Review Article

Perioperative Management of Patients with Prosthetic Heart Valves-A Narrative Review

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ABSTRACT

Worldwide, about 13% of the 200,000 annual recipients of prosthetic heart valves (PHV) present for various surgical procedures. Also, more and more females are opting for pregnancies after having PHV. All patients with PHV present unique challenges for the anesthesiologists, surgeons and obstetricians (in case of deliveries). They have to deal with the perioperative management of anticoagulation and a host of other issues involved. We reviewed the English language medical literature relevant to the different aspects of perioperative management of patients with PHV, particularly the guidelines of reputed societies that appeared in the last 20 years. Regression of cardiac pathophysiology following valve replacement is variable both in extent and timeline. The extent to which reverse remodeling occurs depends on the perioperative status of the heart. We discussed the perioperative assessment of patients with PHV, including focused history and relevant investigations with the inferences drawn. We examined the need for prophylaxis against infective endocarditis and management of anticoagulation in such patients in the perioperative period and the guidelines of reputed societies. We also reviewed the conduct of anesthesia, including general and regional anesthesia (neuraxial and peripheral nerve/plexus blocks) in such patients. Finally, we discussed the management of delivery in this group of high-risk patients. From the discussion of different aspects of perioperative management of patients with PHV, we hope to guide in formulating the comprehensive plan of management of safe anesthesia in such patients.

Keywords: Anticoagulation bridging therapy, heparin, infective endocarditis, low molecular weight heparin, neuraxial block, prosthetic heart valve, vitamin K antagonist

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INTRODUCTION

More than 200,000 heart valve replacement surgeries are performed annually worldwide, with a predicted increment to 8,50,000 per year by 2050. About 13% of the recipients of prosthetic heart valves need non-cardiac surgery later on.[1,2] The perioperative management of these patients presents unique problems for the anesthesiologists and surgeons. We review the literature available in tackling these challenges as we go step by step in the course of perioperative management of patients with prosthetic heart valves (PHV) undergoing non-cardiac non-dental surgery [Table 1].

Replacement of a diseased native valve with a PHV had been aptly described as akin to swapping one heart disease for another, necessitating long term follow up and management.[3] The anesthetic concerns in a patient with PHV are manifold. These include the effects of residual valvular and cardiac pathology, functional status of the

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patient following surgery, prophylaxis against infective endocarditis, the status of anticoagulation, risk of bleeding, reversal of anticoagulants, neurological evaluation for detecting any impairment due to thromboembolism, anticoagulation resumption in the postoperative period and switching to oral therapy and performing neuraxial and nerve/plexus blocks in the presence of anticoagulation.

Common types of prosthetic valves

Presently, two broad types of prosthetic valves are used- mechanical and bioprosthetic, for replacing diseased aortic and mitral valves, though tricuspid and pulmonary valve replacements are also not uncommon. The mechanical prosthetic heart valves (MPV) have the advantages of easy availability, are comparatively economical, durable, but demand lifelong anticoagulation.[4] Failure to maintain anticoagulation within a narrow range is associated with the risk of bleeding and thromboembolism that can lead to devastating effects, like stroke, valve thrombosis, etc.

Bioprosthetic valves (BPV) are xenografts (bovine or porcine pericardium and porcine aortic valve pre-treated with glutaraldehyde.[5] Patients with BPV need anticoagulation in the form of vitamin K antagonist (VKA) for only initial 3-6 months, followed by lifelong aspirin.[6] BPV provides excellent hemodynamic properties similar to those of native valves.[5] However, they are less durable and are prone to structural valve degeneration, which is inevitable and irreversible. This degeneration gets evident in five to ten years from implantation, leading to the re-appearance of symptoms.[5] These are usually reserved for patients with limited life expectancy because of age or comorbidities but are also implanted in young females of childbearing age who intend to become pregnant (to avoid the teratogenic effects of VKA, discomfort of repeated injections, risk of peripartum hemorrhage and retroplacental hematoma formation). The latter group of patients often needs reoperation.[4] It was revealed that pregnant women with BPV had a lower risk of thrombotic and hemorrhagic complications and lesser miscarriages (<24 weeks) than those with MPV. The maternal mortality rates were similar in both MPV or BPV.[7]

Recently, transcatheter aortic valve implantation (TAVI) has emerged as the standard of care for symptomatic severe aortic stenosis (AS). Patients with TAVI are usually on dual anti-platelet therapy for the initial six months (clopidrogrel 75 mg/day and aspirin 75-100 mg/day) followed by lifelong aspirin.[8] So, issues relevant to BPV which are being discussed subsequently hold for TAVI too.

Regression of cardiovascular changes after valve replacement

The cardiovascular compensatory changes that take place secondary to the valvular pathology had been reported to regress once the culprit valve is replaced by a PHV, but the extent to which this happens and the time it takes varies.

Mitral valvular diseases

In the case of mitral stenosis (MS), the major effect is seen on the left atrium (LA), which dilates and is associated with atrial fibrillation (AF) in large proportion of patients with MS.[9] With time and disease progression, backpressure changes in pulmonary circulation led to pulmonary hypertension (PHT). Swaminathan N *et al.* (2020)[10] reported that in patients with severe rheumatic MS, following MVR, there is deterioration of parameters of global RV function (RVFAC and Tei index) in the initial one week. Thereafter, the RV function improved at three months due to reverse remodeling of the right ventricle (RV), leading to improvement in its function. There was a significant improvement in the New York Heart Association (NYHA) functional status of the patients following MVR. However, this improvement in RV's global and longitudinal function was not noted in patients with severe preoperative PHT.

In primary Mitral Regurgitation (MR), retrograde flow from the LV into the LA results in left atrial enlargement to accommodate the regurgitant volume without increased pressure and also an increase in LV volume.[11] Finally, ventricular remodeling occurs in an attempt to maintain cardiac output. Over time, ventricle develops eccentric hypertrophy, the actin-myosin cross-bridges stretch, eventually deviating from the point of optimal contractility, therefore, resulting in a gradual decrease in ejection fraction (EF). As the EF deteriorates, the patient experiences symptoms of heart failure.[9] There is scant data on the temporal response of reverse ventricular remodeling following correction of MR. Suri RM *et al.* (2009)[12] found that normalization of EF was possible after surgical correction, after an initial decline in the early postoperative period. Mean EF improved steadily and significantly with time. Better outcomes were observed in patients who underwent MVR for severe MR with preserved LV function (EF >65%), and smaller left heart dimensions (LVESD <36 mm). Pandis D *et al.*[13] (2010) reported that following MVR, LV volumes decreased significantly within 4 to 6 months after surgery. Shafi AE *et al.* (2012)[14] reported a significant reduction of LV diastolic and systolic diameters and LV mass within the first postoperative year. Also, a modest increase in LV EF following surgery was noted. Patients most likely to achieve

favorable reverse remodeling were those who did not exhibit preoperative changes consistent with long-standing disease, such as LV dilatation, LA enlargement, and LV dysfunction. A follow-up study of LV mass regression following MV repair showed greater residual LV mass index (LVMI) in patients with reduced preoperative EF and secondary tricuspid regurgitation, suggesting incomplete reverse remodelling.[14]

The prevalence of AF in patients with MS had been seen in more than 60% of cases.[15] AF had been associated with decreased exercise tolerance, systemic embolization and higher long term mortality. In patients with preoperative AF, not more than 10%–20% regain sinus rhythm (SR) spontaneously after MVR. Another 15% who had SR develop AF following MVR. Preoperative duration of AF and left atrial size are independent factors related to SR recovery. After the radiofrequency Maze procedure, 70% maintained SR at discharge, and 42% were in SR at five years follow up.[16] MVR combined with LA volume reduction with cryoablation led to high rates of sustained relief from AF with incidences of 84.2%, 74.3% and 54.5%, at 1, 3 and 5 years respectively, compared to 49.0%, 33.2% and 28.4%, respectively in non-reduction group ($P = 0.013$).[17]

2. Aortic valvular Diseases: Aortic Stenosis (AS) induces a pressure overload on the left ventricle leading to concentric left ventricular hypertrophy (LVH), and aortic regurgitation (AR) imposes both a pressure and a volume overload leading to eccentric remodeling and LV dilatation. Lund O *et al.* (2000)[18] studied the cardiac changes following AVR in patients with AS. Although a significant reduction in LVH occurred during the first 18 months, only in 18% of patients, LVMI regressed to the normal level. Postoperative LVMI was independently related to the preoperative LV end-systolic dimension. Similarly, LV end-diastolic volume index was inversely related to preoperative EF. Sequential measurements of LV dimensions showed a steep decline of indexed LV diameters in the early postoperative period and at 1- to 2-year follow-up with stabilization of this reduction even after that.[19,20] Interestingly, it was reported that patients with AR showed a larger but slower LV mass regression as compared to patients with AS, following AVR, although both showed a steep decline in LVMI during the first 24 months.[21] The reduction (within 1 year) in LV end-diastolic dimensions as a response to the relief of volume overload led to a reduction in LVMI and, according to the Frank-Starling law, an impairment in left ventricular global longitudinal strain (LV GLS) in AR patients. However, a significant improvement of LV GLS normalized for LV end-diastolic volume at 229 ± 159 days and 26 (16–64) months, respectively, was demonstrated by Smedsrud *et al.* (2011)[22] and Regeer *et al.* (2016).[23] Vollema EM (2019) reported that in both AS and AR, there is increased formation of interstitial fibrosis, which is unlikely to regress when the volume/pressure overload is relieved. They also reported that LV GLS was impaired in patients with AR following AVR (in the initial period till one year) compared to patients of AS. Further, there was a marked decline in LVMI in both patient groups within 1 and 2 years after AVR, continuing until five years.[24]

Thus, regression of diseased valve induced cardiac pathophysiology following valve replacement is variable, might take years, and there is a lack of unanimity among the researchers regarding the course and extent. Nevertheless, the recurrent theme of the various reports is that the extent to which reverse remodeling occurs depends on the heart's perioperative status.[12,14,18] Since, in many parts of the world, patients opt for surgery quite late when substantial changes in the heart had already taken place because of the valvular pathology, it would be wise to expect modest reverse remodeling post valve replacement.

Preoperative assessment

(a) History: It is essential to note detailed history from the patient and peruse the medical records meticulously. The following points need to be emphasized:
   (i) The date of PHV implantation, course thereafter and index transthoracic echocardiography (TTE) done prior to discharge. This TTE report is helpful to compare the present TTE findings.[25]
   (ii) Symptoms and present functional status: The symptoms of the patient, particularly dyspnea, its relief or otherwise, and their temporal relation with valve replacement speak volumes about the status of the implanted valve, other cardiac and pulmonary conditions. [Table 2]. Present functional status as per NYHA classification is also helpful. The presence of palpitation suggests AF.
   (iii) Indication for replacement because the prognosis after valve replacement is influenced largely by the underlying disease and the state of the coronary circulation.[26]
   (iv) Which valve was replaced? Whether aortic, mitral, tricuspid or pulmonary valve or any combination of these were replaced? The aortic valve works in a high-pressure system, so a lower INR (2.5) suffices, whereas the mitral valve is in a low-pressure system and more susceptible to thrombosis. Hence, it is essential to maintain a higher value of INR.[3]
   (v) Type of valve: Mechanical or bioprosthetic or TAVI.
   (vi) Any history of jaundice. The presence of

Table 1: List of abbreviations or acronyms (arranged in alphabetical order)

ACC	American college of cardiology
ACE Inhibitors	Angiotensin Converting enzyme inhibitors
AHA	American Heart Association
AF	Atrial Fibrillation
APTT	Activated partial thromboplastin time
AR	Aortic regurgitation
ARB	Angiotensin receptor blockers
AS	Aortic stenosis
ASRA	American Society of Regional Anesthesia and Pain Medicine
AVR	Aortic valve replacement
BPV	Bioprosthetic valve
CVA	Cerebrovascular accident
EF	Ejection fraction
ESC	European Society of Cardiology
FFP	Fresh frozen plasma
GI	Gastrointestinal
GLS	Global longitudinal strain
GU	Genitourinary
HIT	Heparin induce thrombocytopenia
IE	Infective endocarditis
INR	International Normalized Ratio
i.v.	intravenous
LA	Left atrium
LDH	Lactate Dehydrogenase
LMWH	Low molecular weight heparin
LSCS	lower segment cesarean section
LV	Left ventricle
LV EF	Left ventricular ejection fraction
LVESD	Left ventricular end systolic diameter
LV GLS	Left ventricular global longitudinal strain
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index
MS	Mitral stenosis
MPV	Mechanical prosthetic valve
MR	Mitral Regurgitation
MVR	Mitral valve replacement
NICE	The National Institute for Health and Care Excellence
NYHA	New York Heart Association
PCC	Prothrombin complex concentrate
PHT	Pulmonary hypertension
PHV	Prosthetic heart valve
PNB	Peripheral nerve block
PPH	Post partum hemorrhage
PRBC	Packed red blood cell
RV	Right ventricle
s.c.	Subcutaneous
SR	Sinus rhythm
TAVI	Transcatheter aortic valve implantation
TE	Thromboembolism
TTE	Transthoracic echocardiography
UFH	Unfractionated heparin
VKA	Vitamin K antagonist

prolonged jaundice mightsuggest paravalvular or transvalvular leak

(vii) Any neurological deficit Suggests history of thromboembolism (ischemic CVA) or could be because of excessive anticoagulation (hemorrhagic CVA).

(viii) Medication history:

(ix) History of hospitalization with cardiorespiratory symptoms (dyspnea, angina, anasarca, bleeding diathesis, prolonged fever, etc.) after valve replacement

(a) Examination:

(i) General examination- One should look for the presence of pallor, icterus, edema, the character of the pulse (irregularly irregular pulse suggests the presence of AF).

(ii) Systemic Examination: Presence of crepitation on auscultation of lungs, sharp click sounds of the mechanical valve on auscultation of heart and presence of any unusual murmur, presence of hepatic enlargement on palpation of the abdomen and any neurological deficit should be ascertained.

(b) Investigation: Indicated Investigations and inferences to be drawn are listed in Table 3 Regarding echocardiography, the implanted valve imposes limitations, (due to acoustic shadowing, reverberations, refraction, and mirror artefacts) as a result of which often transthoracic (TTE) and transesophageal (TEE) examination need to be combined. The left/right atrial side of prosthetic mitral or tricuspid valve is concealed by acoustic shadowing from TTE approach. Thus, TTE might not detect prosthetic mitral or tricuspid regurgitation, thrombus, pannus, or vegetation. TEE is more useful in such cases. Similarly, the posterior aspects of valve is masked on TTE, whereas, the anterior aspect of the valve is hidden on TEE. Usually, TEE is reserved for severely symptomatic patient in whom, pathology of PHV is suspected, but TTE results are inconclusive.[27]

(c) Preparation

(i) Remember the drugs they are on and their interaction with anesthetics like diuretics, beta-blockers, ACE inhibitors, less commonly, digitalis.

Intravascular hemolysis of varying degrees is common in patients with PHV.

(ii) Subclinical hemolysis might be present in patients with normally functioning PHV of all types, but more likely with MPV. Parameters of hemolysis, for instance, serum LDH, haptoglobin and blood reticulocyte, will be raised. Less uncommonly, hemolysis could be severe enough to result in anemia because of either severe paravalvular leak or structural deterioration of BPV. In such cases, beta-blockers may be prescribed to reduce the transvalvular flow velocity and the resultant shear stress to red blood cells.[28]

Anticoagulation bridging therapy

Bridging therapy can be a double-edged sword in low-risk patients and might prove to be counterproductive, as patients who experience any bleeding incident

Table 2: Temporal Relationship of symptoms with Prosthetic Heart Valve Implantation and their inference

Prior to Valve Replacement	Early Postoperative Course after Valve Replacement	Late Postoperative Course after Valve Replacement	Inference
Symptomatic	Relieved of symptoms	Relieved of symptoms	Valve is functioning properly, Cardiac remodeling likely
Symptomatic	Relieved of symptoms	Symptoms redeveloped	The other valve is getting involved Valve thrombosis or pannus ingrowth Valve degeneration Paravalvular leak New onset cardiac disease, like coronary artery disease.
Symptomatic	Symptoms not relieved	Symptoms not relieved	Valve malfunction Valve size mismatch Paravalvular leak Inadequate improvement in LV function

Table 3: List of investigations and their implications

Parameter	Implications
Blood Hemoglobin	Anemia is common because of dietary restrictions. Also possible in case of severe paravalvular leak
Platelet count	As they are often on anti-platelet agents. Also, patient receiving UFH/LMWH for more than 4 days are susceptible to develop heparin induced thrombocytopenia
Reticulocyte count	Rises along with serum LDH because of paravalvular or transvalvular leak. In cases of sub clinical hemolysis, haptoglobin level might be low
Liver Function Tests	Features of intravascular hemolysis like raised indirect bilirubin, raised serum lactate dehydrogenase (LDH) and mildly raised serum aspartate transaminase (AST), suggest paravalvular or transvalvular (due to pannus ingrowth or thrombus formation on the mechanical valve) leak
Prothrombin time (PT) and international normalized ratio (INR)	To confirm adequacy of anticoagulation VKA therapy.
Activated partial thromboplastin time (APTT)	To confirm adequacy of anticoagulation if the patient is on UFH
Kidney Function Test	Might be deranged in case of valve dysfunction (low cardiac output state), choice of bridging therapy will depend upon presence of renal dysfunction.
Serum electrolytes (sodium & potassium)	Patients are usually on a salt restricted diet and diuretic, and so might have sub clinical hyponatremia. They are also commonly on ACE inhibitors or ARBs, which can cause hyperkalemia
Posteroanterior view of chest skiagram	To look for evidence of pulmonary hypertension, as they are more prone to develop pulmonary edema, atelectasis and pulmonary complications.
Transthoracic Echocardiography	Function of valve (movement of leaflets, pressure gradient across the implanted prosthetic valve, determination of effective valvular area, para-valvular leak, any vegetation), Regional and global left and right ventricular systolic function and size, Atrial size, enlarged LA with auto contrast, Function of native valves (Other than the one (s) replaced) Estimate of pulmonary artery pressure.
Transesophageal Echocardiography	Assessment of LV function in case of Mitral valve prosthesis For assessment of posterior aspect of aortic valve and is sensitive in detection of vegetation and abscess formation Provides superior imaging of LA side of mitral valve prosthesis

UFH-Unfractionated heparin, LMWH: Low molecular weight heparin, VKA: Vitamin K antagonist, ACE: Angiotensin converting enzyme inhibitor, ARB: Angiotensin II receptor blockers, LA: Left atrium, LV: Left ventricle

because of bridging therapy are likely to have their anticoagulation held back for a more extended period until the risk of bleeding resolves.[3] An observational study reported an almost fivefold increased risk of bleeding in patients with mechanical PHV who received periprocedural bridging (5.8%) compared to those who did not (1.2%).[29] Another observational study showed that the risk of thromboembolism (TE) was low in those whose anticoagulation therapy with VKA was interrupted perioperatively and received periprocedural bridging therapy. Incidence of TE (cerebral ischemia, unstable angina and myocardial infarction) in such patients was 0.9% with no fatalities, whereas the incidence of major bleeding was 3.6% with 0.2% fatalities.[30] The ratio of bleeding incidents to those of thrombosis when bridging therapy is resorted to was 13:1 compared to 5:1 when no bridging was prescribed. Since the complications of TE are far more distressing in the long run, bleeding complications may be a lesser evil. Without bridging, the risk of symptomatic perioperative TE was 0.7% to 1.2%, while it was 0.08 to 0.36% with bridging.[2] While contemplating for bridging in patients in whom oral VKA might need to be interrupted to ensure safe surgery, one should take into consideration the type of surgery, the type

and location of PHV, risk factors of thromboembolism, the length for which oral anticoagulation might have to be withheld and risk of bleeding.[31] The European Society of Cardiology (ESC) guidelines recommend the use of unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH) for bridging in all patients when VKA therapy had to be interrupted,[32] whereas, American College of Cardiology (ACC) and American Heart Association (AHA) guidelines use a risk-based approach and recommend the following[25]:

(i) For patients with mechanical PHV and on oral VKA anticoagulant undergoing minor procedures (dental extractions, cataract/glaucoma surgery, surgeries on skin), oral VKA need not be stopped.[25]
(ii) In patients with bi-leaflet mechanical AVR and no other risk factors for TE, oral VKA may be stopped 2-4 days before the planned procedure and restarted as soon as the risk of surgical bleeding has waned, usually within 24 hours.[25]
(iii) For patients with either mechanical mitral valve, mechanical aortic valve with any other risk factors of TE (hypercoagulable state, AF, previous TE events, LV EF <35%), or older generation mechanical aortic valve, stoppage of VKA and bridging anticoagulant therapy is indicated. Bridging anticoagulation is started once the INR falls below the therapeutic range. It is achieved by intravenous UFH or subcutaneous LMWH, usually 36-48 hours before surgery. If UFH is used, it should be stopped 4-6 hours, and in the case of LMWH, it should be stopped 12 hours before start of the procedure. VKA should be restarted as soon as the risk of surgical bleeding becomes minimal, usually within 24 hours and when the patient is allowed to take orally. If oral intake is not allowed, UFH or LMWH should be continued until the patient can take oral feed (24). In stage IV chronic kidney disease (creatinine clearance less than 30 ml/min) or stage V, only UFH should be used for bridging.[2]
(iv) For patients with mechanical PHV whose therapeutic anticoagulation was maintained with VKA and who needs emergency surgery, anticoagulation may be corrected by either administration of intravenous prothrombin complex concentrate (PCC) or transfusion of fresh frozen plasma (FFP). PCC replaces vitamin K dependent coagulation factors (Factors II, VII, IX and X), has faster onset (5-15 mins) and longer duration of action (12-24 hours). However, it is costly and not widely available. FFP, on the other hand, has a longer onset of action (1-4 hours) and a shorter duration of action (<6 hours).[25]

The issues pertaining to the perioperative anticoagulation management of patients with PHV are summarized in Table 4.

Prophylaxis for Infective Endocarditis (IE)

The prophylaxis against IE depends on the incidence of nosocomial infections and community acquired infections prevalent in the health care facility and community, respectively.

Non-pharmaceutical prophylaxis, though less discussed, but is equally essential include, (i) preoperative intra-nasal treatment of patients who are nasal carriers of *Staphylococcus aureus (S. aureus),* (ii) meticulous skin preparation before surgery, (iii) scrupulous care and early removal of intravenous and central venous lines and urinary catheter, (iv) maintaining oral hygiene and regular dental care.[28]

The concept of antimicrobial prophylaxis of IE had evolved over the years. Though IE is a relatively rare condition, it is associated with severe morbidity and mortality. Concerns with IE prophylaxis include the risk of promoting antibiotic resistance, adverse drug reactions (particularly allergic reactions to penicillin and cephalosporin antibiotics), *Clostridium diffi*cile diarrhea (due to clindamycin) and the cost of treating a large number of patients to avert a single case of IE.[33] In 2008, the guidelines brought out by the National Institute of Health and Clinical Excellence (NICE) of the United Kingdom altogether forbade antibiotic prophylaxis to prevent IE to patients at risk, undergoing dental or non-dental procedures.[34] However, because of a significant rise in the number of cases of IE, from 2008 to2013, reasons though not fully understood,[35] NICE modified its recommendation. NICE left it to the doctors to offer the most appropriate treatment options to patients.[34] The ESC and AHA continue to advocate IE prophylaxis for patients with PHV or those who had undergone valve repair using prosthetic material, as they are believed to be at the highest risk of adverse outcomes from IE.[36,37] The lifetime risk of acquiring IE for a patient with PHV was 308-383 per 100,000 patient-years. The risk of death of a patient with PHV developing IE with *Streptococcus viridian* is about 20% compared to 5% in native valve IE.

Prophylaxis for IE should be administered as a single dose before the procedure. If the pre-procedure dose is missed, dosage may be administered within two hours of the procedure. Drug regimens for various procedures are:

(a). For respiratory tract procedures: No IE prophylaxis is indicated for patients undergoing bronchoscopy unless it involves incision of respiratory tract mucosa. For procedures like a tonsillectomy, adenoidectomy, drainage of abscess or empyema or biopsy of the respiratory mucosa, an agent active against *S. viridians*

Table 4: Anticoagulation related issues in patients with prosthetic heart valves

Type of PHV	Anticoagulant/ Antiplatelet	Target	Bridging Needed	Technique of bridging	Monitoring during bridging	Drug Dosage
Mechanical bileaflet/single tilting AVR & no risk factor for TE	VKA	INR-2.5	No			Titrated to effect
Mechanical MVR, AVR (with ball in cage) or with additional risk factor for TE	VKA	INR -3.0	Not for minor surgeries, needed for invasive procedures	Bridging with either i.v. UFH or s.c. LMWH	For UFH, APTT 2.5 to 3.0 times normal, For LMWH, trough factor Xa level >0.6 IU/ml	80 units/kg i.v. bolus followed by 18 units/kg i.v. infusion, or 8000-10,000 units s.c. every 8 hours or 15,000-20,000 units every 12 hours Enoxaparin: 1.0 mg/kg twice daily or 1.5 mg/kg daily, s.c. Dalteparin: 100 IU/Kg twice daily or 200 IU/kg daily, s.c. Fondaparinux 5 mg daily (BW <50 kg) & 7.5 mg (BW 50-100 kg), s.c.
Bioprosthetic SAVR/MVR without any other indication for anticoagulation	VKA for 3-6 months,	INR 2.5	Yes, if on VKA therapy			
	followed by lifelong aspirin		No			75-100 mg daily

TE: Thromboembolism, SAVR: Surgical Aortic Valve Replacement, MVR: Mitral valve replacement, VKA: Oral vitamin K antagonist, i.v.: Intravenous, s.c.: Sub cutaneous, UFH: Unfractionated heparin, LMWH: Low molecular weight heparin, BW- Body weight, IU: International units

should be included, e.g., 2 gm of either ampicillin, cefazolin or ceftriaxone i.v. For those allergic to penicillin, 600 mg of clindamycin i.v. may be administered. If there is a pre-existent infection suspected to be caused by *S. aureus*, the regimen should contain an agent with activity against *S. aureus*, like first- or second-generation cephalosporin or clindamycin (600 mg i.v.) may be given. Vancomycin may be administered if methicillin-resistant *S aureus* is known or suspected.[33,37]

(b) For Gastrointestinal (GI) or genitourinary (GU) procedures: There is no published literature to support a conclusive link between procedures of GI or GU tract and the development of IE, nor are there any data to prove that IE prophylaxis prevents IE in patients who underwent procedures performed on the GI or GU tract. IE prophylaxis is not indicated in diagnostic esophagogastroduodenoscopy or colonoscopy. Patients with GI or GU infections often have enterococcal bacteremia, and enterococci are likely to cause IE. Hence, a prophylactic regimen should include an agent active against enterococci. For elective procedures like cystoscopy or other urinary tract manipulations, who have enterococcal urinary tract infection or colonization, measures to eradicate enterococci from urine may be done by the appropriate antibiotic. Amoxicillin or ampicillin (2 gm i.v.) may be administered if the procedure is not elective. In those patients known to be allergic to these drugs, one can go for vancomycin (1 gm i.v.).[38]

(c) For procedures on infected skin, skin structures or musculoskeletal tissue: Infections to these areas are often polymicrobial, but only *Staphylococci* and β*ahemolytic streptococci* are the possible causative organisms of IE. Thus, for patients undergoing a surgical procedure involving infected skin, skin structures or musculoskeletal tissues, the regimens for prophylaxis against IE should include agents against *Staphylococci* and β *-hemolytic streptococci*, like anti-*staphylococcal* penicillin or a first/second-generation cephalosporin. For those allergic to these, clindamycin or vancomycin are alternatives.[38]

Technique of anesthesia

(a) For elective Surgeries: There is no recommendation regarding the choice of anesthesia for patients with PHV. As described in section B, these patients are likely to have a variable amount of residual cardiac lesion, so it would be prudent to opt for general anesthesia. The technique adopted should minimize myocardial depression optimize myocardial oxygen requirement and cardiac output. The goals of anesthesia would depend on the original cardiac lesion and their present cardiac status as evident on TTE findings (LVH, PHT, AF, LV Dysfunction etc.)

(b) Patients with BPV and no other risk factors are maintained on aspirin only, and aspirin is continued. Neuraxial block- subarachnoid block or epidural anesthesia (single injection or catheter technique) and peripheral nerve or plexus blocks are both safe in patients on aspirin.[38,39] For patients on dual anti-platelet therapy, neuraxial block is not safe and clopidogrel should be stopped before attempting such block.

(c) For neuraxial blocks in patients with MPV (subarachnoid block and epidural analgesia): American Society of Regional Anesthesia and Pain Medicine (ASRA) has the following recommendations[38]:

(i) For patients on therapeutic heparin. Platelet count should be checked to rule out heparin-induced

thrombocytopenia (HIT) in all patients who received heparin i.v/s.c for more than four days. Heparin should be discontinued for 4-6 hours, and normal coagulation confirmed before attempting neuraxial block. Heparin administration should be deferred by at least one hour after needle placement. If an epidural catheter had been inserted for anesthesia or postoperative analgesia, then the catheter may be removed 4-6 hours after the last heparin dose and heparin restarted at least one hour after removal. The patient should be closely monitored postoperatively for early detection of motor blockade and consider the minimal concentration of local anesthetic to enhance the early detection of spinal hematoma.[38]

(ii) For those on LMWH: Patients receiving LMWH for more than four days are also at risk of developing HIT, so the platelet count should be assessed. Anti-factor Xa level is not predictive of the risk of bleeding and the safe level of residual anti-factor Xa for the performance of neuraxial block in patients on LMWH is not known. Needle/catheter placement for a neuraxial block should be at least 24 hours after the last dose of LMWH. The catheter should be removed before re-initiating LMWH postoperatively and the dose delayed by at least four hours. A therapeutic dose of LMWH should be started 24 hours after non-high bleeding risk surgery and 48-72 hours after high bleeding risk surgery.[38]

(iii) For nerve and plexus blocks: There are no studies on PNBs in patients on heparin. ASRA recommends the same guidelines for PNBs as are available for neuraxial blocks.[38] These need to be followed for lumbar plexus and paravertebral nerve blocks (to avoid retroperitoneal hematoma), as well as for visceral sympathetic nerve blocks.[39] Thus, the ASRA guidelines are helpful while performing nerve/plexus blocks in vascular and non-compressible areas, such as coeliac plexus blocks and lumbar nerve blocks. Clinicians should weigh the pros and cons of such blocks and closely follow up with the patients after the procedure. The ASRA guidelines had been deemed too restrictive for PNBs by the European Society of Anesthesiology, and they suggested that these do not routinely apply for PNBs.[40] The Austrian Society for Anesthesiology, Resuscitation and Intensive Care had also advocated that superficial PNBs can be safely performed in the presence of anticoagulants.[41]

(iv) For emergency surgeries: This will involve rapid correction of oral VKA induced anticoagulation. Hence, general anesthesia should be the preferred choice.

Management of delivery

Safe management of the delivery of a lady with PHV is tricky and demands team effort and close collaboration of cardiologist, obstetrician and anesthesiologist. It should be performed in a tertiary care center. Women with MHV have only a 58% chance of experiencing an uncomplicated pregnancy with live birth, and expected maternal mortality in such patients is 1.4% compared to a mortality of 0.2% in those without.[7] The three primary concerns while dealing with pregnant patients with PHV include,

(i) Enhanced risk of valve thrombosis as a result of the hypercoagulable state induced by pregnancy.[25]

(ii) The transvalvular gradient increases during pregnancy because of increased heart rate, raised plasma volume and stroke volume, as seen in patients with normal native valves.[42] These changes would make women with PHV and compromised hearts susceptible to heart failure.

(iii) There is no anticoagulation strategy available presently, which proved to be equally efficacious for the mother and safe for the fetus.[25]

(a) Management of delivery in pregnant women with PHV becomes much simpler if they had a BPV, in which case they would be on the anti-platelet agent (aspirin) only. Vaginal delivery is preferred if there is no obstetric indication for LSCS. In case LSCS is planned, aspirin continues uninterrupted. Neuraxial block- subarachnoid block or epidural anesthesia (single injection or catheter technique) are safe in patients on aspirin.[38,39]

(b) For those with MHV, the following is the line of management:

(i) All patients should be shifted to UFH or LMWH from oral VKA by the 36th week of pregnancy (40) or one week (24) before the planned delivery. If UFH was chosen, then it should be administered as a continuous i.v. infusion and dose should be adjusted to maintain APTT two times of normal. In the case of LMWH, it should be administered twice daily, targeting anti-factor Xa level between 0.8-1.2 U/ml at 4-6 hours after the last dose.

(ii) Those maintained with LMWH should switch over to continuous i.v. infusion of UFH at least 36 hours prior to delivery, with dose adjusted to maintain APTT two times of normal.

(iii) UFH infusion should be stopped at the start of labor (26) or, better, 6 hours before delivery.[25]

(iv) One should be vigilant regarding major bleeding in the post-partum period, which is defined as a drop in hemoglobin concentration ≥2 gm/dl or need for transfusion of at least two units of PRBC.[43]

(v) UFH infusion should be restarted 4-6 hours after delivery once major bleeding has been ruled out. Oral VKA should be resumed after 24 hours with heparin continuing till a therapeutic level of INR is reached.[29]

(vi) If labor occurs preterm, when the patient is taking oral VKA therapy, LSCS should be performed after reducing INR <2.0 by transfusing PCC or FFP (29). It is pertinent to note that fetal INR takes longer to normalize than maternal INR, and attempting vaginal delivery in patients on oral VKA poses a severe risk of hemorrhage to the fetus, including intracranial bleeding.[43,44]

(c) The technique of anesthesia for LSCS: There is no unanimity regarding the technique of anesthesia while conducting LSCS in patients with PHV. General anesthesia should be the preferred technique for conducting LSCS.[43] It had been suggested that stopping UFH at least 6 hours prior to delivery or in consultation with the obstetrician would reduce the chances of PPH and allow insertion of an epidural catheter for labor analgesia or neuraxial block LSCS.[25] But one should be very cautious, confirm normal APTT value and other parameters of coagulation, particularly platelet count, before attempting epidural catheter insertion or subarachnoid block or removal of the catheter.[45]

Safety issues regarding Magnetic Resonance Imaging (MRI) of patients with PHV

The MPV has several metals and like titanium, and alloys of cobalt and chromium, and those of nickel, molybdenum and tungsten in them.[46] MRI at 3 Tesla had been found to produce forces on the MPV which were smaller than exerted by gravity or beating heart or the pulsatile blood flow. The effect of minimal temperature changes due to radiofrequency pulses as a result of magnetic field is further attenuated as the heat is carried away by the continuous flow of blood.[46] Further, the presence of MPV had not been shown to adversely affect image interpretation. Similar safety profile had been documented for the sternal sutures and mediastinal clips.[47]

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Conflicts of interest

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