

Valvular Heart Disease: Changing Concepts in Disease Management

Prosthetic Heart Valves

Selection of the Optimal Prosthesis and Long-Term Management

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The introduction of valve replacement surgery in the early 1960s has dramatically improved the outcome of patients with valvular heart disease. Approximately 90 000 valve substitutes are now implanted in the United States and 280 000 worldwide each year; approximately half are mechanical valves and half are bioprosthetic valves. Despite the marked improvements in prosthetic valve design and surgical procedures over the past decades, valve replacement does not provide a definitive cure to the patient. Instead, native valve disease is traded for “prosthetic valve disease,” and the outcome of patients undergoing valve replacement is affected by prosthetic valve hemodynamics, durability, and thrombogenicity. Nonetheless, many of the prosthesis-related complications can be prevented or their impact minimized through optimal prosthesis selection in the individual patient and careful medical management and follow-up after implantation. The purpose of this article is to provide an overview of the current state of knowledge and future perspectives with regard to optimal prosthesis selection and clinical management after valve implantation.

Types of Prosthetic Heart Valve Design

The ideal valve substitute should mimic the characteristics of a normal native valve. In particular, it should have excellent hemodynamics, long durability, high thromboresistance, and excellent implantability. Unfortunately, this ideal valve substitute does not exist, and each of the currently available prosthetic valves has inherent limitations.

Mechanical Valves

Three basic types of mechanical valve design exist: bileaflet, monoleaflet, and caged ball valves (Figure 1A, 1B, and 1C).

Caged Ball Valves

Caged ball valves, which consist of a silastic ball with a circular sewing ring and a cage formed by 3 metal arches, are no longer implanted. However, several thousands of patients still have caged ball valves, and these patients require follow-up.

Monoleaflet Valves

Monoleaflet valves are composed of a single disk secured by lateral or central metal struts. The opening angle of the disk relative to valve annulus ranges from 60° to 80°, resulting in 2 distinct orifices of different sizes.

Bileaflet Valves

Bileaflet valves are made of 2 semilunar disks attached to a rigid valve ring by small hinges. The opening angle of the leaflets relative to the annulus plane ranges from 75° to 90°, and the open valve consists of 3 orifices: a small, slit-like central orifice between the 2 open leaflets and 2 larger semicircular orifices laterally.

Bioprosthetic Valves

Stented Bioprostheses

The design of bioprostheses purports to mimic the anatomy of the native aortic valve (Figure 1D and 1E). Porcine bioprosthetic valves consist of 3 porcine aortic valve leaflets cross-linked with glutaraldehyde and mounted on a metallic or polymer supporting stent. Pericardial valves are fabricated from sheets of bovine pericardium mounted inside or outside a supporting stent.

Stentless Bioprostheses

In an effort to improve valve hemodynamics and durability, several types of stentless bioprosthetic valves have been developed (Figure 1F). Stentless bioprostheses are manufactured from whole porcine aortic valves or fabricated from bovine pericardium.

Percutaneous Bioprostheses

Percutaneous aortic valve implantation is emerging as an alternative to standard aortic valve replacement (AVR) in patients with symptomatic aortic stenosis considered to be at high or prohibitive operative risk (Figure 1G and 1H).^{1–5} The valves are usually implanted using a percutaneous transfemoral approach.^{4,5} To reduce the problems of vascular access and associated complications, a transapical approach through a small thoracotomy may also be used. At present, the procedure appears promising, but it remains experimental and is currently undergoing further investigation.

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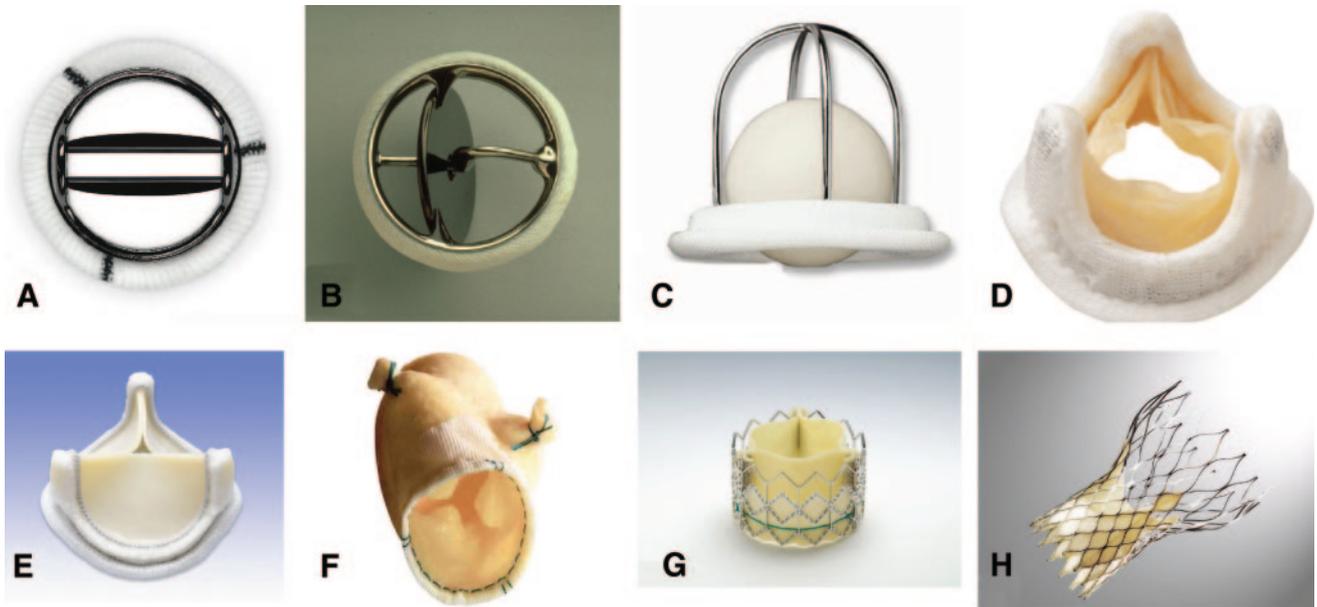


Figure 1. Different types of prosthetic valves. A, Bileaflet mechanical valve (St Jude); B, monoleaflet mechanical valve (Medtronic Hall); C, caged ball valve (Starr-Edwards); D, stented porcine bioprosthesis (Medtronic Mosaic); E, stented pericardial bioprosthesis (Carpentier-Edwards Magna); F, stentless porcine bioprosthesis (Medtronic Freestyle); G, percutaneous bioprosthesis expanded over a balloon (Edwards Sapien); H, self-expandable percutaneous bioprosthesis (CoreValve).

Selecting the Optimal Prosthesis in the Individual Patient

Bioprosthetic Versus Mechanical Valve

Choosing the right valve for the right patient is a difficult but essential process to optimize the outcome for patients undergoing valve replacement. The first step in this decision-making process is to choose between a mechanical and a

bioprosthetic valve (Figure 2). The most important factors that should be considered in this first step are the patient's age, life expectancy, preference, indication/contraindication for warfarin therapy, and comorbidities. In the recent American College of Cardiology/American Heart Association and European guidelines,^{6,7} the weight given to patient age has been reduced, whereas much greater importance is now given

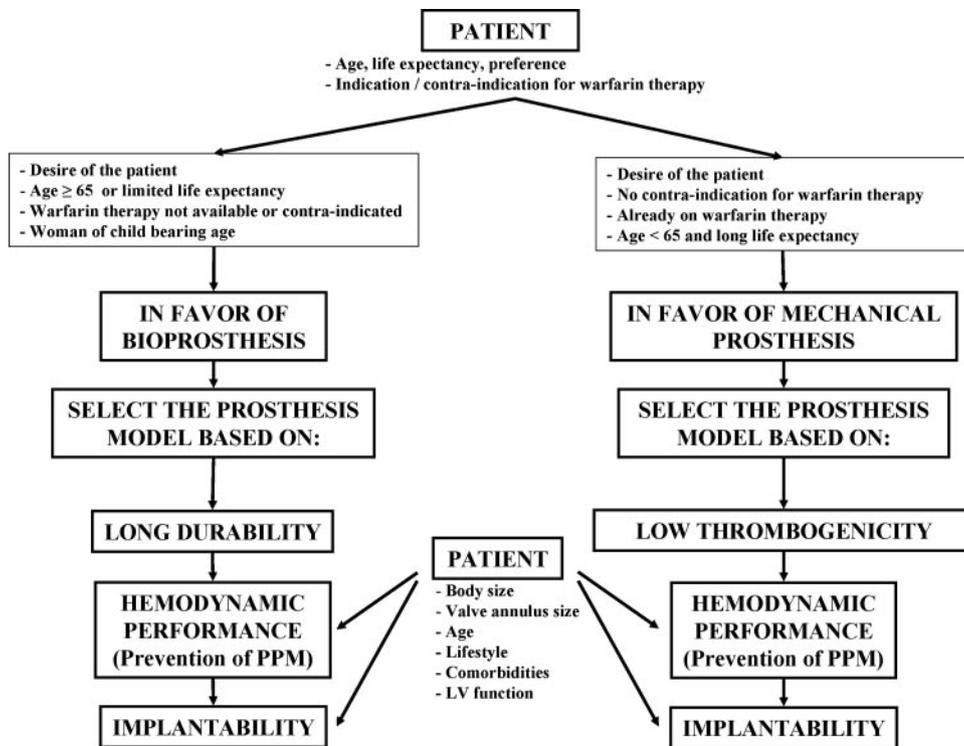


Figure 2. Algorithm for the selection of the optimal prosthesis in the individual patient.

Table 1. Normal Reference Values of EOAs for the Aortic Prostheses

	Prosthetic Valve Size, mm						Reference
	19	21	23	25	27	29	
Aortic stented bioprosthesis							
Mosaic	1.1±0.2	1.2±0.3	1.4±0.3	1.7±0.4	1.8±0.4	2.0±0.4	10
Hancock II	...	1.2±0.1	1.3±0.2	1.5±0.2	1.6±0.2	1.6±0.2	10
Carpentier-Edwards Perimount	1.1±0.3	1.3±0.4	1.50±0.4	1.80±0.4	2.1±0.4	2.2±0.4	10
Carpentier-Edwards Magna*	1.3±0.3	1.7±0.3	2.1±0.4	2.3±0.5	11, 20
Biocor (Epic)*	...	1.3±0.3	1.6±0.3	1.8±0.4	12
Mitroflow*	1.1±0.1	1.3±0.1	1.5±0.2	1.8±0.2	13
Aortic stentless bioprosthesis							
Medtronic Freestyle	1.2±0.2	1.4±0.2	1.5±0.3	2.0±0.4	2.3±0.5	...	10
St Jude Medical Toronto SPV	...	1.3±0.3	1.5±0.5	1.7±0.8	2.1±0.7	2.7±1.0	10
Aortic mechanical prostheses							
Medtronic-Hall	1.2±0.2	1.3±0.2	10
Medtronic Advantage*	...	1.7±0.2	2.2±0.3	2.8±0.6	3.3±0.7	3.9±0.7	14
St Jude Medical Standard	1.0±0.2	1.4±0.2	1.5±0.5	2.1±0.4	2.7±0.6	3.2±0.3	10
St Jude Medical Regent	1.6±0.4	2.0±0.7	2.2±0.9	2.5±0.9	3.6±1.3	4.4±0.6	27
MCRI On-X	1.5±0.2	1.7±0.4	2.0±0.6	2.4±0.8	3.2±0.6	3.2±0.6	27
Carbomedics Standard	1.0±0.4	1.5±0.3	1.7±0.3	2.0±0.4	2.5±0.4	2.6±0.4	10

EOA is expressed as mean values available in the literature.

*These results are based on a limited number of patients and thus should be interpreted with caution.

to the patient's preference. The criteria in favor of using a mechanical valve include the following: (1) the informed patient wants a mechanical valve and has no contraindication for long-term anticoagulation; (2) the patient is already on anticoagulation (mechanical prosthesis in another position or at high risk for thromboembolism); (3) the patient is at risk of accelerated bioprosthesis structural deterioration (young age, hyperparathyroidism, renal insufficiency); and (4) the patients is <65 years of age and has a long life expectancy. On the other hand, a bioprosthesis may be preferred in the following situations: (1) the informed patient wants a bioprosthesis; (2) good-quality anticoagulation is unavailable (contraindication or high risk, compliance problems, lifestyle); (3) the patient is ≥65 years of age and/or has limited life expectancy; and (4) the patient is a woman of childbearing age. Bioprostheses degenerate more rapidly in young patients and during pregnancy. Hence, a woman in her late 30s or early 40s who has completed her family should probably be advised to have a mechanical valve.⁸

Selection of the Prosthesis Model and Size

After the prosthesis type, ie, mechanical versus biological, is selected, one should logically contemplate the prosthesis models that have a well-established track record with regard to long-term durability (bioprostheses) and low thrombogenicity (mechanical prostheses) (Figure 2). Thromboembolic rates are a poor indicator of the valve thrombogenicity because they can be highly influenced by patient risk factors and antithrombotic management.⁹ Thrombogenicity of the individual prosthesis should thus be determined on the basis of reported valve thrombosis rates for that prosthesis in relation to anticoagulation intensity and valve position. In this regard, it should be noted that prostheses cannot be conve-

niently categorized according to basic design (eg, bileaflet, monoleaflet, etc) or date of introduction to determine the level thrombogenicity (see the Antithrombotic Therapy section).

The next step is to choose a prosthesis model that provides superior hemodynamic performance to prevent prosthesis-patient mismatch (PPM) and thereby minimize postoperative transprosthetic gradients. Hence, among bioprostheses with similar durability or mechanical valves with similar thrombogenicity, one should preferably select the model that provides the largest valve effective orifice area (EOA) in relation to the patient's annulus size (Tables 1 and 2).^{10–15} The hemodynamic performance or "EOAbility" of the prosthesis is essentially determined by the size of prosthesis that can fit into the patient's annulus and by the proportion of the total cross-sectional area of that prosthesis that is actually available for blood flow. To this effect, it should be underlined that the hemodynamic performance is not equivalent for all models of prostheses. Indeed, it is generally superior in newer compared with older generations of prostheses, in mechanical compared with stented bioprosthetic valves,¹⁶ in stentless compared with stented bioprosthetic valves,^{17,18} and in supraannular compared with intra-annular stented bioprostheses.^{19,20} A recent meta-analysis¹⁸ shows that, compared with stented bioprostheses, stentless valves provide larger EOAs, reduced transprosthetic gradients, and greater left ventricular (LV) mass regression, but at the expense of prolonged cardiopulmonary bypass time.

It is also important to emphasize that major discrepancies exist among the different prosthesis models between the actual dimensions of the prosthesis and the labeled prosthesis size given by the sizers provided by the manufacturers.

Table 2. Normal Reference Values of EOAs for the Mitral Prostheses

	Prosthetic Valve Size, mm					Reference
	25 mm	27 mm	29 mm	31 mm	33 mm	
Stented bioprosthesis						
Medtronic Mosaic	1.5±0.4	1.7±0.5	1.9±0.5	1.9±0.5	...	15, 28
Hancock II	1.5±0.4	1.8±0.5	1.9±0.5	2.6±0.5	2.6±0.7	29
Carpentier-Edwards Perimount*	1.6±0.4	1.8±0.4	2.1±0.5	28
Mechanical prostheses						
St Jude Medical Standard	1.5±0.3	1.7±0.4	1.8±0.4	2.0±0.5	2.0±0.5	28
MCRI On-X†	2.2±0.9	2.2±0.9	2.2±0.9	2.2±0.9	2.2±0.9	28

EOA is expressed as mean values available in the literature.

*These results are based on a limited number of patients and thus should be interpreted with caution.

†The strut and leaflets of the MCRI On-X valve are identical for all sizes (25 to 33 mm).

Consequently, it is inappropriate to compare the hemodynamic performance of different prosthesis models on the basis of their labeled sizes (Tables 1 and 2).²¹ Indeed, based on the sizes, the same annulus might, for instance, accommodate a size 23 of prosthesis X compared with only a size 21 of prosthesis Y.

Once the prosthesis model and size have been selected, it is important to implant the prosthesis using an optimal surgical technique. In particular, for mitral valve replacement (MVR), it is recommended that the chordae be preserved to prevent postoperative deterioration in LV geometry and function.²² Moreover, in the mitral position, the surgeon should implant bileaflet valves in the antianatomic position and monoleaflet valves with their larger orifice oriented posteriorly to ensure more physiological flow patterns.²³

Prosthesis-Patient Mismatch

The term valve PPM was first proposed in 1978 by Rahimtoola.²⁴ PPM occurs when the EOA of a normally functioning prosthesis is too small in relation to the patient's body size (and therefore cardiac output requirements), resulting in abnormally high postoperative gradients. The most widely accepted and validated parameter for identifying PPM is the indexed EOA, ie, the EOA of the prosthesis divided by the patient's body surface area.^{10,25–27} Table 3 shows the threshold values of indexed EOA generally used to identify PPM and to quantify its severity. Moderate PPM may be quite frequent in both the aortic (20% to 70%) and mitral (30% to 70%) positions, whereas the prevalence of severe PPM ranges from 2% to 10% in both positions.^{10,27–29}

Clinical Impact of PPM

Several studies have reported that aortic PPM is associated with less improvement in symptoms and functional class,³⁰

impaired exercise capacity,³¹ less regression of LV hypertrophy,³² less improvement in coronary flow reserve,³³ and more adverse cardiac events.^{30,34} Moreover, PPM has a significant impact on both short-term^{35,36} and long-term mortality.^{34,36,37} Recent studies also have reported that the impact of PPM is most significant in patients with depressed LV function with regard to heart failure and mortality after AVR.^{34,35} These findings reflect the fact that an increased hemodynamic burden is less well tolerated by a poorly functioning ventricle than by a normal ventricle. The impact of PPM also is more pronounced in young patients than in older patients,¹⁶ which might be related to the fact that younger patients have higher cardiac output requirements and are exposed to the risk of PPM for a longer period of time. Mitral PPM is independently associated with persisting pulmonary hypertension, increased incidence of congestive heart failure, and reduced survival after MVR.^{28,29}

Prevention of PPM

In light of data published in the literature, the surgeon should attempt to avoid severe PPM in every patient undergoing AVR or MVR. Likewise, every effort should be made to avoid moderate PPM in patients undergoing AVR and presenting with the following coexisting conditions: preexisting LV dysfunction and/or severe LV hypertrophy, age <65 to 70 years, and regular and/or intense physical activity.

Previous studies^{10,38,39} have demonstrated that aortic PPM can largely be avoided by systematically calculating the projected indexed EOA of the prosthesis to be inserted (Tables 1 and 2) and, in the case of anticipated PPM, by using alternate procedures such as insertion of a prosthesis model with better hemodynamic performance and aortic root enlargement to accommodate a larger size of the same prosthesis model. Recent studies have reported that this procedure can be performed safely for this purpose,^{39–41} whereas earlier studies showed evidence to the contrary.⁴² Hence, root enlargement should probably be considered only in patients in whom the risk of severe PPM cannot be avoided with the use of a better-performing prosthesis and in whom the risk-to-benefit ratio of doing such a procedure is considered advantageous (eg, young patients with no or mild aortic calcification). The prevention of PPM in the mitral position represents a much greater challenge than in the aortic position

Table 3. Threshold Values of Indexed Prosthetic Valve EOA for the Identification and Quantification of PPM

	Mild or Not Clinically Significant, cm ² /m ²	Moderate, cm ² /m ²	Severe, cm ² /m ²
Aortic position	>0.85 (0.8–0.9)	≤0.85 (0.8–0.9)	≤0.65 (0.6–0.7)
Mitral position	>1.2 (1.2–1.3)	≤1.2 (1.2–1.3)	≤0.9 (0.9)

Numbers in parentheses represent the range of threshold values that have been used in the literature.

because valve annulus enlargement or stentless valve implantation is not an option in this situation.^{27,28}

Long-Term Management

Antithrombotic Therapy

Patients with prosthetic valves are at risk of thromboembolic complications, including systemic embolization, most commonly cerebral, and prosthetic thrombosis causing valve obstruction and/or regurgitation. The risk of thromboembolic events is higher with mechanical than with bioprosthetic valves, higher with mitral than with aortic prosthetic valves, and higher in the early (<3 months) versus late postoperative phase.^{6,7,43} The risk also is increased in the presence of concomitant risk factors for thromboembolism, including atrial fibrillation, LV dysfunction, left atrial dilation, previous thromboembolism, and hypercoagulable condition. Table 4 summarizes the general recommendations for antithrombotic therapy based on the prosthesis type and position and the presence of risk factors.^{6,43,44} Patients with mechanical prostheses require lifelong anticoagulation with warfarin. The choice of optimum international normalized ratio (INR) target for oral anticoagulation should also take into account the thrombogenicity of the individual prosthesis (Table 4).⁹

For patients with bioprostheses, warfarin therapy is generally recommended during the first 3 months after implantation on the rationale that endothelialization of the valve sewing cuff may take several weeks to complete (Table 4).^{6,7,9,43,45} However, several investigators^{46–48} have questioned the relevance of this recommendation in patients with no thromboembolic risk factors, and according to a recent survey, ≈30% of centers use only aspirin during the first 3 months in these patients.⁴⁹ After 3 months, warfarin therapy is indicated in patients with a bioprosthesis only if they have ≥1 risk factors for thromboembolism.

Anticoagulation management in pregnancy requires a comprehensive evaluation of risks versus benefits.⁸ Warfarin is probably safe during the first 6 weeks of gestation, but a risk of embryopathy exists if warfarin is taken between 6 and 12 weeks of gestation.^{6,8} A possible strategy therefore consists of using heparin during the first trimester to avoid warfarin embryopathy, followed by oral anticoagulation up to the 36th week, with subsequent replacement by heparin until delivery.^{6,9}

Noncardiac Surgery and Dental Care

In the anticoagulated patient, the risk of increased bleeding during a noncardiac procedure must be weighed against the increased risk of thromboembolism caused by stopping the antithrombotic therapy. Many surgical procedures (including dental procedures) in which bleeding can be controlled easily do not require complete cessation of oral anticoagulation. When oral anticoagulation cessation is necessary, the optimum timing of drug withdrawal depends on the level of INR and the duration of action of the oral anticoagulant drug used. In patients with a bileaflet mechanical valve or a Medtronic Hall monoleaflet valve AVR and no risk factors, warfarin can be stopped 48 to 72 hours before the procedure (so that the INR falls below 1.5) and restarted within 24 hours after the procedure after control of active bleeding.^{6,7,9,43,50} In other

Table 4. Antithrombotic Therapy in Patients With Prosthetic Heart Valves

	Warfarin (INR 2–3)	Warfarin (INR 2.5–3.5)	Aspirin (75–100 mg)
Mechanical prostheses			
First 3 mo after replacement		+	+
After first 3 mo			
Aortic valve			
Low thrombogenicity*	+		(+)
Medium thrombogenicity*	+		(+)
High thrombogenicity*		+	+
Aortic valve plus risk factor†		+	+
Mitral valve with/without risk factor†		+	+
Bioprostheses			
First 3 mo after replacement			
Aortic valve	(+)		+
Aortic valve plus risk factor†		+	+
Mitral valve	+		+
Mitral valve plus risk factor		+	+
After first 3 mo			
Aortic valve			+
Aortic valve plus risk factor†	+		+
Mitral valve			+
Mitral valve plus risk factor†		+	+

(+) Indicates that although the guidelines generally recommend the therapy, recent studies do not support this recommendation and/or evidence in favor of the recommendation is lacking.

*Prosthesis thrombogenicity: low: St Jude Medical, On-X, Carbomedics, Medtronic Hall; medium: bileaflet valves with insufficient data, Bjork-Shiley; high: Lillehei-Kaster, Omniscience, Starr-Edwards. Note that the European guidelines recommend higher INR target for prostheses with medium and high thrombogenicity (AVR and no risk factors, 3.0 for medium and 3.5 for high; MVR and/or risk factors, 3.5 for medium and 4.0 for high).

†Risk factors: atrial fibrillation, LV dysfunction (LV ejection fraction ≤35%), left atrial dilation (left atrial diameter ≥50 mm), previous thromboembolism, spontaneous echocardiographic contrast, and hypercoagulable condition.

Modified from McNulty JH, Rahimtoola SH. Antithrombotic therapy for valvular heart disease. In: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P, eds. *Hurst's The Heart*. New York, NY: McGraw-Hill; 2008:1800–1807.⁴⁴ Reprinted with permission from the publisher, copyright © 2008, the McGraw-Hill Companies.

patients with mechanical valves (MVR or AVR with ≥1 risk factors), warfarin is generally stopped 72 hours before the procedure, and heparin is started when the INR falls below 2.0, then stopped 4 to 6 hours before the procedure, restarted as soon as bleeding stability allows, and continued until the INR is again therapeutic. The validated approach is to use intravenous unfractionated heparin, but potential benefits

exist to using low-molecular-weight heparin, which can be given on an outpatient basis and, according to recent studies,⁵¹ appears to have acceptable risk. The safety of this approach, however, remains to be established in patients at high risk of valve thrombosis. Hence, for the time being, close monitoring with anti-Xa assays is recommended when low-molecular-weight heparin is used in patients with mechanical valves.⁹

Future Perspectives

High variability of the INR is the strongest independent predictor of reduced survival after mechanical valve replacement.⁵² In patients with mechanical prosthetic valves, the Early Self-Controlled Anticoagulation Trial (ESCAT) has revealed that self-management of anticoagulation allows patients to be maintained within a lower and smaller INR range, which results in fewer thromboembolic events rates and in a 23% improvement in long-term survival.^{53,54} Although these results are encouraging, it is important to emphasize that self-management is not feasible for all patients and that it requires proper identification and education of suitable candidates.

In addition, alternatives to warfarin therapy are now under investigation, including the use of direct thrombin inhibitors administered at fixed doses that do not require regular monitoring, as well as the use of antiplatelet drugs or lower doses of warfarin in newer-generation bileaflet prosthesis with a low thrombogenicity profile.

Self-management of anticoagulation and/or the replacement of warfarin therapy by newer approaches may help to improve the outcome of patients with mechanical valves and thus expand their use.

Endocarditis Prophylaxis

Patients with prosthetic valves are at high risk for endocarditis because of the foreign valve surface and sewing ring. Therefore, a lifelong requirement exists for antibiotic prophylaxis for dental, endoscopic, and surgical procedures in patients with a prosthetic valve.^{6,7,9} Patients and their treating physicians/dentists should be aware of the importance of ensuring rigorous dental hygiene and obtaining blood cultures for any febrile illness before starting antibiotic therapy.

Echocardiographic Follow-Up

Echocardiography is the method of choice to evaluate prosthetic valve function. This evaluation follows the same principles used for the evaluation of native valves with some important caveats described below. A complete echocardiography includes 2-dimensional imaging of the prosthetic valve, evaluation of leaflet morphology and mobility, measurement of the transprosthetic gradients and EOA, estimation of the degree of regurgitation, evaluation of LV size and systolic function, and calculation of systolic pulmonary arterial pressure. After valve replacement, echocardiographic examination should be performed at discharge or 30 days and 6 to 12 months after operation and/or when a clinical suspicion of prosthetic valve dysfunction is present.⁴³ Moreover, regular follow-up is recommended after 5 years in patients with a bioprosthesis.

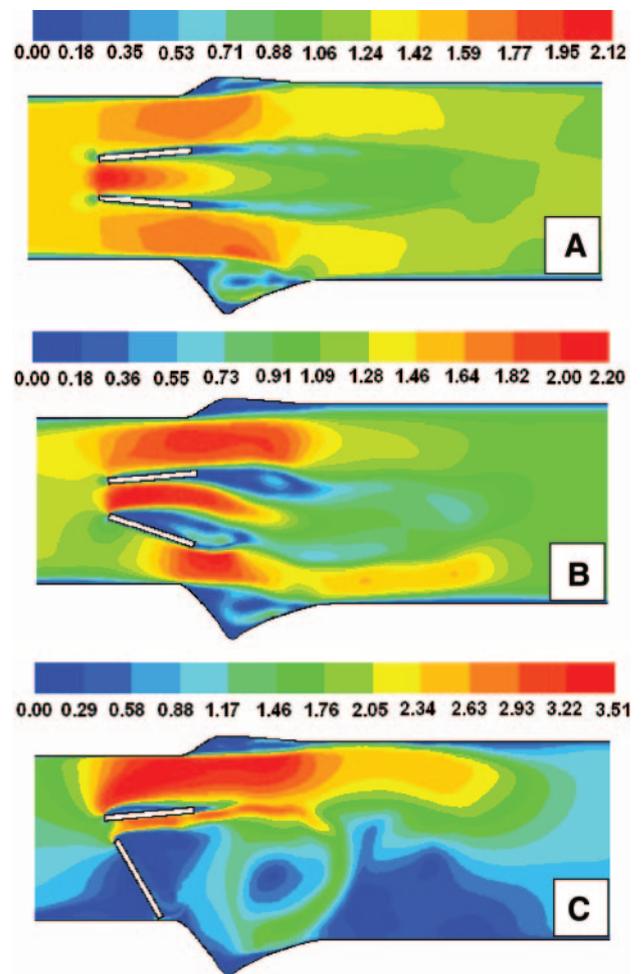


Figure 3. Numerical simulation showing the flow velocity distribution in bileaflet mechanical valves at a cardiac output of 5 L/min. A, Normally functioning bileaflet prosthesis. The flow velocity within the central orifice is higher than that in the lateral orifices. Accordingly, the peak gradient across the central orifice is 19 mm Hg, which is higher than the actual peak transprosthetic gradient (10 mm Hg). B, Mild prosthesis dysfunction with 25% restriction in the opening of 1 leaflet. The peak gradient is 20 mm Hg. C, Severe prosthesis dysfunction with 1 leaflet blocked in the closed position. The peak gradient is 50 mm Hg. Courtesy of Drs Othman Smadi and Lyes Kadem, Concordia University, Montreal, Québec, Canada.

Parameters of Prosthesis Function

Leaflet Morphology and Mobility

Echocardiographic imaging of the valve occluder is limited by reverberations and shadowing caused by the valve components. Transesophageal echocardiography (TEE) can provide improved image quality and thereby improved detection of cusp calcification and thickening, valvular vegetations caused by endocarditis, thrombus or pannus, and reduced leaflet mobility.⁵⁵ In the case of mechanical prosthesis, evaluation of leaflet mobility can be attempted with some degree of success, but in our experience, valve fluoroscopy is definitely the best, most economical, and least invasive technique that can be used for this purpose.

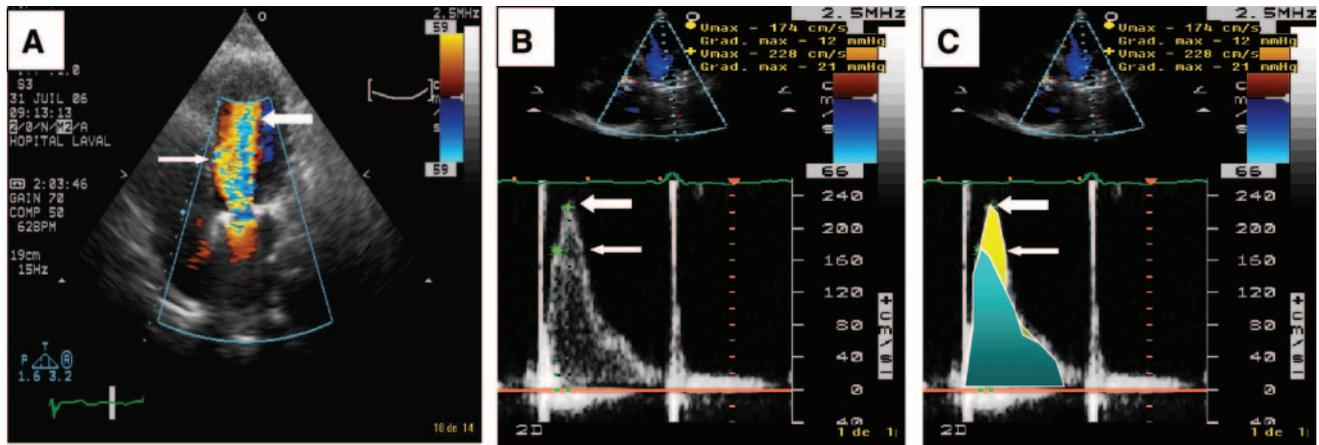


Figure 4. Localized high gradient in a mitral bileaflet valve. A, Visualization of lateral (narrow arrow) and central (large arrow) jets on color Doppler image. B, C, Two Doppler envelopes are superimposed. The highest one, which presumably reflects the velocity within the central orifice, yields a value of peak gradient of 21 mm Hg, whereas the smallest one (lateral orifices) provides a gradient of 12 mm Hg.

Quantitative Parameters

Transprosthetic Velocity and Gradient

The fluid dynamics of mechanical valves may differ substantially from those of native valves. The flow is eccentric in monoleaflet valves and composed of 3 separate jets in the bileaflet valves (Figure 3). Because the direction of the transprosthetic jet may be eccentric, apical, right parasternal, and suprasternal windows should be examined carefully to detect the highest-velocity signal in aortic prosthetic valves. Occasionally, an abnormally high jet gradient corresponding to a localized high velocity may be recorded by continuous-wave Doppler interrogation through the smaller central orifice of bileaflet mechanical prostheses in the aortic or mitral position (Figures 3 and 4).⁵⁶ This phenomenon may lead to an overestimation of gradient and a false suspicion of prosthesis dysfunction.

Effective Orifice Area

EOA is calculated with the continuity equation, similar to native aortic valve area.^{25,26} When the EOA of a prosthetic valve is measured, a few specific caveats should be taken into consideration. The substitution of the LV outflow tract (LVOT) diameter by the labeled prosthesis size in the continuity equation is not a valid method to determine the EOA of aortic prostheses.⁵⁷ For mitral prostheses, the EOA is calculated by the continuity equation using the stroke volume measured in the LVOT. It is important to emphasize that the pressure half-time is not valid to estimate the valve EOA of mitral prostheses.^{25,58} Tables 1 and 2 show the normal reference values of EOA for the most commonly used prosthetic valves.

Doppler Velocity Index

The Doppler velocity index (DVI) is a dimensionless ratio of the proximal velocity in the LVOT to that of flow velocity through the prosthesis: $DVI = V_{LVOT} / V_{PV}$. This parameter can therefore be helpful to screen for valve obstruction, particularly when the cross-sectional area of the LVOT cannot be obtained.⁵⁹

Interpretation of High Gradients: Distinguishing Between High-Flow States, PPM, and Pathological Valve Obstruction

The presence of increased transprosthetic gradient (mean gradient >15 to 20 mm Hg for aortic prostheses and >5 to 7 mm Hg for mitral prostheses) cannot be equated with intrinsic prosthesis dysfunction.^{27,59} Hence, a high gradient can be due to an associated subvalvular obstruction or a high-flow state (eg, hyperadrenergism, valvular regurgitation); such occurrences can be suspected when the DVI is normal (>0.35 for aortic or >0.45 for mitral prostheses). Conversely, the combination of a high gradient and a low DVI suggests valvular obstruction. In such cases, an integrative evaluation must be done; in particular, the distinction must be made between obstruction resulting from PPM, which is by far the most frequent cause of high postoperative gradients, and intrinsic prosthesis dysfunction, which is a pathological condition requiring more investigation and treatment. For this purpose, the following algorithm can be used (Figure 5).

Step 1

As a first screening step, the possibility of PPM as a contributing factor can be assessed by calculating the projected indexed EOA of the prosthesis implanted. This is accomplished by dividing the EOA reference value for the model and size of the prosthesis (Tables 1 and 2) by the patient's body surface area. If this projected indexed EOA is >0.85 cm²/m² in the aortic position or >1.2 cm²/m² in the mitral position (Table 3), then PPM is not a contributing factor. However, if the indexed EOA is below this value, PPM may be partially or totally responsible for the high gradient.

Step 2

The second step consists of comparing the EOA as measured by Doppler with the EOA reference value (Tables 1 and 2). The measured EOA of a normally functioning prosthesis should be close to the reference value for the same model and size of prosthesis, whereas a substantially lower value is compatible with intrinsic prosthesis dysfunction.

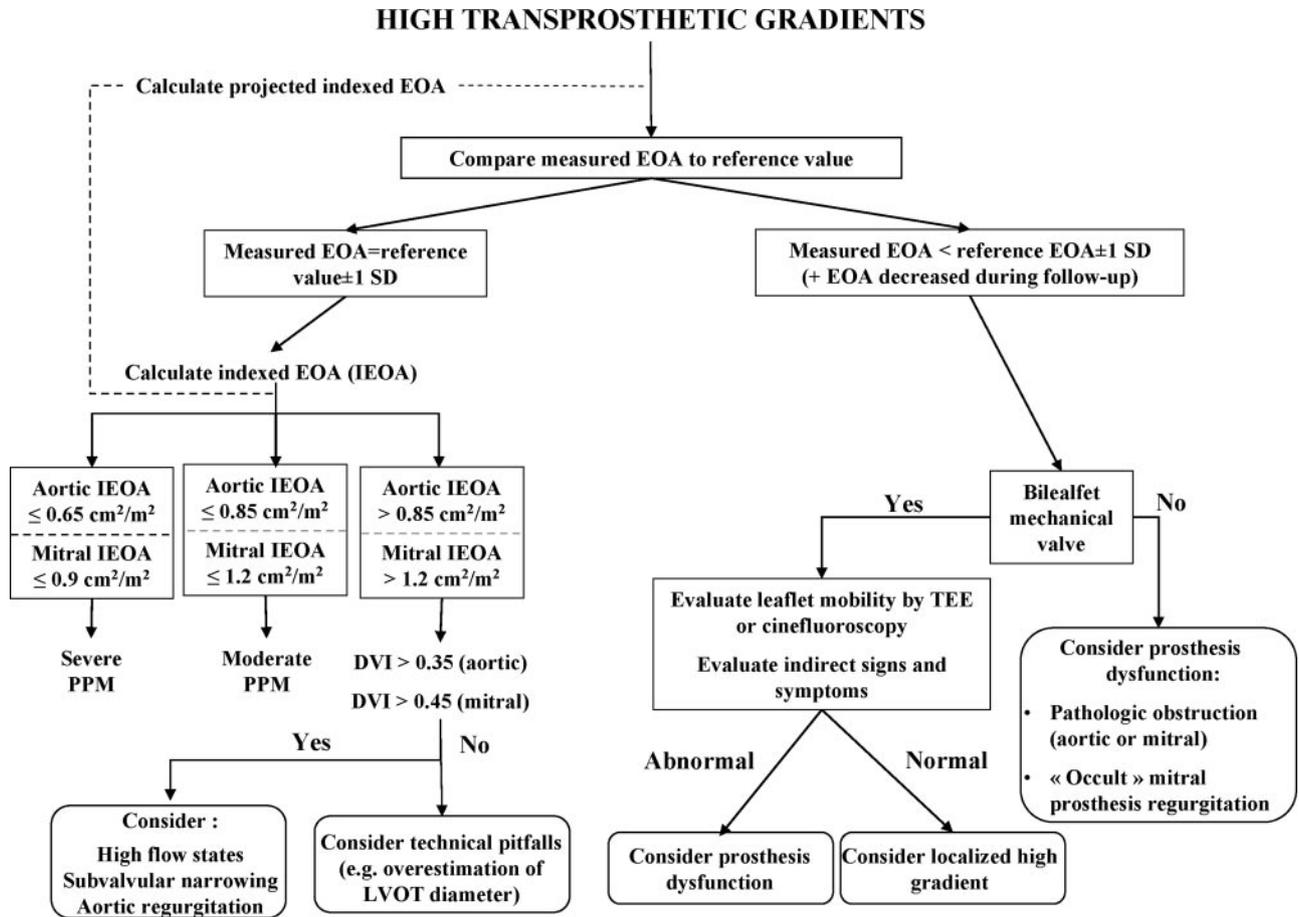


Figure 5. Algorithm for the interpretation of high transprosthetic gradient. IEOA indicates indexed EOA.

Step 3

If the measured EOA is similar to its reference value ± 1 SD, intrinsic dysfunction is unlikely, and the presence/severity of PPM should be confirmed by calculating the indexed EOA. If no PPM is present, a technical pitfall or a high-flow state is likely.

Step 4

If the EOA is below the reference value and if the prosthesis is not a bileaflet mechanical valve, prosthesis valve dysfunction should be envisioned, and confirmation should be sought with other examinations such as TEE, fluoroscopy, computed tomography, or cardiac catheterization. If, on the other hand, the prosthesis is a bileaflet mechanical valve and the patient is asymptomatic, localized high gradient is the likely cause (Figures 3 and 4). Unfortunately, this phenomenon is often difficult to confirm or exclude from the transthoracic echocardiography (TTE). In case of doubt, valve leaflet mobility can be evaluated with fluoroscopy (or TEE) and by looking for indirect signs of prosthesis dysfunction.

Evaluation and Interpretation of Prosthetic Valve Regurgitation

The approach to detecting and grading prosthesis regurgitation is similar to that for native valves and involves evaluation of several Doppler echocardiographic indexes.⁶⁰ However, care is needed to separate physiological from pathological prosthesis regurgitation. Mechanical prostheses

indeed have a normal regurgitant volume known as leakage backflow. This “built-in” regurgitation theoretically prevents blood stasis and thrombus formation using a washing effect. As opposed to the pathological regurgitant jets, the normal leakage backflow jets are characterized by being short in duration, narrow, and symmetrical. In the case of pathological regurgitation, it is also important to localize the origin of the regurgitant jet(s) to distinguish paravalvular from transvalvular regurgitation.

Prosthetic Aortic Regurgitation

TTE generally provides a good visualization of the LVOT and prosthetic aortic regurgitation. Multiple views should be used, as well as the same principles and methods used for quantitation of native valvular regurgitation.⁶⁰ It must be remembered, however, that very limited data are available on the application and validation of quantitative parameters such as the width of the regurgitant jet, effective orifice area, and regurgitant volume in the context of prosthetic valves.⁶¹ TEE may provide important causal information such as flail bioprosthetic cusp, presence of pannus or thrombus interacting with leaflet closure, prosthesis dehiscence, and location and size of paravalvular jets.⁵⁵

Prosthetic Mitral Regurgitation

Assessment of prosthetic mitral regurgitation by TTE is problematic because the left atrium is largely occulted by the acoustic shadowing caused by the metallic components of the

prosthesis. This problem is more frequent in mechanical valves than bioprosthetic valves. The presence of "occult" mitral prosthesis regurgitation should be suspected when the following signs are present: flow convergence downstream of the prosthesis during systole, increased mitral peak E-wave velocity (>2 m/s) and/or mean gradient (>5 to 7 mm Hg), DVI <0.45 , or unexplained or new worsening of pulmonary arterial hypertension. A decision tree analysis such as that proposed by Fernandes et al⁵⁹ using multiple parameters can also be useful. TEE should be performed systematically when a clinical or TTE suspicion of pathological mitral regurgitation is present.⁵⁵

Identifying Indirect Signs of Dysfunction

The size and function of the LV and atrial chambers and the level of systolic pulmonary arterial pressure can be used to corroborate prosthesis dysfunction severity. In particular, these measurements can be compared with previous measurements and often are the first sign to alert attention when the regurgitation is difficult to visualize.

Additional Diagnostic Tests

Exercise testing and plasma natriuretic peptides are additional tests that can be used to further document decreased functional capacity and/or early heart failure resulting from prosthesis dysfunction or PPM.

Long-Term Complications: Identification and Management

Mechanical valves have a substantial risk of thromboemboli and thrombotic obstruction and therefore require long-term anticoagulation therapy, which in turn is associated with an increased risk of hemorrhagic complications. Nonetheless, contemporary mechanical valves have excellent durability. In contrast, bioprosthetic valves have a low risk of thromboembolism without anticoagulation, but their durability is limited by calcific or noncalcific tissue deterioration.⁶²

Thromboembolic and Bleeding Complications

Thromboembolic complications are an important cause of morbidity and mortality in patients with a prosthetic heart valve, with an estimated incidence of clinical events ranging from 0.6% to 2.3% per patient-year.^{6,50} The risk of thromboembolic complications is similar for patients with mechanical valves on warfarin therapy and bioprosthetic valves without warfarin therapy. The risk of thromboembolism depends not only on prosthesis type but also on valve position and thrombogenicity, patient risk factors, and antithrombotic treatment.

Systemic Emboli

In patients with a prosthetic valve, thromboembolic events are presumed to be related to the valve unless proven otherwise. The presence of a thrombus on the prosthesis may not be confirmed by echocardiography because the thrombus is no longer present, is too small to be detected, or is occluded by the shadowing caused by the valve components. The first step in the management of a patient with a prosthetic valve and a systemic embolic event is to carefully assess the adequacy of anticoagulation control. If it is inadequate, therapy is adjusted or reinstated to achieve and maintain a

therapeutic effect. If anticoagulation has been adequate, warfarin therapy should be increased to achieve a higher INR target, and notwithstanding bleeding risk assessment and the results of the investigation, aspirin may also be added or increased.⁶ Moreover, in patients with recent cerebral embolism who are at high risk for hemorrhagic transformation of the cerebral infarct (infarct size $>35\%$ of the cerebral hemisphere and/or uncontrolled hypertension), it is preferable to withhold oral anticoagulation for at least 5 days and use intravenous heparin in the meantime.⁹

Prosthesis Thrombosis

Obstruction of prosthetic valves may be caused by thrombus formation (Figure 6A), pannus ingrowth (Figure 6B), or their combination. Pannus ingrowth alone may be encountered in both bioprosthesis and mechanical valves. It may present as a slowly progressive obstruction caused by a subvalvular annulus, in which case it may be difficult to visualize and thus distinguish from progressive structural valve deterioration (SVD). Valve thrombosis is most often encountered in patients with mechanical valves and inadequate antithrombotic therapy. Thrombosis also may be seen in bioprosthetic valves where it most often occurs in the early postoperative period. Pannus and thrombosis may be present alone or in combination and cause acute or subacute valve obstruction. The incidence of obstructive valve thrombosis varies between 0.3% and 1.3% per patient-year in patients with mechanical valves.^{50,63}

Diagnosis

Valve thrombosis should be suspected in any patient with any type of prosthetic valve who presents with a recent increase in dyspnea or fatigue because valve thrombosis can develop gradually and insidiously over several days or weeks.⁹ Suspicion should be higher if there has been a period of interrupted or subtherapeutic anticoagulation in the recent past. In such cases, echocardiography should be done promptly and should include TEE, particularly if the prosthesis is in the mitral position.

Treatment

In nonobstructive left-sided prosthetic valve thrombosis confirmed by TTE or TEE, treatment consists of a short course of intravenous heparin with close echocardiographic follow-up plus adjustment of warfarin therapy and addition of aspirin (100 mg) (Figure 7).⁶³ However, if the medical treatment is unsuccessful, surgery should be considered in patients with large (>5 to 10 mm as determined by TEE) or mobile thrombi; thrombolysis with urokinase, streptokinase, or recombinant tissue plasminogen activator is recommended in other patients.^{6,7,63}

Urgent or emergent surgery is the treatment of choice in critically ill patients with obstructive valve thrombosis (Figure 7). In a recent series, operative mortality was 4% to 5% for patients with New York Heart Association class III or lower, whereas it reached 15% to 20% in patients with class IV.⁶³ The intervention may involve simple thrombectomy or valve replacement. Rescue thrombolysis should be considered in patients unlikely to survive surgery or when surgical treatment is unavailable and the patient cannot be trans-

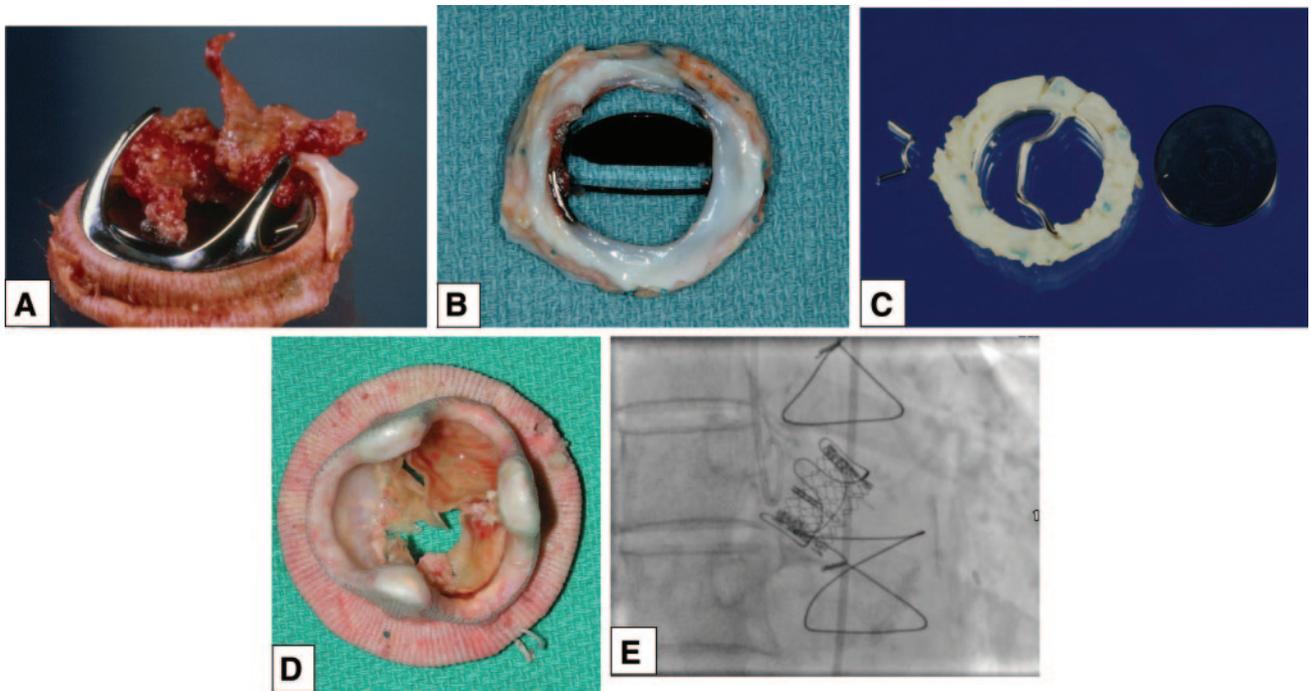


Figure 6. Prosthetic valves explanted for severe dysfunction. A, Obstructive thrombosis of a Lillehei-Kaster prosthesis. B, Pannus ingrowth interacting with leaflet opening in a St Jude Medical bileaflet valve. C, Rupture of the outlet strut and leaflet escape in a Björk-Shiley prosthesis. D, Leaflet calcific degeneration and tear in a porcine bioprosthesis. E, One of the first in-human valve-in-valve cases. A Sapien-Edwards percutaneous valve is implanted within a failed aortic Carpentier-Edwards Perimount bioprosthesis (6-month follow-up). Courtesy of Drs Jacques Métras (A, C) and Christian Couture (B), Laval Hospital, Québec, Canada; Gosta Petterson, Cleveland Clinic, Cleveland, Ohio (D); and John Webb, St Paul's Hospital, Vancouver, BC, Canada (E).

ferred.^{6,7,63} Effective anticoagulation treatment is paramount to the prevention of recurrent prosthetic valve thrombosis (Table 4).

Anticoagulant-Related Hemorrhage

In patients on long-term anticoagulation, the annual risk of a hemorrhagic event is $\approx 1\%$ per patient-year.^{50,64} Randomized comparative studies of bioprosthetic versus mechanical prostheses reported that thromboembolism rates are similar with the 2 types of valves but bleeding is more common with a mechanical valve.^{64,65} In patients with mechanical valves, the bleeding events are most often due to excessive anticoagulation, which can be managed by withholding warfarin and monitoring the level of anticoagulation with serial INR determinations.⁶

Structural Valve Deterioration

Incidence of SVD

Mechanical prostheses have an excellent durability, and SVD is extremely rare with contemporary valves, although mechanical failure (eg, strut fracture, leaflet escape, occluder dysfunction caused by lipid adsorption) has occurred with some models in the past (Figure 6C).

The rate of SVD in bioprosthetic valves (Figure 6D) increases over time, particularly after the initial 7 to 8 years after implantation. With conventional stented bioprostheses, the freedom from structural valve failure is 70% to 90% at 10 years and 50% to 80% at 15 years.^{6,43,50,62,66}

Predictors of SVD

Risk factors previously found to be associated with bioprosthetic SVD include younger age, mitral valve position, renal

insufficiency, and hyperparathyroidism.^{43,62,66} Hypertension, LV hypertrophy, poor LV function, and prosthesis size also have been reported as predictors of SVD in bioprostheses implanted in the aortic position.⁶⁶

Host-Related Factors

Bioprosthetic SVD is strongly influenced by the age of the patient at the time of implantation.^{43,62} The rate of failure of bioprostheses is $<10\%$ at 10 years in elderly patients (>70 years of age) but is $\approx 20\%$ to 30% in patients <40 years of age.^{43,62} Several studies also suggest that bioprosthetic structural failure is more frequent in the mitral than in the aortic position.^{43,66} This difference is likely related to the higher mechanical stress imposed on the valve leaflets of mitral bioprostheses during systole. Likewise, SVD of aortic bioprostheses may be accelerated by systemic hypertension, possibly as a result of a chronically increased diastolic closure stress.

Valve-Related Factors

Several studies tend to show that newer-generation bioprostheses are more durable than older ones.^{43,62,66} Some reports also suggest that pericardial valves might be better than porcine valves in this regard,⁶⁷ but other recent studies show no appreciable difference between these 2 types of prosthesis.⁶⁸

Pathogenesis of SVD

Degenerative Process

Bioprosthetic valve tissues are cross-linked in glutaraldehyde to reduce its antigenicity and to ensure chemical stabilization;

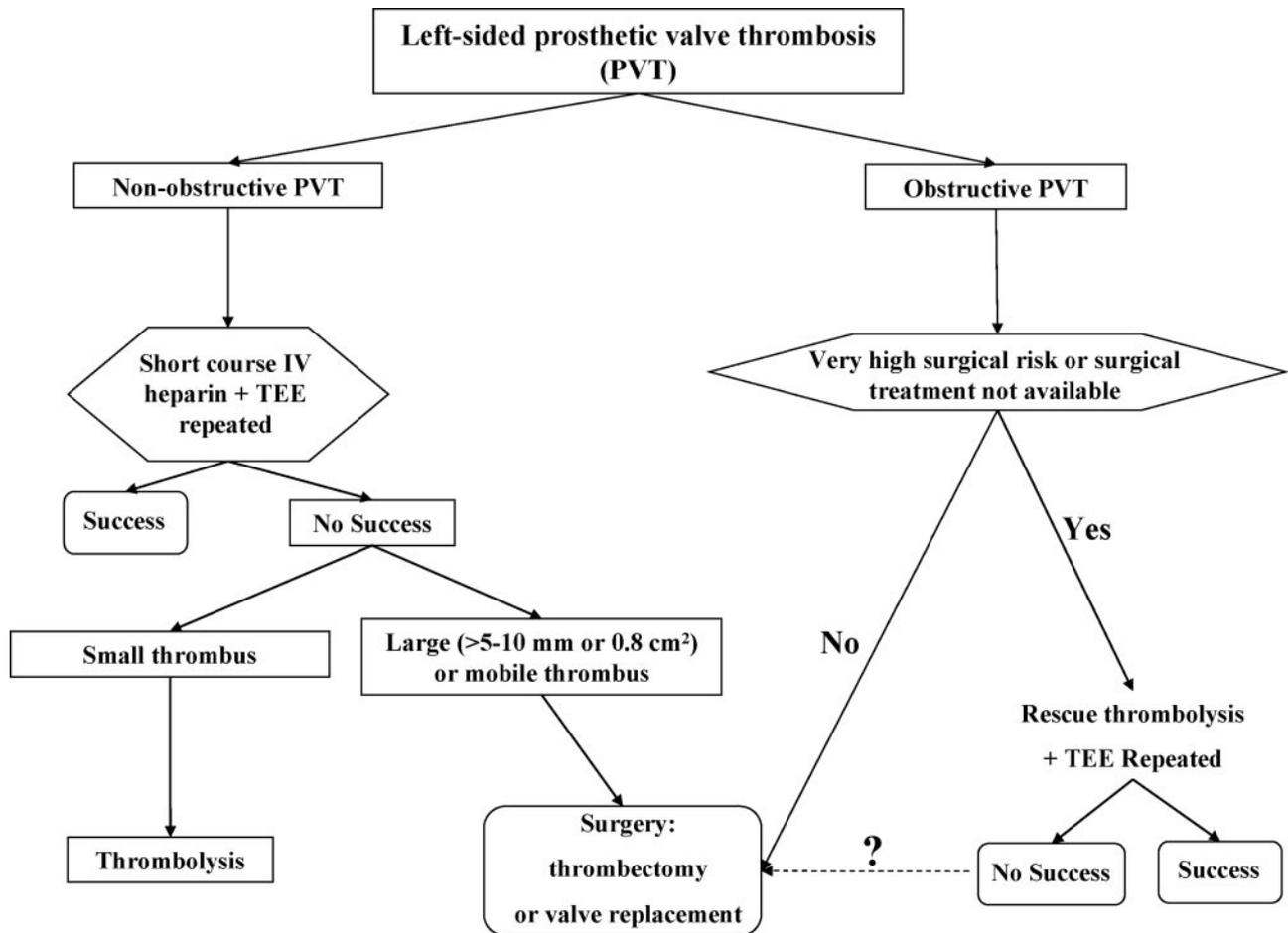


Figure 7. Algorithm for the management of patients with left-sided prosthetic valve thrombosis.

however, this chemical treatment may predispose to bioprosthetic tissue degeneration (Figure 8).⁶² Indeed, tissue fixation with glutaraldehyde induces a calcium influx as a result of membrane damage, which provides, along with the residual phospholipids of the membranes, an environment prone to calcium crystal nucleation. Host factors and mechanical stress then contribute to calcium crystal growth. Such findings have prompted manufacturers to try different anticalcifying treatments on bioprosthetic tissue in the hope of avoiding or slowing SVD. Opposing previous beliefs, recent studies^{69–74} suggest that SVD may not be a purely passive degenerative process but may also involve active mechanisms such as immune rejection and atherosclerosis (Figure 8).

Immune Process

Recent studies suggest that bioprosthetic valves are not in fact completely “immunologically inert” (Figure 8).⁷³ Hence, residual animal antigens could elicit humoral and cellular immune responses, leading to tissue mineralization and/or disruption. A more robust immune system might also explain the more rapid SVD usually observed in younger patients.

Atherosclerotic Process

Recent studies also demonstrate an association between bioprosthetic SVD and several atherosclerotic risk factors, including hypercholesterolemia, diabetes, metabolic syndrome, and smoking.^{66,70,72} Moreover, 1 retrospective study

reported that statin therapy is associated with slower progression of SVD.⁷¹ These recent findings support the hypothesis that similar to the native aortic valve, the SVD of bioprostheses may be related, at least in part, to an atherosclerotic process (Figure 8). The infiltration of low-density lipoproteins within the bioprosthetic tissue and their oxidation may trigger an inflammatory process and the formation of foam cells.⁷⁴ In turn, the inflammatory cytokines and oxidized low-density lipoproteins may induce an osteoblastic differentiation of stem/progenitor cells that have colonized the bioprosthetic tissue.⁷⁵

Future Perspectives for the Prevention of SVD

This new knowledge raises the possibility that, beyond the pretreatment of the cusp tissue by anticalcifying agents before bioprosthesis implantation, treatment of the patient after implantation could help to avoid or delay SVD and thereby enhance valve durability. In particular, the antiatherogenic and antiinflammatory effects of statins might contribute to slowing of the progression of SVD.^{71,75} In addition, lifestyle changes to counter the effects of the metabolic syndrome could have beneficial effects.⁷² Evidently, randomized trials are needed to confirm these hypotheses.

Treatment of SVD

SVD is the most frequent cause of reoperative valve replacement in patients with a bioprosthesis. Whenever possible, the

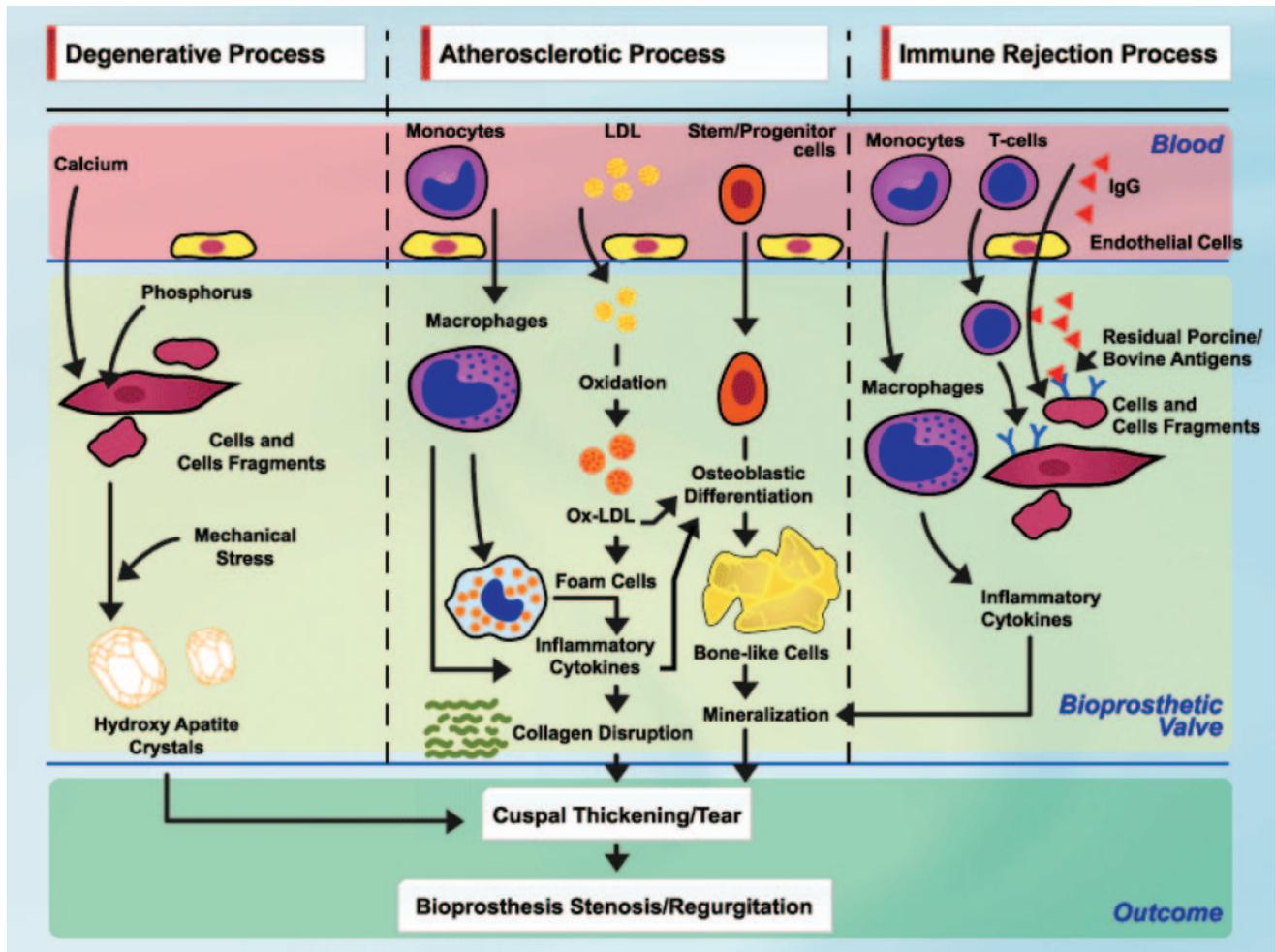


Figure 8. Hypothetical model for the structural deterioration of bioprosthetic valves. OxLDL indicates oxidized low-density lipoprotein.

reoperative procedure should be performed early in the disease process before LV function and symptomatic status deteriorate significantly.⁴³

Future Perspective

Percutaneous implantation of a new bioprosthesis within the failed bioprosthesis implantation (“valve in valve”) may provide a good alternative to surgical replacement of the prosthesis, particularly in high-risk patients (Figure 6E).⁷⁶

Infective Endocarditis

The incidence of prosthetic valve endocarditis is $\approx 0.5\%$ per patient-year, even with appropriate antibiotic prophylaxis. Prosthetic valve endocarditis is an extremely serious condition with high mortality rates (30% to 50%).^{9,50} The diagnosis relies predominantly on the combination of positive blood cultures and echocardiographic evidence of prosthetic infection, including vegetations, paraprosthesis abscesses, or a new paravalvular regurgitation.⁷⁷ TEE is essential because of its greater sensitivity in detecting these abnormalities.⁵⁵ Despite prompt and appropriate antibiotic treatment, many patients with prosthetic valve endocarditis will eventually require surgery. Medical treatment alone is more likely to succeed in late prosthetic valve endocarditis (occurring >6 months after surgery) and in nonstaphylococcal infections. Surgery should

be considered in the following situations: failure of medical treatment; hemodynamically significant prosthesis regurgitation, especially if associated with deterioration of LV function; large vegetations; and development of intracardiac fistulas.^{6,9,77}

Paravalvular Regurgitation

Paravalvular regurgitation typically is due to infection, suture dehiscence, or fibrosis and calcification of the native annulus, leading to inadequate contact between the sewing ring and annulus. Small paravalvular regurgitant jets are frequently (10% to 25% of cases) seen on intraoperative TEE before cardiopulmonary bypass weaning^{78,79} and may significantly decrease or resolve after the injection of protamine or in the days, weeks, or months after operation as the healing process evolves. Moderate or severe paravalvular regurgitation is rare (1% to 2%) and requires returning to cardiopulmonary bypass for immediate correction. Dehiscence of the prosthesis in the late postoperative period may be related to operative technical factors but is most often caused by endocarditis, in which case emergency surgical treatment is generally required.

Long-term prognosis is generally benign in patients with mild paravalvular regurgitation identified by perioperative echocardiography, with progression of regurgitation requiring

reoperation in <1% of patients at follow-up at >1 to 2 years.⁷⁸ Hence, closer follow-up appears justified in these patients, with surgical intervention warranted only for those who develop symptoms, hemolysis, and/or progressive LV dysfunction.⁸⁰ The paravalvular leaks can be repaired without valve replacement in ≈50% of cases. In patients with severe paravalvular mitral regurgitation refractory to aggressive medical therapy who are not candidates for surgical intervention, percutaneous implantation of an Amplatzer septal occluder device offers an alternative therapeutic option.⁸¹

Hemolysis

Blood tests for hemolysis (lactate dehydrogenase) should be part of routine follow-up. A large proportion (50% to 95%) of patients with mechanical valves have some degree of intravascular hemolysis.⁵⁰ However, anemia caused by hemolysis is rare unless prosthetic regurgitation has occurred. Patients with mild to moderate anemia can generally be treated conservatively with iron and folate, β -blockers, and erythropoietin.⁷ However, repeat valve surgery or surgical repair of a paravalvular leak may be needed when prosthetic valve hemolysis is associated with severe refractory anemia.

Conclusions

Many prosthesis-related complications can be prevented or their impact minimized by individualized selection of the optimal prosthesis at the time of valve replacement and by careful medical management and periodic monitoring of valve function after operation. Prompt recognition of valve dysfunction allows early treatment, often with repeat surgical intervention. Several recent developments, including the rapidly evolving field of percutaneous valve implantation, lifestyle and/or pharmacological interventions for the prevention of bioprosthetic valve degeneration, and patient self-management of oral anticoagulation, may change the face of the current practice for the surgical management of valve disease in the near future.

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