, femoral, or popliteal artery with limb ischemia requiring embolectomy are moderately large embolism. In patients presenting within first 3 h of significant neurological deficit, and clear cut history of discontinuing Coumadin in the absence of bleeding, INR sample should be drawn, bleeding and hepatitis should be excluded by history and examination, and immediate treatment with tPA or full dose intravenous heparin can be started without delays for laboratory confirmation or CT scan. Invasive reperfusion is indicated wherever adequate onsite stroke intervention program exists.

Massive embolism presents as saddle embolism in abdominal aorta with absent femoral pulsations and abdominal pain. It may occur after starting thrombolysis for prosthetic valve thrombosis. CNS is usually spared, and history of under dosing is almost always present. The presentation is acute, and rapid transfer to cath lab facility is mandatory. The patient should receive i.v. heparin and be transferred to cath lab. Thrombolysis may be given before transfer if more than 2 h transfer time is anticipated. Mechanical clot fragmentation with catheter is necessary. Brisk flow in celiac, superior mesenteric, both renals, and popliteals should be ensured by mechanical thrombus fragmentation, and the patient should be kept NPO till adequate GI recovery.

Prosthetic valve thrombosis is diagnosed by symptoms (Recent onset of symptoms attributable to valve dysfunction) and high echo gradients. Low INR, very high gradients (mean mitral flow velocity above 2 m/s or peak aortic velocity >4.5 m/s), and corroborative 2-D findings of obstruction or thrombus should be looked for. Other causes of high gradients like anemia, tachycardia, fever should be excluded. If valve thrombosis seems likely from history, echo and other corroborative evidence, patients with class 4 symptoms, or mean mitral gradients over 16 mm should receive thrombolysis without delay. A 10% risk of embolism during thrombolysis is expected, and occurs within the first 8 h.

The standard thrombolytic dose should be infused over 10–12 h. Streptokinase, urokinase, and tPA are all effective. 20–30% of the dose is given as a loading dose, the remaining dose is infused over 10 h. With streptokinase an acceptable dose is about 3 lakhs over 2–5 min followed by 1 lakh per hour. The gradient should be checked 4–6 hourly, and just before the end of infusion. If the clinical status and gradient are acceptable (mean mitral gradient less than 10 mm, peak aortic velocity less than 4.0), additional thrombolysis is not required. If the mean gradient remains above 15, infusion may be continued for up to 48–72 h. An echo shortly before the end of each vial of thrombolytic is a useful way to decide about need for further thrombolysis. Patients with acceptable improvement should undergo aggressive anticoagulation for 16 weeks, further reduction of gradient is usual. In the absence of high bleeding risk an INR of 4–4.5 should be maintained during this period, along with one or two antiplatelet agents.

Surgical treatment is seldom needed; it should be considered for patients with recurrent thrombosis and bleeding despite adequate therapy, which occurs in 1% of cases. Such patients may have protein C or S deficiency, and are unsuited for Coumadin therapy. They should be considered for change over to bioprosthesis. A trial of direct oral thrombin inhibitor may be considered before resorting to surgery. Surgery is still indicated, but very rarely, when gradients are unacceptably high (>15 mm mean gradient in mitral, >4.5 velocity in aortic prosthesis) despite thrombolysis.

13.2. *Management of bleeding*

Like thrombosis, bleeding is most likely in the first year of therapy, or when medicines that affect INR are changed; or when the diet is drastically altered. Acute viral hepatitis is another important cause.

Spontaneous bleeds occur with high or therapeutic range INRs. It may be major, moderate, or minor. Major bleeds are intracranial bleeds and massive GI bleeds requiring multiple transfusions. Moderate bleeds are major haem-arthrosis, symptomatic serous cavity bleeds, bleeds requiring hospitalization, and bleeding causing 2 g fall in hemoglobin level. Painful ecchymosis, oral and nasal bleeds, and persistent positive stool occult blood (without significant anemia) are classified as minor.

Increased menstrual bleeding is frequent, and should be classified as major or minor.

INR should be checked promptly whenever bleeding is reported. If there is a 1–2 day delay in obtaining INR, the patient should omit one day's dose.

Superficial bleeding may be amenable to local measures. Cold compresses, or topical application of lysine analogs like tranexamic acid or amino caproic acid can control bleeding. Available preparations may be crushed or poured on gauze for local use.

Major bleedings should be treated with fresh frozen plasma, or fresh whole blood, after drawing sample for INR measurement. Use of intravenous vitamin K should generally be avoided. 1 mg i.v. may be used if INR is over ten, and 2 or 4 mg i.v. may be used if there is active bleeding and INR above 10, or during active CNS bleeding. It can be given for major bleedings if FFP or fresh blood is not available. Patients treated with intravenous vitamin K may become Coumadin resistant for 2–6 weeks, requiring treatment with heparin till they regain Coumadin response. The use of oral vitamin K is less problematic. One to 4 mg of the vitamin K injection may be given p.o. if INR is high and significant bleeding occurs, or if the INR is >10 and minor bleeding is present. Precipitating causes like addition of interfering drugs, mistakes in dosing, hepatitis, drastic change in diet should be identified. If the INR is in acceptable range, and significant bleeding occurs, treat with fresh frozen plasma. Lower the target INR for a few weeks or months by 0.5 when bleeding occurs despite therapeutic range INR.

13.3. *Menstrual bleeding*

In the first year excessive bleeding without fall in hemoglobin levels should be managed with iron supplement, without reducing Coumadin dose. In stable patients after the first year, the patient is encouraged to continue Coumadin; although skipping drug for 1 day, followed by half dose on day 2 of menses can be allowed in very stable patients (event free for over 3 years).

Heavy menstrual bleeding in the first year should be controlled with progesterones. 21 day cycles of norethisterone, 5–15 mg daily, or monthly injections of depot preparations like mehoxy-progesterone. In very stable patients after the first 3 years, skipping acenocoumarol for 2 days or warfarin for 3–4 days is an alternative. A 'catch up' dose may be advised post-menses.

14. Care during non-cardiac admissions

14.1. *MRI scans*

All metallic prosthesis and sternal wires are safe for 1.5 and 3 T scanning. Patients with endocarditis and risk of valve dehiscence cannot undergo MRI.

14.2. *Cath lab procedures*

Emergency cath can be done without correcting INR, with careful hemostasis. For elective procedures stopping acenocoumarol for 1–2 days, or warfarin for 3–4 days is adequate. In high risk patients omitting one night's dose is recommended. Pacemaker implants require stopping OACT and operating when INR is <1.6 or <2. Coumadin may be resumed within 24 h when hemostasis is satisfactory.

14.3. *Elective surgery*

Elective operations should be deferred in the first 12 months of valve surgery. Very stable patients should discontinue Coumadin for 3–6 days before major elective surgery, INR should be checked on morning of operation; a value of 1.5 or less is acceptable. It should be restarted after surgery after 24 h if hemostasis is satisfactory, without a loading dose. Bridging therapy with heparin is not recommended for very stable patients. For minor operations in accessible sites (tooth extraction, superficial procedures, banding of haemorrhoids) the dose should be omitted for 2 days, and Coumadin may be restarted on the same night if post op hemostasis is satisfactory. There is a hypercoagulable state for 24 h after starting Coumadin, and there is very little risk of increased bleeding with early restart of medications.

14.4. *Emergency surgery*

Coumadin should be discontinued for 72 h before semi-urgent surgery. In emergencies, the patient should receive fresh frozen plasma to correct the INR, and post op Coumadin therapy is administered as for elective surgery.

14.5. *Pregnancy and contraception*

Bioprosthesis is preferable in women in child bearing age. In women with metallic prosthesis, pregnancy should generally be avoided, although, with good perinatal care, stable patients can undergo pregnancy with less than 10% risk of serious morbidity, and 1% risk of maternal mortality. Pregnancy should be cautioned against, but is not completely contraindicated. Switch over to heparin from before conception, or from 6th week is widely used, but it is not always needed. Patients with high daily Anti-vitamin K dose (>3 mg acenocoumarol, >5 mg warfarin) should be considered for heparin therapy, but patients requiring smaller doses may be managed with oral anticoagulant.[20] In stable patients requiring high maintenance doses, the target INR may be lowered by 0.5 and aspirin added for the first trimester to avoid heparin. Prolonged heparin therapy carries substantial risks.

INR should be measured every month throughout pregnancy and for 3 months post-delivery. Planned caesarean section has advantages in this setting. If caesarean section is planned, Coumadin can be discontinued 3 days before section as for elective surgery. If vaginal delivery is expected Coumadin should be discontinued at 34 weeks and low molecular weight heparin started. Safe LMW therapy requires monitoring of factor X assays. If labor starts unexpectedly. 2–4 mg i.v. vitamin K and fresh frozen plasma should be administered to normalize PT through labor and to reduce risk of fetal cerebral injury. Labor should be initiated at 36–37 weeks. After delivery, oral Coumadin is restarted on day 1–2 in usual maintenance dose when hemostasis is adequate. Loading dose, and bridging therapy is indicated only in patients with previous history of thrombotic and hemorrhagic events. When bridging therapy is needed, it should be given as detailed for elective surgery.

14.6. *Contraception*

Patients need guidance about contraception, as unplanned pregnancies are hazardous.[20,21] Prosthetic valve patients have shorter life expectancy, and this need makes vasectomy

unattractive. Barrier methods can be recommended, but have higher failure rates. Oral contraceptives increase thromboembolic risk, but these are low with progesterone only pills. Oligo-menorrhea is common with progesterone only pills, and this is an added advantage. Intrauterine devices (IUDs) carry risk of increased bleeding and also of endocarditis. They are contra-indicated in patients with past history of endocarditis.

14.7. *Unexplained fever*

Patients must be aware of the significance of fever occurring in the first 6 months, and casual antiobiotic therapy should be avoided.

Fever appearing 1–6 weeks after discharge from hospital (and 1 week after stopping of post op antibiotics): causes include endocarditis, post-pericaridiotomy syndrome, pleural effusion, malaria, urinary infection, wound infection. Unless the cause is obvious, blood cultures must be drawn. Post-pericardiotomy patients have milder systemic symptoms, and preserved appetite. If endocarditis seems unlikely, NSAIDs are effective for postpericardiotomy fever, and should be instituted while culture reports are awaited.

Fever occurring beyond 6 weeks of operation: unexplained fevers require exclusion of endocarditis. Patients must be aware of the need for drawing blood cultures before starting antibiotics whenever there is unexplained fever. When fever is unexplained and lasts >1 week, blood cultures must be drawn. In fever due to endocarditis occurring beyond 6 weeks of hospital discharge, other corroborative evidence, splenomegaly, clubbing, very high ESR and active urinary sediment, are often present.

14.8. *SBE prophylaxis*

After the initial period, endocarditis in uncommon in metallic prosthetic valves, usually occurring when there are predisposing co-morbidities like very old age, diabetes, malignancy.[22] Bioprosthesis are prone to late endocarditis when degeneration and regurgitation supervene.

In view of the serious nature of prosthetic valve endocarditis, antibiotic prophylaxis is still recommended for certain dental procedures like gingival or periapical (root) procedures with perforation of the mucosa; and also for infected GI and urogenital tract procedures.[23] For dental procedures, a single oral dose of amoxicillin (2 g), or cephalexin (2 g) or azithromycin (500 mg). If oral medications not possible ampicillin (2 g) or ceftriaxone (1 g). Patients allergic to penicillins and cephalosporins should be given clindamycin (p.o. 600 mg, i.v. dose is 300 mg). Other dental procedures like polishing, braces, superficial drilling, filling, tooth loss, minor oral injuries do not require prophylaxis.

Routine GI, genitourinary procedures, bronchoscopy, TEE do not require prophylaxis. Patients requiring these procedures for infective diseases should receive antibiotic dose just before procedure. Similarly, all significant bacterial infections requiring antibiotics should receive intravenous bolus antibiotic just before debridement etc. of infected area.

15. Diet, exercise, vocational advice

Every prosthetic valve patient requires counseling and education about care of the prosthetic valve. Information booklets or printouts should be given to the patient, and verbally explained to the patient before discharge. Include advice on: a) not stopping Coumadin, b) scheduled INR tests, c) a list of vitamin K rich foods that should be restricted initially and the risk of drug interactions with various prescription medicines. Net savvy patients should be informed about drug interaction information sites like drug.com d) the patient should be taught to monitor prosthetic valve sounds, dull sounds and exertional dyspnea may be warning symptoms of obstruction. e) Instructions about bleeding and its management with cold compresses, pressure, and need for INR check. f) instructions on fever include use of paracetamol or ibuprofen. Unexplained fevers should be treated with antipyretics alone, with need for blood cultures before starting antibiotics if unexplained fever is prolonged beyond 1 week g) instructions on effect of hepatitis on INR. The patient should be aware of the symptoms of hepatitis. When suggestive symptoms occur, immediate review by physician is required, and anticoagulant dose may be skipped overnight if needed.

15.1. *Diet*

INR varies with diet, and any drastic change in diet requires pre phoning INR monitoring. Patients should be advised a diet low in green leafy vegetables like spinach, and mustard greens for the first year. Websites provide additional details (eg: www.ods.od.nih.gov/pubs/factsheets/Coumadin). In stable patients, normal diet can be taken after the first year. A diet low in fats and cholesterol is generally recommended for cardiac patients. Such advice should be specifically avoided.

15.2. *Exercise*

Although various benefits of exercise are well known, patients with prosthetic valves should be advised ample rest, not regular exercise. As a general rule, the patient should do less than what can be done comfortably, not more.

15.3. *Vocational advice*

Prosthetic valve patients are unsuited for jobs requiring high levels of physical fitness. Sedentary jobs should be advised. Women with metallic prosthesis should avoid pregnancies. Accelerated degeneration of bioprosthesis occurs during pregnancies. Counseling and information should be provided by the physician to help the family reach an informed decision.

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