Prosthetic Valves: An Update

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"Patients who have undergone valve replacement are not cured but still have serious heart disease. They have exchanged native valve disease for prosthetic valve disease and must be followed with the same care as patients with native valve disease." [1]

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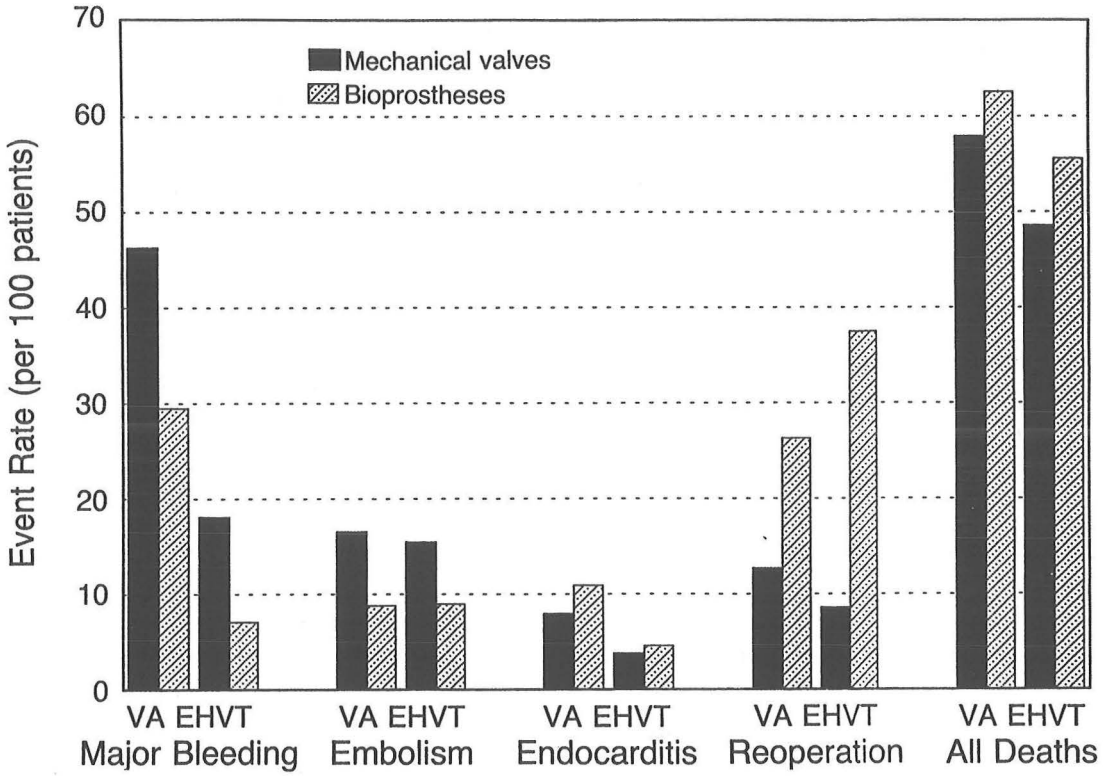
The first prosthetic valve surgery was performed by Hufnagel in 1952 [2] and the first successful valve replacements were performed in 1960. [3] [4] [5] Substantial improvements have been made in valve design and technology over the last several decades and currently there is a broad variety of prostheses available for the cardiac surgeon to implant. For the primary care physician who is responsible for the long-term care of the patient, it is important have a basic understanding of the types of prostheses that they may encounter, an understanding of the anticoagulation requirements of the various prostheses, and a knowledge of the various complications and management issues that may arise in these patients. The purpose of this review is to provide the primary care provider with the basic information required to optimally manage patients with prosthetic valves.

Mechanical versus Biologic prostheses:

Heart valve prostheses may be mechanical (with a rigid, man-made occluder) or biologic in origin (derived from either animal or human tissue). In general, the major differences between mechanical and biologic valves are thrombogenicity and durability. Mechanical prostheses are highly thrombogenic and require chronic anticoagulation to minimize the risk of valve thrombosis and thromboembolic complications. [6] [7] However, durability of mechanical prostheses is excellent with structural failure occurring uncommonly. In contrast, biologic prostheses are less thrombogenic and usually do not require long-term anticoagulation but the life-span of biologic prostheses is limited due to structural deterioration. These major differences between mechanical and biologic prostheses were illustrated by two prospective randomized trials - the Edinburgh Heart Valve Trial [8] and the VA Cooperative Study on Valvular Heart Disease. [9] Both were prospective trials which randomized patients to receive either a tilting disk mechanical prosthesis (Bjork-Shiley valve) or a porcine bioprosthesis. Patients were followed for an average of 12 years in the Edinburgh trial and for 11 years in the VA study. Using life-table analyses, 12-year event rates were calculated for the VA trial and the 12-year event rates for valve complications were compared between the VA trial and the Edinburgh trial (figure 1). In both trials, there was no difference in the incidence of embolic events or endocarditis. As expected, bleeding complications were significantly more common in patients with mechanical valves and reoperation for structural valve deterioration was much more common in patients with biologic valves. Although neither trial was able to demonstrate a clear difference in long-term survival between recipients of a mechanical versus a porcine bioprosthesis, the Edinburgh trial did demonstrate improved survival with a mechanical prosthesis in the subgroup of patients receiving a mitral prosthesis while the VA trial demonstrated a small survival benefit among the subgroup of patients receiving an aortic prosthesis.

Figure 1. Event Rates at 12 years in the Veterans Affairs Cooperative Study on Valvular Heart Disease (VA) and the Edinburgh Heart Valve Trial (EHVT).



A review of the various types of prosthetic valves:

The earliest prostheses to be designed for human implantation were the ball and cage valves. The most popular and durable of these valves were the Starr Edwards valves which have undergone multiple modifications over the years but are still in use today. Over 200,000 of these valves have been implanted. With the current version, the ball is made of a silicone, rubber polymer impregnated with barium sulfate. In an earlier version of the valve, the occluder ball was made of silastic. Unfortunately, this material was prone to lipid infiltration which would cause the ball to swell and crack (a complication was known as "ball variance"). Thrombus could form on the damaged surface of the ball and embolization of either thrombus or a piece of the ball could occur. Ball variance is not a problem with the current version of the Starr Edwards valve. With over 40 years of experience, no cases of cage fracture have been reported. Because of its design, the valve is inherently obstructive, especially in smaller sizes. Transvalvular gradients are higher with ball and cage valves than with tilting disk valves, although the hemodynamic performance is usually satisfactory. [10 11]

Disk valves were the next valve design to be developed. Initially, a central disk occluder which occillated up and down within a cage (like a manhole cover) was tried but these

valves were found to be very obstructive and thrombogenic and were soon abandoned. Tilting disk valves use a circular disk held in position by struts. The disk pivots on or within the struts and opens and closes much like a toilet seat. Bjork-Shiley introduced the first successful version of a tilting disk valve in 1969. [12] A variety of modifications to the Bjork-Shiley prosthesis have been made and approximately 360,000 valves have been implanted. A specific model, the convexo-concave valve, was introduced in 1976 and was subsequently found in the early 1980's to be prone to fracture of one of the valve struts which would result in embolization of the disk. The risk of this catastrophic complication is quite low (ranging from 0.02% to 0.29% per year), depending on prosthesis size. All Bjork-Shiley convexo-concave valves were withdrawn from the market in 1986 and extensive guidelines were developed for prophylactic valve replacement. [13] In general, larger convexo-concave prostheses (31 or 33mm) and those in the mitral position appear to be more prone to strut fracture. In addition, the company has identified certain specifics regarding valve manufacture (welding date, welder identity, etc.) that can be used to further assess risk. Using valve size, valve position, patient age and the specifics of the valve manufacturing, a risk calculation is made in order to determine whether or not prophylactic valve replacement is recommended. [14] Chest x-ray and fluoroscopy play an important role in following patients with this type of prosthesis as partial strut separation may be identified, indicating a patient at high risk for valve failure. [15] Other tilting disk valves remain on the market, including the Medtronic Hall valve, the Omniscience valve, and the Monostrut valve. No structural valve failures have been described for these prostheses.

The bileaflet prosthesis was first introduced by St. Jude Medical in 1977 and is an extremely popular prosthesis with over >600,000 valves implanted. The Duromedics and Carbomedics valves are newer versions of the bileaflet prosthesis with minor modifications. In general, bileaflet mechanical prostheses are less obstructive than other types of mechanical prostheses and have a somewhat lower thrombogenic potential. Prior to this year, structural failures of the St. Jude prosthesis had not been reported. [16] [17] [18] [19] In 1997, St. Jude Medical released a new valve series (the Master mechanical heart valve with silzone) which incorporated elemental silver into the sewing cuff of the prosthesis. It was hypothesized that the silzone coating would decrease the incidence of prosthetic valve endocarditis and a randomized trial (the AVERT trial -Artificial Valve Endocarditis Reduction Trial) was undertaken to compare silzone-coated versus standard St. Jude valves. Based on preliminary results from this trial, the Data and Safety Monitoring Board recommended in January of this year that the trial be stopped due to an increased incidence of paravalvular regurgitation in patients who had received a Silzone-coated product. St. Jude Medical initiated a voluntary recall of Silzone-coated products at that time. [20] In the AVERT trial, a total of 398 patients had received a Silzone-coated prosthesis and paravalular leaks were seen in 11 patients (2.76%) with 8 of those patients (2.01%) requiring valve explant and replacement for the leak. In contrast, among 394 patients receiving a conventional St. Jude prosthesis, 4 patients (1.02%) were found to have a paravalvular leak and only 1 patient (0.25% of the total group) required valve explant. Currently, there is insufficient data to identify a specific subset of patients who are at risk for developing paravalvular leaks. It is recommended that patients who have

received a Silzone-coated prosthesis have standard follow-up with special attention to careful auscultation and identification of cardiac symptoms. Routine echocardiograms are not recommended but should be obtained if the physical examination is abnormal or if the patient has cardiac symptoms. [20]

Table 1. Common mechanical prosthetic valves in the United States	
Ball and cage prostheses	Starr-Edwards
Tilting disk valves	Bjork-Shiley (no longer available)
	Medtronic Hall
	Omniscience
Bileaflet valves	St. Jude
	CarboMedics

The term bioprosthesis refers to animal or human tissue used for valve replacement. Porcine heterografts have been used since the late 1960's. [21] Traditionally, porcine aortic valves are harvested and preserved in glutaraldehyde, then mounted on stents to support the leaflets and attached to a sewing ring. The glutaraldehyde preservation sterilizes the tissue, destroys antigenicity, and stabilizes the collagen cross-links, providing for a more durable valve. However, the glutaraldehyde preservation also generates free aldehyde groups on the leaflet surfaces which bind circulating calcium, particularly at points of maximal stress. This process is known as dystrophic calcification and is responsible for the limited lifespan of these prostheses. [22 23] On average, 30% of porcine valves will fail within 10-15 years of implant. [24 25] In the Edinburgh Heart Valve Trial, the reoperation rate for structural failure of bioprostheses was 37.1% at 12 years and the reoperation rate was substantially higher for valves in the mitral position (43.1%) than for the aortic position (22.6%). [8] In the VA Cooperative Trial, the structural failure rate for porcine valves in the mitral position was 47% at 11 years and was 15% for valves in the aortic position. [9] Structural failure appears to occur much more rapidly in younger patients, with a very high failure rate in patients under the age of 35.[26] Interestingly, when these valves are used in older patients (greater than age 60-70), the rate of structural deterioration is much slower with only 10% valve failure rate at 10 to 15 years. [27 28] Despite their limited lifespan, the valves remain quite popular. The tremendous advantage of these prostheses (as compared with mechanical prostheses) is that they are much less thrombogenic and, in general, anticoagulation is not required.

The stent material in traditional porcine heterografts (made of plastic or metal) provides some degree of obstruction to blood flow, making these valves somewhat obstructive. More recently, stentless porcine valves have been designed and approved for use. These valves consist of the complete porcine aortic root which is implanted either in place of the patient's own aortic root or placed inside the patient's native aorta. These implantation techniques are more difficult and time-consuming than for traditional porcine heterografts. However, these stentless valves appear to have excellent hemodynamics. Data on durability is limited. [29 30]

Bioprosthetic valves may be fashioned from pericardial tissue. The Ionescu-Shiley valve was made of bovine pericardium but had a very high failure rate with some valves lasting as little as six years. [31] This valve was taken off of the market and many surgeons have been reluctant to consider pericardial valves. However, the failure of the Ionescu-Shiley valve appears to have been related to the mechanical design of the valve rather than the unsuitability of bovine pericardium. The Carpentier-Edwards bovine pericardial valve is now available with a different structural design and appears to have excellent hemodynamics, especially in small prosthesis sizes. [32] It is becoming a popular valve option for patients with small aortic roots. Freedom from structural valve deterioration at 10 years after aortic valve replacement ranges from 87-91% [33] [34] while freedom from structural deterioration in the mitral position is lower (48%). [35]

Human valves can also be used for valve replacement. Homograft valves are harvested from autopsy or donor hearts and can be implanted in either the aortic or pulmonary position. Harvest and preservation techniques vary but, in the United States, valves are cryopreserved and stored in liquid nitrogen with low-dose antibiotics. The valve is thawed and prepared in the operating room just prior to implant. Fresh, unpreserved homografts (so-called homovital grafts) have also been used (stored in tissue culture medium and used within three days).[36] In theory, fibroblasts in the cryopreserved valve leaflets can remain viable, allowing for potential growth of the valve. However, the persistence of viable cells within the homograft causes expression of major histocompatibility antigens and a humoral immune response can be demonstrated in some patients with homografts. The long-term consequences of this immune response are unknown. [37] These valves are more technically difficult to implant compared to mechanical prostheses and stented porcine valves. Also, the valve size must be determined prior to surgery (usually by echocardiography) and, because of limited supply, an appropriate sized valve may not be available when needed. Homograft longevity has been somewhat disappointing as these valves also develop structural deterioration over time. In the largest and longest series (from Prince Charles Hospital in Brisbane, Australia), actuarial survival rates were 77% at 10 years and 45% at 20 years. Freedom from valve dysfunction requiring reoperation was 69% at 15 years. [38]

The Ross procedure is another option for using a human valve for aortic valve replacement. Ross first described autotransplantation of a patient's own pulmonary valve to the aortic position with subsequent replacement of the pulmonic valve with a homograft in 1967. [39] This so-called Ross procedure has become increasing popular although the operation is technically much more demanding (requiring two valve replacements) than a standard aortic valve replacement. [40] In Ross's original series of patients, survival was 85% at 10 years and 61% at 20 years after surgery with freedom from autograft replacement 88% at 10 years and 75% at 20 years. Freedom from replacement of the pulmonary valve was 89% at 10 years and 80% at 20 years. [41]

Table 2. Common bioprosthetic valves in the United States	
Porcine heterografts	
Stented	Hancock
	Carpentier-Edwards
Stentless	St. Jude Toronto stentless valve
	Medtronic Hall Free Style stentless
Bovine Pericardial valves	Ionescu-Shiley (no longer available)
	Carpentier-Edwards pericardial valves
Human tissue	cryopreserved homografts (aortic/pulmonary)
	allografts (patient's own valve)

While the number of available prosthetic valves continues to expand, surgical techniques for valve repair have also evolved. In general, valve repair is preferrable to valve replacement when feasible as there is a lower operative mortality, lower risk of thromboembolism, better preservation of left ventricular geometry and function, and a potentially lower risk of endocarditis. [42]

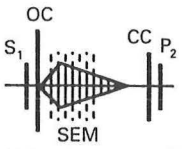
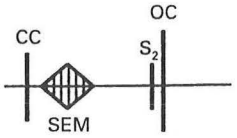
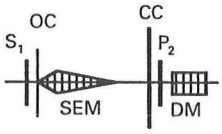
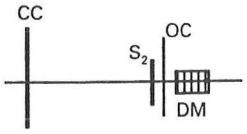
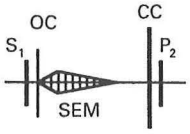
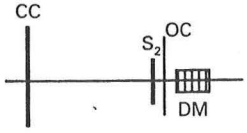
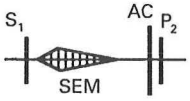
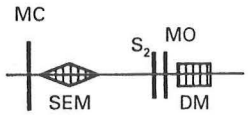
In summary, for patients requiring aortic valve surgery there are multiple options including mechanical valves (either tilting disk or bileaflet prostheses), traditional porcine heterografts or the newer stentless porcine valves, bovine pericardial valves, aortic homografts, or the Ross procedure. In some cases, aortic valve repair may be an option. In the mitral position, valve repair should always be considered.[42] For those patients requiring a mitral prosthesis, options include a mechanical valve (tilting disk or bileaflet) or a stented porcine heterograft. Current pericardial valves offer no advantage over traditional porcine valves in the mitral position. Mitral homografts and stentless pericardial quadricuspid valves are currently under development and may expand the options for mitral valve replacement in the future.

What type of prosthesis does my patient have?

Identification of the type of prosthesis that a patient has is critical for the long-term management of the patient. Patients are given an identification card at the time of the valve surgery which specifies the prosthesis type, size, model number, and date of implant. When available, the operative report can also provide this information. When asked, patients usually know whether they have a "pig valve" or a "metal valve" and may be able to provide further specifics regarding the valve type. On physical examination, biologic valves are often indistinguishable from native valves whereas mechanical prostheses have audible closing (and sometimes opening) sounds as long as the valve is functioning normally. As all prosthetic valves are inherently stenotic, flow across the valve is frequently associated with a flow murmur, especially in the aortic position. While some mechanical prostheses allow for trivial amounts of regurgitation through the valve, an audible murmur of mitral or aortic regurgitation is always abnormal. Normal and abnormal auscultatory findings for common valve types have been reviewed and are demonstrated in figure 2. [43 44] A chest x-ray may be useful in

determining the location and possibly the type of prosthesis [45] [46] [47] although many prostheses are radiolucent (including older St. Jude bileaflet valves, stentless procine valves, and homografts). By echocardiography, the location of the prosthesis can be determined and biologic versus mechanical valves can be easily differentiated. [48]

Figure 2. Normal and abnormal auscultatory findings for common prosthetic valves.

Type of Valve	Aortic Prosthesis		Mitral Prosthesis	
	Normal Findings	Abnormal Findings	Normal Findings	Abnormal Findings
Caged-Ball (Starr–Edwards)		Aortic diastolic murmur Decreased intensity of opening or closing click		Low-frequency apical diastolic murmur High-frequency holosystolic murmur
Single-Tilting-Disk (Bjork–Shiley or Medtronic–Hall)		Decreased intensity of closing click		High-frequency holosystolic murmur Decreased intensity of closing click
Bileaflet-Tilting-Disk (St. Jude Medical)		Aortic diastolic murmur Decreased intensity of closing click		High-frequency holosystolic murmur Decreased intensity of closing click
Heterograft Bioprosthesis (Hancock or Carpentier–Edwards)		Aortic diastolic murmur		High-frequency holosystolic murmur

Management of anticoagulation for prosthetic valves.

Several organizations have issued guidelines for the management of anticoagulation for prosthetic valves, including The American College of Chest Physicians and the American College of Cardiology and the American Heart Association Joint Committee. The Fifth ACCP Consensus Conference on Antithrombotic Therapy [49] and the ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease [1] were both published in 1998 and, while there is substantial agreement between these standards, there is some variation in the recommendations. Both recommendations are listed below in tabular form (tables 3 and 4).

Table 3. Recommendations for antithrombotic therapy with prosthetic valves – 5th ACCP Consensus Conference Guidelines [49]

Mechanical Prosthetic Heart Valves

1. For bileaflet mechanical valves in the aortic position without associated risk factors for thromboembolism, the goal is an INR of 2.5 (range 2.0 to 3.0).
2. For all other patients with mechanical valves, the goal is an INR of 3.0 (range of 2.5 to 3.5). Add aspirin (80-100mg/day) for ball and cage valves.
3. Any patient with additional risk factors for thromboembolism (atrial fibrillation, LA thrombus at surgery, h/o systemic embolic event, LV dysfunction), use aspirin 81mg/day in addition to warfarin.

Bioprosthetic Heart Valves

1. Give anticoagulation for 3 months after valve implant, goal is INR of 2.5 (range 2.0 to 3.0), then aspirin 162mg/day if no risk factors.
2. For patients with risk factors (atrial fibrillation, LA thrombus at surgery, h/o systemic embolic event, LV dysfunction) continue warfarin at same level.

Table 4. Recommendations for antithrombotic therapy for prosthetic valves – ACC/AHA guidelines [1]

1. First 3 months after valve replacement	Warfarin, INR 2.5 to 3.5
2. ≥ 3 months after valve replacement	
Mechanical valve	
AVR and no risk factor	
Bileaflet or Medtronic Hall	Warfarin, INR 2.0 to 3.0
Other disk valves or ball-cage	Warfarin, INR 2.5 to 3.5
AVR and risk factor*	Warfarin, INR 2.5 to 3.5
MVR	Warfarin, INR 2.5 to 3.5
Bioprosthesis	
AVR and no risk factor*	ASA, 80-100mg/day
AVR and risk factor*	Warfarin, INR 2.0 to 3.0
MVR and no risk factor*	ASA, 80-100mg/day
MVR and risk factor	Warfarin, INR 2.5 to 3.5

*Risk factors: atrial fibrillation, h/o systemic embolism,

While lower thrombogenicity is one of the major advantages of bioprostheses, there is still a risk of thromboembolism which appears to be highest in the first 3 months after valve implant. [50] [51] For this reason, it is recommended that all patients with a bioprosthetic valve receive anticoagulation for the first 3 months after implant. This appears to be most important for valves in the mitral position and may not be required for valves implanted in the aortic position. [52] After 3 months, the tissue valve is considered to be fully endothelialized and anticoagulation can usually be discontinued. Therapy with aspirin is recommended. Some patients with bioprostheses remain at risk for embolic events and should remain on chronic anticoagulation. These include patients

with atrial fibrillation, a history of a systemic embolic event, a known hypercoagulable state, the presence of LA thrombus at the time of surgery, and those with severe left ventricular dysfunction.

For patients with mechanical prostheses, life-long anticoagulation is required. The intensity of anticoagulation depends on the prosthesis type and location, as well as the presence of other risk factors. [53] The level of anticoagulation should be adequate to effectively prevent thromboembolism without causing excessive bleeding. [54] In a large series of patients with mechanical valves, Cannegieter et al demonstrated that the optimal intensity of anticoagulation for patients with mechanical prosthetic valves was an INR between 2.5 and 4.9. [53] Increasing age, the presence of multiple prostheses, and the presence of a ball and cage valve were all associated with a higher incidence of adverse events. Recommendations vary but, in general, the target INR for mechanical prostheses should be between 2.5 and 3.5. For bileaflet valves and Medtronic Hall valves in the aortic position, an INR of 2.0 to 3.0 is acceptable [55 56 57 58 59] but a higher INR (2.5 to 3.5) is required for other types of tilting disk valves. Even higher levels of anticoagulation may be required for ball and cage prostheses. [53]

Despite appropriate anticoagulation, patients with prosthetic valves may experience thromboembolic events (event rate of approximately 1-2% per year for mechanical prostheses, <1% per year for bioprotheses). [8 9 1] The dosage and intensity of anticoagulation should be increased (see table 5). The addition of aspirin therapy to warfarin therapy has been shown to reduce thromboembolic events as well as reducing mortality. [60 56 61 62] In most studies, there was also an increased risk of bleeding. When low-dose aspirin (100mg/day) was used, the risk of major gastrointestinal bleeding was reduced. [60] Dipyridamole may be effective as well but has not been shown to be superior to aspirin.

Table 5. Management of thromboembolic events during antithrombotic therapy–ACC/AHA guidelines [1]

1. For patients on Warfarin, INR 2.0 to 3.0	Increase INR to 2.5 to 3.5
2. For patients on Warfarin, INR 2.5 to 3.5	May increase INR to 3.5 to 4.5
3. For patients not on aspirin	Add ASA 80-100mg/day
4. For patients on Warfarin + ASA (80-100mg/day)	May increase ASA to 325mg/day
5. For patients on ASA alone	Increase ASA to 325mg/day +/or add Warfarin, INR 2.0 to 3.0

Interruption of anticoagulation.

Management of the anticoagulated patient undergoing dental treatment has been somewhat controversial in the past. A recent review of the available literature was performed by Wahl in 1998. [63] He identified reports of 2014 dental surgeries in 774 patients on chronic anticoagulation therapy. Surgical procedures included single and

multiple simple extractions, surgical extractions, alveoectomies, and other surgical procedures. Despite the fact that many patients had INR levels above the currently recommended ranges, more than 98% of patients had no serious bleeding problems. Twelve patients (<2%) had post-operative bleeding problems; 5 of these had supratherapeutic INR levels. Wahl also identified reports of 542 dental surgical procedures in 493 patients in whom anticoagulation was interrupted specifically for the dental procedure. Serious embolic complications (including 4 deaths) occurred in 0.9% of patients. Therefore, dental authorities (including the American Dental Association) state that dental surgery can be performed with minimal risk at or above therapeutic levels of anticoagulation. [64] Local measures to improve hemostasis should be used when needed, including application of local pressure, gelatin sponges, topical thrombin, additional sutures, electrocautery and possibly antifibrinolytic mouthwashes. In addition, more extensive surgical procedures can often be divided into several separate, smaller procedures to minimize the bleeding risk. Thus, anticoagulation should not be withheld or the level of intensity decreased for dental surgical procedures.

The management of patients undergoing elective surgical procedures is somewhat more complicated. For most surgical procedures, the risk of bleeding in an anticoagulated patient is substantial and reversal of anticoagulation is necessary to avoid undue risk to the patient. However, interruption of anticoagulation places the patient at increased risk of thromboembolism. Thus, the optimal management of antithrombotic therapy involves balancing the risk of bleeding in the perioperative period with the short-term risk of valve thrombosis and thromboembolism during the period when the level of anticoagulation is subtherapeutic. In situations where the risk of bleeding is miminal (i.e. skin or eye surgery) anticoagulation need not be altered. However, for most surgical procedures, anticoagulation must be stopped. Traditionally, this was accomplished by stopping warfarin and allowing the INR to fall. When the INR became subtherapuetic, the patient was hospitalized and placed on intravenous heparin until shortly before surgery. Surgery was performed in the unanticoagulated patient and heparin was resumed as soon as possible in the postoperative period and continued until the patient was restarted on warfarin and had achieved a therapeutic protime/INR. [65] However, the cost-effectiveness of this approach has been questioned. [66] [67] Kearon and Hirsh performed a risk/benefit analysis of perioperative management of anticoagulation for patients with prosthetic valves and compared an "aggressive strategy" in which IV heparin was given for 2 days preoperatively (while the INR is decreasing) and 2 days postoperatively as compared to a "minimalist strategy" of no heparin (withholding warfarin for 4 days preoperatively and restarting warfarin after surgery, assuming a total of 4 days of subtherapeutic protimes). [68] They predicted that the aggressive strategy would prevent 3 thromboembolic events per 10,000 patients treated while causing 300 episodes of major bleeding per 10,000 patients treated and causing death or significant disability in 12 per 10,000 patients treated. Thus, they recommended that warfarin be withheld for 4 doses prior to surgery to allow the INR to fall to 1.5 or less before surgery. Postoperatively, subcutaneous heparin may be administered to decrease the risk of venous thromboembolism.

The ACCP Consensus Conference makes no specific recommendations regarding the optimal management of anticoagulation in patients with prosthetic valves undergoing

elective surgery, indicating simply that "several approaches can be used..... the choice depends on personal preference and the risk of thrombosis." [65] The ACC/AHA Guidelines are more definitive, recommending that the minimalist strategy (as outlined by Kearon and Hirsh) is acceptable for "most patients." [1] Determining which patients are at highest risk and therefore deserving of the "aggressive strategy" requires "clinical judgement." Risk factors which may identify those patients at highest risk of thromboembolic events (and therefore to be managed "aggressively) include the presence of a ball and cage valve or an older generation tilting disk valve, the presence of multiple prosthetic valves, atrial fibrillation, severe left ventricular dysfunction, history of a prior thromboembolic event, and a known hypercoagulable state.

Maintenance of a therapeutic level of anticoagulation is difficult in some patients and patients with either subtherapeutic or supratherapeutic levels of anticoagulation are commonly encountered. Obviously, the patient who has a subtherapeutic level of anticoagulation is at risk for thromboembolic events and a decision must be made whether or not to adjust the warfarin dosage as an outpatient or to initiate heparin therapy acutely to establish adequate anticoagulation while the warfarin dosage is being adjusted. Patients should be risk stratified to determine whether inpatient or outpatient management is appropriate. In determining the short-term risk of thromboembolism for an individual patient, the type and location of the prosthesis should be considered as well as the presence of other risk factors for thromboembolism (i.e. atrial fibrillation, a history of previous embolic event, severe LV dysfunction, or a hypercoagulable state). In general, patients with a mitral prosthesis are at higher risk than those with an aortic prosthesis and should usually be hospitalized. Patients with multiple prosthetic valves are at very high risk and should be treated aggressively. Patients with a bileaflet aortic prosthesis and no associated risk factors can be treated more conservatively. The reliability of the patient to follow dosage instructions and to comply with follow-up laboratory testing should also be assessed before deciding whether or not to treat conservatively. While low molecular weight heparin is a theoretically attractive option for treating patients with subtherapeutic INR as their warfarin dosage is adjusted, there is no data regarding its use for this indication. The etiology of the change in anticoagulation status should also be addressed. Potential etiologies include medication noncompliance, inadequate patient education, changes in other drug therapy, and dietary changes. In questioning patients about changes in medication, it is also important to ask about over the counter medications, including dietary supplements and vitamins. Consultation with a dietician may prove helpful in improving the patient's understanding of the interaction of diet and warfarin metabolism.

Bleeding complications occur in patients receiving anticoagulation for prosthetic valves and annual bleeding rates reported in various trials range from 0.4% per year to 6.6% per year. [49] Higher intensity anticoagulation (INR greater than 5) is associated with an increased risk of bleeding. [53] However, rapid overcorrection of anticoagulation that results in subtherapeutic INR levels will increase the risk of thromboembolism. Withholding warfarin alone usually results in a drop in the INR of 1.0 to 1.5 points per day. [69] Administration of vitamin K can produce a more rapid decrease in the INR and

oral vitamin K appears to be effective and safe. [70] The following treatment strategy (which follows the ACCP guidelines) has been recommended: [71] For an INR of less than 5.0, warfarin should be withheld for 1-2 days, then restarted at a lower dose (10-20% dose decrease usually recommended). For an INR between 5.0 and 9.0, a small dose of oral vitamin K (2.5mg) can also be administered while withholding warfarin. The INR should be repeated in 24 hours and warfarin therapy resumed when the INR is therapeutic (20-30% reduction in dose of warfarin). For an INR greater than 9.0, oral vitamin K should be given at a dose of 2.5 mg or 5.0mg while withholding warfarin. Repeat vitamin K dosing may be necessary. Warfarin should be restarted (dose decreased by at least 20-30%) when the INR is therapeutic. For patients with major warfarin overdosage (INR > 20) and/or serious bleeding, more rapid reversal of anticoagulant effect is needed. Patients should receive a slow infusion of IV vitamin K (10mg dose), supplemented with fresh frozen plasma or prothrombin concentrate complex as determined by the severity of the situation. Repeat vitamin K injections may be needed every 12 hours to achieve the target INR. The IV route for vitamin K should be used only for high-risk patients because of the potential for serious adverse reactions such as anaphylaxis, hypotension, chest pain, cerebral thrombosis and death. In addition to treatment directed at corrected the excessive anticoagulation, the etiology of the elevated INR should also be determined. Common causes include excessive warfarin dosing, drug-drug interactions (especially antibiotics), altered nutritional states, and worsening liver function.

Prosthetic valve dysfunction – structural failure:

Structural failure of prosthetic valves is a recognized complication that can be predicted based on the type of prosthesis. In general, structural failure of mechanical prostheses is uncommon. Ball variance in association with ball and cage valves and strut fracture with disk embolization with Bjork-Shiley convexo-concave valves are examples of this uncommon situation. Failure of mechanical prostheses is much more likely to be due to valve thrombosis, to be discussed later. Structural failure of bioprosthetic valves is much more common and is the major limitation of these prostheses. Porcine hetergrafts have a fairly predictable failure rate of 30% by 10-15 years due to degeneration of the leaflets. [24 25 8 9] Degeneration of porcine valves occurs much more rapidly in younger patients and also occurs more commonly in valves in the mitral position. As discussed above, the glutaraldehyde fixation of the porcine leaflets leads to the generation of free aldehyde radicals on the leaflet surfaces which bind circulating calcium. Over time, the bioprosthetic leaflets become progressively more calcified and rigid with loss of leaflet mobility. These valves may become progressively stenotic but more often develop regurgitation when a portion of a leaflet tears, resulting in acute regurgitation. Aortic homografts, although prepared differently from porcine valves, also develop dystrophic calcification and leaflet dysfunction which limits their longevity. Most often, patients present with recurrent cardiac symptoms and are found to have a murmur of valvular regurgitation or stenosis. Patients may present more acutely with severe regurgitation. The possibility of prosthetic valve endocarditis should be considered and the diagnosis ruled out in the setting of any patient with a bioprosthesis who develops acute regurgitation. Patients should be stabilized medically prior to considering valve replacement.

Prosthetic valve endocarditis:

Prosthetic valve endocarditis is a dreaded complication of prosthetic valves which occurs in 4-6% of patients. [72] [73] [74] Prosthetic valve endocarditis is divided into early and late forms. Early prosthetic valve endocarditis is defined as an infection identified within 60 days of valve replacement. The most common organisms involved are staph epidermidis and staph aureus as well as gram-negative bacteria, diphtheroids, and fungi. Late prosthetic valve endocarditis is defined as that occurring > 60 days after valve replacement and the organisms responsible are similar to those causing native valve endocarditis with the exception that staph epidermidis remains common. There is no difference in the incidence of prosthetic valve endocarditis in patients with mechanical or traditional porcine bioprostheses. [8] [9] The incidence of prosthetic valve endocarditis does appear to be lower with aortic homografts [38] [75] [76] and this prosthesis is becoming the valve of choice for many cases of aortic valve endocarditis. [77]

Manifestations of prosthetic valve endocarditis include fever, changing murmurs, systemic embolization, and congestive heart failure. [73] [74] When compared with native valve endocarditis, prosthetic valve endocarditis is more likely to be associated with valve ring abscesses, conduction abnormalities, and hemodynamically significant valve dysfunction. [78] In most cases, surgical replacement of the infected prosthesis is required and at times most be performed urgently or emergently. [73] [79] For this reason, some authors recommend that when a diagnosis of prosthetic valve endocarditis is made in an anticoagulated patient, warfarin (and aspirin) be stopped and IV heparin substituted. Surgery is recommended for all cases of early prosthetic valve endocarditis, all patients with prosthetic valve dysfunction, infection with certain organisms (fungal endocarditis, staphylococcal endocarditis that fails to respond to antibiotics, gram negative infections, infection with highly resistant organisms), and patients with evidence of tissue damage (paravalular leaks, abscesses, aneurysms, conduction disturbances). [80] [81] Patients who remain bacteremic after 7-10 days of antibiotics and those with recurrent peripheral emboli should also undergo surgery.

Hemolysis:

Subclinical hemolysis due to mechanical trauma to red blood cells is common with mechanical prostheses, especially the older valves such as ball and cage and first-generation tilting disk valves. [82] Clinically significant hemolysis may develop in patients with either mechanical or bioprosthetic valves and suggests the development of a paravalvular leak which represents partial dehiscence of the suture line. [83] [84] [85] This may be due to infection and prosthetic valve endocarditis must always be considered as a potential etiology of a new paravalvular leak. [86] Patients with hemolysis due to a paravalvular leak can usually be managed with iron and folate supplementation to treat their anemia. On occasion, patients require valve replacement for severe hemolysis. [87]

Prosthetic valve dysfunction – valve thrombosis:

Patients with mechanical prosthetic valves are at risk for developing acute prosthetic valve thrombosis, occurring in between 0.1% and 4% per patient year depending on the type of prosthesis, location, and intensity of anticoagulation.[53] Prompt recognition of the signs and symptoms and an understanding of the mechanism of valve dysfunction is required in order to effectively treat (and potentially save the lives of) these patients. [88] [89] Thrombus formation places the patient at markedly increased risk for thromboembolic events and should be suspected in any patient who presents with a systemic embolic event. Valve thrombosis may also cause valve obstruction or regurgitation. With acute valve obstruction, patients present with acute hemodynamic deterioration (decreased cardiac output, poor peripheral perfusion, pulmonary congestion) and may present with cirulatory collapse. However, some patients may have a more insidious onset of symptoms or may even be asymptomatic. [89] At times, the diagnosis is only made at autopsy. [90] Dyspnea at rest is the most common symptom. Other symptoms and physical findings include fatigue, low cardiac output, chest pain, absent valve clicks, shock or cardiac arrest. Symptomatic patients are usually in New York Heart Association class III or IV at presentation.

The diagnosis of prosthetic valve dysfunction requires a high level of suspicion. A careful history should be taken to assess for new or recurrent cardiac symptoms. Next a careful physical examination should be performed. The normal findings for auscultation of various prosthetic valves has been reviewed (see figure 2). Prosthetic valve obstruction/thrombosis should be suspected if there are decreased, muffled, or absent valve clicks, and/or a new murmur on examination. Frequent repeat examinations may be required as abnormal physical exam findings may be intermittent. When a diagnosis of suspected prosthetic valve obstruction/thrombosis is suspected, echocardiography is often used as the next diagnostic tool and can be very valuable. [48] The echo may demonstrate decreased motion or absence of motion of the valve leaflets, disturbance of flow patterns through the prosthesis, and/or the presence of abnormal regurgitation through the prosthesis. Doppler assessment of flow through the prosthesis may indicate increased flow velocities and gradients in the setting of valve obstruction. However, there are some technical limitations to the assessment of valve gradients be Doppler. Since flow velocities and patterns of regurgitation vary with the size and type of prosthesis, this information should be provided to the echocardiographer in order to improve their ability to accurately make a diagnosis of prosthetic valve dysfunction. Transesophageal echocardiography provides improved visualization of prosthetic valves in the mitral postion and often provides additional information (complementary to transthoracic echo) for valves in the aortic position. [91] [92] Acoustic shadowing from mechanical prostheses is a significant limitation to the accuracy of echocardiography for diagnosing prosthetic valve dysfunction. While echocardiography is an invaluable tool for evaluating patients with prosthetic valves, it is important to acknowledge the limitations of echocardiography in the diagnosis of prosthetic valve dysfunction. In a recent report of 170 patients who underwent surgery for suspected prosthetic valve dysfunction diagnosed by echocardiography, there were 25 diagnostic errors (12%)

although most did not affect patient management. [93] Cinefluoroscopy to observe and document leaflet motion is a simple test that should be considered in any case of mechanical prosthetic valve dysfunction, especially if leaflet motion cannot be fully evaluated by echocardiography. [94 95]

Obstruction of mechanical prosthetic valves is usually caused by the formation of thrombus on the valve. However, in some patients, there is an ingrowth of fibrous tissue known as pannus which can also cause prosthetic valve obstruction as well as providing a nidus for thrombus formation. [89 96] With pannus formation, the clinical presentation is usually more insidious and patients may be asymptomatic.

With valve thrombosis and a small thrombus by echocardiography (<5mm) that does not obstruct the valve, treatment with anticoagulation alone is adequate. However, larger thrombi (>5mm) need more aggressive therapy due to the much higher risk of complications (thromboembolism and valve obstruction). [97] Thrombolytic therapy can be used to treat valve thrombosis but is ineffective in treating valve obstruction due to pannus formation. Overall, thrombolytic therapy for left-sided prosthetic valve thrombosis has an 82% initial success rate, an overall thromboembolism rate of 12%, a stroke rate of 5-10%, a 6% death rate, a 5% rate of major bleeding episodes and an 11% rate of recurrent thrombosis. [98] The operative mortality for surgical valve replacement in the setting of valve thrombosis ranges between 0% and 69%, with the outcome largely dependent on the hemodynamic stability of the patient. [89 99] For patients in functional class I or II, operative mortality is less than the risk of thromboembolism with thrombolytic therapy and thus surgery should be performed on these patients. For patients in class III or IV who are considered to be high risk for surgery or to have a contraindication for surgery, thrombolytic therapy can be offered. [98] Streptokinase and urokinase have been used most commonly. The duration of therapy is determined by following valve function and gradients by echocardiography. Failure to improve valve function and hemodynamics after 72 hours should be considered a failure of thrombolytic therapy. Patients with highly mobile thrombi as well as patients who fail thrombolytic therapy should undergo valve replacement.

Prosthetic valves in pregnancy:

The optimal valve replacement for women of child-bearing age remains controversial. [100] Bioprostheses are assocated with an increased risk of structural deterioration while mechanical valves require life-long anticoagulation and carry a lifelong risk of thromboembolic events despite anticoagulation. Pregnancy further complicates this issue. Bioprosthetic valves undergo more rapid structural deterioration in younger patients, although there is no evidence that pregnancy accelerates this process. [101 102 103] Patients with mechanical valves require some form of anticoagulation throughout their pregnancy and remain at increased risk for thromboembolic complications despite apparently adequate anticoagulation. [104 105 106 107] However, warfarin use in pregnancy is associated with a higher risk of fetal loss, prematurity and stillbirth as well

as the potential for warfarin embryopathy (in 4-10% of exposed fetuses). [108] The risk of warfarin embryopathy appears to be highest with warfarin exposure during the 6^{th}-12^{th} weeks of gestation. [109] Substitution of heparin improves fetal outcome but appears to provide inadequate anticoagulation in some patients. In a recent series of 40 pregnancies in 37 women treated with subcutaneous heparin from the 6^{th}-12^{th} weeks of gestation, there were 2 cases of massive, fatal valve thrombosis. [107] In other series, valve thromboembolic complications (including valve thrombosis) occurred in 12-24% of pregnant women with mechanical valves treated with heparin. A recent, small study of pregnant women with mechanical prosthetic valves who remained on warfarin throughout their pregnancies demonstrated that the fetal complications appear to be dose-dependent. Fetal complications such as spontaneous abortion, stillbirth, and growth retardation were seen in 88% of pregnancies (including warfarin embryopathy in 9%) when the daily warfarin dose was > 5md/day while fetal complications were seen in only 15% (no warfarin embryopathy) when the daily warfarin dose was $\leq$ 5mg/day. [110] While low molecular weight heparin is theoretically an option and has been used successfully for treatment of DVT in pregnancy, there is inadequate data regarding its use in patients with prosthetic valves (several case reports to date). Clear guidelines for managing anticoagulation in a pregnant patient with a mechanical valve cannot be given at this time. Recommendations from the ACC/AHA guidelines are shown.

Table 6. Recommendations for anticoagulation in pregnancy in patients with mechanical prosthetic valves:

1. The decision whether to use heparin during the first trimester or to continue oral anticoagulation throughout pregnancy should be made after full discussion with the patient and her partner; if she chooses to change to heparin for the first trimester, she should be made aware that heparin is less safe for her, with a higher risk of both thrombosis and bleeding, and that any risk to the mother also jeopardizes the baby.
2. High-risk women (a history fo thromboembolism or older-generation mechanical prosthesis in the mitral position) who choose not to take warfarin during the first trimester should receive continuous unfractionated heparin intravenously in a dose to prolong the midinterval (6 hours after dosing) aPTT to 2 to 3 times control. Transition to warfarin can occur thereafter.
3. In patients receiving warfarin, INR should be maintained between 2.0 and 3.0 with the lowest possible dose of warfarin, and low-dose aspirin should be added.
4. Women at low-risk (no history of thromboembolism, newer low-profile prosthesis) may be managed with adjusted dose subcutaneous heparin (17,500 to 20,000u BID) to prolong the mid-interval aPTT to 2 to 3 times control.

In conclusion, valve replacement surgery does not represent a cure for valvular heart disease. Rather, it substitutes prosthetic valve disease for the native valvular disease. Therefore, patients with prosthetic heart valves require careful medical attention and management to prevent or minimize the potential complications associated with prosthetic valves.

References:

1. Bonow RO, Carabello B, de Leon ACJ, et al. ACC/AHA Guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). J Am Coll Cardiol 1998; 32:1486-1588.
2. Hufnagel CA. The surgical correction of aortic insufficiency. Bull Georgetown U Med Center 1953; 6:60.
3. Braunwald NS, Cooper TS, Morrow AG. Complete replacement of the mitral valve. J Thorac Cardiovasc Surg 1960; 40:1960.
4. Harken DE, Soroff MS, Taylor MC. Partial and complete prostheses in aortic insufficiency. J Thorac Cardiovasc Surg 1960; 40:744.
5. Starr A, Edwards ML. Mitral replacement: clinical experience with a ball-valve prosthesis. Ann Surg 1960; 154:726.
6. Baudet EM, Oca CC, Roques XF, al e. A 5 1/2 year experience with the St. Jude Medical cardiac valve prosthesis: early and late results of 737 valve replacements in 671 patients. J Thorac Cardiovasc Surg 1985; 90:137-144.
7. Bjork VO, Henze A. Management of thrombo-embolism after aortic valve replacement with the Bjork-Shiley tilting disc valve: medicamental prevention with dicumarol in comparison with dipyridamole-acetylsalicylic acid: surgical treatment of prosthetic valve thrombosis. Scand J Thorac Cardiovasc Surg 1975; 9:183-191.
8. Bloomfield P, Wheatley DJ, Prescott RJ, Miller HC. Twelve-year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprosthesis. N Engl J Med 1991; 324:573-579.
9. Hammermeister KE, Sethi GK, Henderson WG, Oprian C, Kims T, Rahimtoola S. A comparison of outcomes with men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis. N Engl J Med 1993; 328:1289-1296.
10. Miller DC, Oyer PE, Mitchell RS, al e. Performance characteristics of the Starr-Edwards model 6120 aortic valve prosthesis beyond ten years. J Thorac Cardiovasc Surg 1984; 88:193.
11. Milan AP, Bortolotti U, Mazzucco A, al e. Aortic valve replacement with the Hancock standard, Bjork-Shiley, and Lillehie-Kaster prostheses. J Thorac Cardiovasc Surg 1989; 80:37.
12. Bjork VO. A new tilting disc valve prosthesis. Scand J Thorac Cardiovasc Surg 1969; 3:1-10.
13. Hiratzka LF, Kouchoukos NT, Grunkemeir GL, al e. Outlet strut fracture of the Bjork-Shiley 60' convexoconcave valve: current information and recommendations for patient care. J Am Coll Cardiol 1988; 2:1130.
14. Funds TftB-PHVS. Important updated information for physicians about patients with Bjork-Shiley convexo-concave heart valves, 1998.
15. O'Neill WW, Chandler JG, Gordon RE, et al. Radiographic detection of strut separations in Bjork-Shiley convexo-concave mitral valves. N Engl J Med 1995; 333:414-419.

16. Arom KV, Nicoloff DM, Kersten TE, al e. Ten years' experience with the St. Jude Medical valve prosthesis. Ann Thorac Surg 1989; 47:831-837.
17. Crzer LSC, Chaux A, Matloff JM, al e. Ten-year experience with the St. Jude Medical valve for primary valve replacement. J Thorac Cardiovasc Surg 1990; 100:44-55.
18. Kratz JM, Crawford FA, Sade RM, Crumbley AJ, Stroud MR. St. Jude prosthesis for aortic and mitral valve replacement: a ten-year experience. Ann Thorac Surg 1993; 56:462-468.
19. Baudet EM, al e. Long-term results of valve replacement with the St. Jude Medical prosthesis. J Thorac Cardiovasc Surg 1995; 109:858-870.
20. St. Jude Medical I. Medical Device Recall & Advisory Notification, 2000.
21. Carpentier A, Dubost C. From xenograft to bioprosthesis. In: Ionsecu MI, Ross DN, Woller GH, eds. Biological Tissue in Heart Valve Replacement. London, U.K.: Butterworth-Heinemann, 1971:515-541.
22. Schoen FJ, Collins JJ, Cohn LJ. Long-term failure rate and morphologic correlations in porcine bioprosthetic heart valves. Am J Cardiol 1983; 51:957-964.
23. Ferrans VJ, Spray TL, Bllingham ME, al e. Structural changes in glutaraldehyde-treated porcine heterografts used as substitute cardiac valves. Am J Cardiol 1978; 41:1159.
24. Bortolotti V, Milan A, Mazzucco A, al e. Results of reoperation for primary tissue failure of porcine bioprosthesis. J Thorac Cardiovasc Surg 1985; 90:564.
25. Edwards T, Livesey S, Simpson I, al e. Biological valves beyond fifteen years: The Wessex experience. Ann Thorac Surg 1995; 60:211.
26. Magilligan DJ, Lewis JW, Jara FM, al e. Spontaneous degeneration of porcine bioprosthetic valves. Ann Thorac Surg 1980; 30:259.
27. Cohn LC, Collins JJ, Disesa VJ, al e. Fifteen-year experience with 1678 Hancock porcine bioprosthetic heart valve replacements. Ann Surg 1989; 210:435-443.
28. Jones EL, Weintraub WS, Craver JM, al e. Ten-year experience with the porcine bioprosthetic valve: interrelationship of valve survival and patient survival in 1,050 valve replacements. Ann Thorac Surg 1990; 49:370-384.
29. Westaby S, Amarasena N, Ormerod O, al e. Aortic valve replacement with the freestyle stentless xenograft. Ann Thorac Surg 1995; 60:422.
30. Vallejo JL, Gonzalez-Santos JM, Albertos J, al e. Eight year's experience with the Medtronic-Hall valve prosthesis. Ann Thorac Surg 1990; 50:429.
31. Masters R, Walley V, Pipe A, al e. Long-term experience with the Ionescu-Shiley pericardial valve. Ann Thorac Surg 1995; 60:288.
32. Pelletier L, Carrier M, Lecler Y, al e. The Carpentier-Edwards pericardial bioprosthesis: clinical experience with 600 patients. Ann Thorac Surg 1995; 60:297.
33. Pelletier LC, Carrier M, Leclerc Y, Dyrda I. The Carpentier-Edwards pericardial bioprosthesis: clinical experience with 600 patients. Ann Thorac Surg 1995; 60:S297-302.
34. Cosgrove DM, Lytle BW, Taylor PC, et al. The Carpentier-Edwards pericardial aortic valve. J Thorac Cardiovasc Surg 1995; 110:651-665.
35. Kobayashi Y, Nagata S, Eishi K, Nakano K, Miyatake K. Serial Doppler echocardiographic evaluation pf Carpentier-Edwards pericardial valve dysfunction: Comparison with Ionescu-Shiley valve. Am Heart J 1998; 135:1086-95.

36. Staab ME, Nishimura RA, Dearani JA, Orszulak TA. Aortic valve homografts in adults: a clinical perspective. Mayo Clin Proc 1998; 73:231-238.
37. Shaddy RE, Hunter DD, Osborn KA, et al. Prospective analysis of HLA immunogenicity of cryopreserved valved allografts used in pediatric heart surgery. Circulation 1996; 94:1063-1067.
38. O'Brien MF, Stafford EG, Gardner MA, et al. Allograft aortic valve replacement: long-term follow-up. Ann Thorac Surg 1995; 60(Suppl):S65-S70.
39. Ross DN. Replacement of the aortic and mitral valves with a pulmonary autograft. Lancet 1967; 2:956-958.
40. Doty DB. Aortic valve replacement with pulmonary autograft: the Ross procedure. ACC Current Journal Review 1996; September/October:49-53.
41. Chambers JC, Somerville J, Stone S, Ross DN. Pulmonary autograft procedure for aortic valve disease: long-term results of the pioneer series. Circulation 1997; 96:2206-2214.
42. Lawrie GM. Mitral valve repair versus replacement. Cardiology Clinics 1998; 16:437-448.
43. Smith ND, Raizada V, Abrams J. Auscultation of the normally functioning prosthetic valve. Ann Intern Med 1650; 95:594-8.
44. Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. N Engl J Med 1996; 335:407-416.
45. Chun PKC, Nelson WP. Common cardiac prosthetic valves: radiologic identification and associated complications. JAMA 1977; 238:401-403.
46. Mehlman DJ, Resnekov L. A guide to the radiographic identification of prosthetic heart valves. Circulation 1978; 57:613.
47. Mehlman DJ. A guide to the radiographic identification of prosthetic heart valves: an addendum. Circulation 1984; 69:102-105.
48. Nottestad SY, Zabalgoitia M. Echocardiographic recognition and quantitation of prosthetic valve dysfunction. In: Otto CM, ed. The Practice of Clinical Echocardiography. Philadelphia, PA: W.B. Saunders Company, 1997:797-819.
49. Stein PD, Alpert JS, Dalen JE, Horstkotte D, Turpie AGG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest 1998; 114:602S-610S.
50. Heras M, Chesebro JH, Fuster V, et al. High risk of thromboemboli early after bioprosthetic cardiac valve replacement. J Am Coll Cardiol 1995; 25:1111-1119.
51. Ionescu MI, Smith DR, Hasan SS, al e. Clinical durability of the pericardial xenograft valve: ten years' experience with mitral replacement. Ann Thorac Surg 1982; 34:265-277.
52. Moinuddeen K, Quin J, Shaw R, et al. Anticoagulation is unnecessary after biological aortic valve replacement. Circulation 1998; 98:II-95-II-99.
53. Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJM, Vandenbroucke JP, Briet E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. N Engl J Med 1995; 333:11-17.
54. Saour JN, Sieck JO, Mamo LAR, Gallus AS. Trial of different intensities of anticoagulation in patients with prosthetic heart valves. N Engl J Med 1990; 322:428-432.

55. Horstkotte D, Schulte HD, Bircks W, Strauer BE. Lower intensity anticoagulation therapy results in lower complication rates with the St. Jude medical prosthesis. J Thorac Cardiovasc Surg 1994; 104:1136-1145.
56. Acar J, Iung B, Boissel JP, et al. AREVA: Multicenter randomized comparison of low-dose versus standard-dose anticoagulation in patients with mechanical prosthetic heart valves. Circulation 1996; 94:2107-2112.
57. Skudicky D, Essop MR, Wisenbaugh T, et al. Frequency of prosthetic valve-related complications with very low level warfarin anticoagulation combined with dipyridamole after valve replacement using St. Jude Medical prosthesis. Am J Cardiol 1994; 74:1137-1141.
58. Butchart EG, Lewis PA, Grunkemeier GL, Kulatilake N, Breckenridge IM. Low risk of thrombosis and serious embolic events despite low-intensity anticoagulation: experience with 1,004 Medtronic Hall valves. Circulation 1988; 78(suppl I):I-66-I-77.
59. Butchart EG, Lewis PA, Bethel J, Breckenridge IM. Adjusting anticoagulation to prosthesis thrombogenicity and patient risk factors: recommendations for the Medtronic Hall valve. Circulation 1991; 84(suppl III):III-61-III-69.
60. Turpie AGG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. N Engl J Med 1993; 329:524-529.
61. Cappelleri JC, Fiore LD, Brophy MT, Deykin D, Lau J. Efficacy and safety of combined anticoagulant and antiplatelet therapy verus anticoagulant monotherapy after mechanical heart-valve replacement: a metaanalysis. Am Heart J 1995; 130:547-552.
62. Albertal J, Sutton M, Pereyra D, al e. Experience with moderate intensity anticoagulation and aspirin after mechanical heart valve replacement. A retrospective, non-randomized study. J Heart Valve Dis 1993; 2:302-307.
63. Wahl MJ. Dental surgery in anticoagulated patients. Arch Intern Med 1998; 158:1610-1616.
64. Disorders of hemostasis. Accepted Dental Therapeutics. Chicago, Ill: American Dental Association, 1984:39-40.
65. Hirsh J, Dalen JE, Anderson DR, et al. Oral anticoagulants: Mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 1998; 114:445S-469S.
66. Eckman MH, Beshansky JR, Durand-Zaleski I, Levine HJ, Pauker SG. Anticoagulation for noncardiac procedures in patients with prosthetic heart valves: does low risk mean high cost? JAMA 1990; 263:1513-1521.
67. Bryan AJ, Butchart EG. Prosthetic heart valves and anticoagulant managment during non-cardiac surgery. Br J Surg 1995; 82:577-578.
68. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med 1997; 336:1506-1511.
69. White RH, McKittrick T, Hutchinson R, Twitchell J. Temporary discontinuation of warfarin therapy: changes in the international normalized ratio. Ann Intern Med 1995; 122:40-42.
70. Weibert RT, Le DT, Kayser SR, Rapaport SI. Correction of excessive oral anticoagulation with low-dose oral vitamin K. Ann Intern Med 1997; 125:959-962.
71. Kim DR, Kim KY. Managing the over-anticoagulated patient. Hospital Medicine 1999; January:47-49.

72. Calderwood SB, SwinskiL.A., Waternaux CM, Karchmer AW, Buckley MJ. Risk factors for the development of prosthetic valve endocarditis. Circulation 1985; 72:31-37.
73. Threlkeld MG, Cobbs CG. Infectious disorders of prosthetic valves and intravascular devices. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's principals and practice of infectious diseases. Vol. Vol 1. New York: Churchill Livingstone, 1995:783-793.
74. Wilson WR, Danielson GK, Giuliani ER, Geraci JE. Prosthetic valve endocarditis. Mayo Clin Proc 1982; 57:155-161.
75. Tuna IC, Orszulak TA, Schaff HV, Danielson GK. Results of homograft aortic valve replacement for active endocarditis. Ann Thorac Surg 1990; 49:619-624.
76. Dearani JA, Orszulak TA, Schaff HV, Daly RC, Anderson BJ, Danielson GK. Results of allograft aortic valve replacement for complex endocarditis. J Thorac Cardiovasc Surg 1997; 113:285-291.
77. McGiffin DC, Kirklin JK. The impact of aortic valve homografts on the treatment of aortic prosthetic valve endocarditis. Semin Thorac Cardiovasc Surg 1995; 11:53-61.
78. Arnett EN, Roberts WC. Prosthetic valve endocarditis: clinicopathologic analysis of 22 necropsy patients with comparison of observations in 74 necropsy patients with active infective endocarditis involving natural left-sided cardiac valves. Am J Cardiol 1976; 38:281-292.
79. Yu VI, Fang GD, Keys TF, al e. Prosthetic valve endocarditis: superiority of surgical valve replacement versus medical therapy only. Ann Thorac Surg 1994; 58:1073.
80. Larbalestier RI, Kinchla NM, Aranki SF, Couper GS, Collins JJJ, Cohn LF. Acute bacterial endocarditis: optimizing surgical results. Circulation 1992; 86(suppl II):II-68-II-74.
81. Lick SD, Zwischenberger JB. Endocarditis: when to operate? ACC Current Journal Review 1995; November/December:21-23.
82. Kloster FE. Diagnosis and management of complications of prosthetic heart valves. Am J Cardiol 1975; 32:872-885.
83. Crexells C, Aerichide N, Bonny Y, Lepage G, Campeau L. Factors influencing hemolysis in valve prosthesis. Am Heart J 1972; 84:161-170.
84. Falk RH, Mackinnon J, Wainscoat J, Melikian V, Bignell AHC. Intravascular hemolysis after valve replacement: comparative study betweej Starr-Edwards (ball valve) and Bjork-Shiley (disc valve) prosthesis. Thorax 1979; 1.
85. Skoularigis J, Essop MR, Skudicky D, Middlemost SJ, Sareli P. Frequency and severity of intravascular hemolysis after left-sided cardiac valve replacement with Medtronic Hall and St. Jude Medical prostheses, and influence of prosthetic type, position, size, and number. Am J Cardiol 1993; 71:587-591.
86. Jindani A, Neville EM, Venn G, Williams BT. Paraprosthetic leak: a complication of cardiac valve replacement. J Cardiovasc Surg 1991; 32:503-508.
87. Maraj R, Jacobs LE, Ioli A, Kotler MN. Evaluation of hemolysis in patients with prosthetic heart valves. Clin Cardiol 1998; 21:387-392.
88. Kontos GH, Schaff HV, Orszulak TA, Puga FJ, Pluth JR, Danielson GK. Thrombotic occlusion of disc valves: recognition and surgical management. Ann Thorac Surg 1989; 48:60-65.

89. Deviri E, Sarelli P, Wisenbaugh T, Cronje SL. Obstruction of mechanical heart valve prosthesis: clinical aspects and surgical management. J Am Coll Cardiol 1991; 17:646-650.
90. Murphy DA, Levine FH, Buckley MH, al e. Mechanical valves: a comparative analysis of the Starr-Edwards and Bjork-Shiley prostheses. J Thorac Cardiovasc Surg 1983; 86:746-752.
91. Daniel WG, Mugge A, Grote J, et al. Comparison of transthoracic and transesophageal echocardiography for detection of abnormalities of prosthetic and bioprosthetic valves in the mitral and aortic positions. Am J Cardiol 1993; 71:210-215.
92. MacKenzie GS, Heinle SK. Echocardiography and Doppler assessment of prosthetic heart valves with transesophageal echocardiography. Critical Care Clinics 1996; 12:383-409.
93. Faletra F, Constantin C, De Chiara F, et al. Incorrect echocardiographi diagnosis in patients with mechanical prosthetic valve dysfunction: correlation with surgical findings. Am J Med 2000; 108:531-537.
94. Vogel W, Stoll HP, Bay W, Frohlig G, Schieffer H. Cineradiography for determination of nomral and abnormal function in mechanical heart valves. Am J Cardiol 1993; 71:225-232.
95. Montorsi P, De Bernardi F, Muratori M, Cavoretto D, Pepi M. Role of cine-fluoroscopy, transthoracic, and transesophageal echocardiography in patients with suspected prosthetic heart valve thrombosis. Am J Cardiol 2000; 85:58-64.
96. Yoganathan AP, Corcoran WH, Harrison EC, Carl JR. The Bjork-Shiley aortic prosthesis: flow characteristics thrombus formation and tissue overgrowth. Circulation 1978; 58:70-76.
97. Gueret P, Vignon P, Fournier P, et al. Transesophageal echocardiography for the diagnosis and management of nonobstructive thrombosis of mechanical mitral valve prosthesis. Circulation 1995; 91:103-110.
98. Lengyel M, Fuster V, Keltai M, et al. Guidelines for management of left-sided prosthetic valve thrombosis: a role for thrombolytic therapy. J Am Coll Cardiol 1997; 30:1521-1526.
99. Horstkotte D, Burckhardt D. Prosthetic valve thrombosis. J Heart Valve Dis 1995; 4:141-153.
100. Elkayam U. Pregnancy through a prosthetic heart valve. J Am Coll Cardiol 1999; 33:1642-1645.
101. Salazar E, Espinola N, Roman L, Casanova JM. Effect of pregnancy on the duration of bovine pericardial prostheses. Am Heart J 1999; 137:714-720.
102. Jamieson WRE, Miller DC, Akins CW, al e. Pregnancy and bioprostheses: influence on structural valve deterioration. Ann Thorac Surg 1995; 60:5282-5287.
103. North RA, Sadler L, Stewart AW, McCowan LME, Kerr AR, White HD. Long-term survival and valve-related complications in young women with cardiac valve replacements. Circulation 1999; 99:2669-2676.
104. Born D, Martinez EE, Almeida PA, al e. Pregnancy in patients with prosthetic heart valves: the effect of anticoagulation on mother, fetus and neonate. Am Heart J 1992; 124:413-417.
105. Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. Br Heart J 1993; 71:196-201.

106. Hanania G, Thomas D, Michel PL, al e. Grossesses chez les porteuses de prostheses valvulaires: etude cooperative retropspective francaise (155 cas). Arch Mal Coeur 1994; 87:429-437.
107. Salazar E, Izaguirre R, Verdejo J, Mutchinick O. Failure of adjusted doses of subcutaneous heparin to prevent thromboembolic phenomena in pregnant patients with mechnical cardiac valve prostheses. J Am Coll Cardiol 1996; 27:1698-1703.
108. Frewin R, Chisolm M. Anticoagulation of women with prosthetic heart valves during pregnancy. Br J Obstet Gynecol 1998; 105:683-686.
109. Hall JG, Pauli RM, Wilson KA. Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med 1980; 68:122-140.
110. Vitale N, De Feo M, De Santo LS, Pollice A, Tedesco N, Cotrufo M. Dose-dependent fetal complications fo warfarin in pregnant women with mechanical heart valves. J Am Coll Cardiol 1999; 33:1637-1641.