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Evaluating Bioprosthetic Devices in Aortic Valve Surgery : Systematic Assessment and Design of Cardiac Surgical Trials

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EVALUATING BIOPROSTHETIC DEVICES IN AORTIC VALVE SURGERY: SYSTEMATIC ASSESSMENT AND DESIGN OF CARDIAC SURGICAL TRIALS

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ABSTRACT

Producing quality randomized controlled trials in the field of surgery and, in particular, cardiac surgery can be a formidable task. Surgeons face difficulties not frequently encountered in non-surgical studies. Addressing the difficulties peculiar to this medical specialty may improve the quality of future surgical trials. Issues such as blinding, sample size, control groups and bias are but a few of the dilemmas that must be attended to in order to design a good quality surgical study. This thesis evaluates the quality of surgical studies available in the cardiac surgical literature, identifies obstacles encountered, and seeks to develop guidelines for future cardiac surgical protocols. Studies using aortic valve replacement procedures are the focus of the thesis. An extensive literature search on aortic valve replacement encompassing publications from 1986-2004 was used to evaluate the quality of surgical studies. A pool of 646 studies was narrowed down to 23 papers which were selected for detailed analysis. In the second part of the thesis, a list of obstacles to conducting surgical trials was constructed from the literature and the author's experience. A revised list of obstacles based on the experience from the systematic review was developed. This list was then applied to a year of publications of the Journal of Thoracic and Cardiovascular Surgery and the Annals of Thoracic Surgery. A final list was then developed consisting of obstacles encountered in conducting clinical trials in surgery. Finally, the U.K. Medical Research Council guidelines as adapted by the Canadian Institutes of Health Research were used in conjunction with the information procured in this study to generate guidelines for conducting surgical trials and applied in developing a specific protocol for comparing two bioprosthetic heart valves.

EXECUTIVE SUMMARY

Background and Significance

Surgery is an area of medicine that uses operative interventions to treat injuries, diseases and abnormalities of the human body. Cardiac surgery is a specialized domain, which frequently employs the use of medical devices in the course of treatment. Today surgeons are fortunate to have many new and frequently changing materials and technology at their fingertips. The development of new devices has enabled great improvements in the quality of surgical care for patients around the world. However, before new prosthetic devices are widely used, it is important to test their effectiveness in a controlled and regulated manner. The randomized control trial is the gold standard in study designs to test a device or medication. Such a design may be difficult to use in cardiac surgery and allowances must be made to overcome clinical, methodological, or ethical dilemmas. The strength of the study may be affected by an inability to adhere to such scientific principles as randomization, blinding and controls.

Purpose

The purpose of this thesis was to evaluate the quality of surgical studies available in the cardiac literature, to identify obstacles encountered, and to develop guidelines for comparative trials involving bioprosthetic valves used in the treatment of valvular heart disease.

Methods

The first part of the thesis entailed conducting a systematic review of the cardiac literature in order to analyze the quality of the work presently conducted by cardiac surgeons. An extensive literature search on aortic valve replacement encompassing publications from 1986-2004 was used to evaluate the quality of surgical studies. A pool of 646 studies was narrowed down to 23 papers that were selected for detailed analysis. These papers were analyzed using key aspects such as subject composition, outcome, device used, study design and length of follow-up.

A second review of the cardiac surgical literature was then performed in order to compile a list of obstacles encountered by other surgeons while conducting cardiac surgical trials. A one-year period of publications from the peer reviewed Journal of Thoracic & Cardiovascular Surgery and the Annals of Thoracic Surgery was used for this review. Inclusion and exclusion criteria were specified prior to conducting the review. A narrative format was implemented to document the obstacles encountered by the investigators.

Once the journal analysis was complete, a protocol was developed for a prospective surgical trial comparing two bioprosthetic heart valves. The United Kingdom Medical Research Council guidelines, as adapted by the Canadian Institutes of Health Research, were used in conjunction with the information procured throughout the study to help generate a set of guidelines for conducting such a trial. The issues and obstacles encountered when designing a randomized controlled study were considered and discussed throughout this section.

Results

Data extracted from the 23 chosen papers was organized into six categories. These groupings were: study design, subject characteristics, study demographics, study methodology, outcomes assessed and actual outcomes. The studies used varied in date of publication from 1986 to 2004 and employed a variety of comparative study designs. While three studies were prospective randomized designs, the majority of the studies did not use or indicate use of randomization. Many of the studies were comparative cohort studies and entered their patients in a selective rather than a consecutive fashion. On the whole, large volume centres enrolled more patients in their studies and were more complete in their data collection both over the short and long term.

A list of obstacles that were hypothesized to be agents in preventing good comparative surgical trials from being designed and successfully implemented was acknowledged. A systematic review of the cardiac surgical literature consisting of a full year of

publications from the Journal of Thoracic and Cardiovascular Surgery and the Annals of Thoracic Surgery was then used to revise the initial list of obstacles devised. Some of the primary obstacles were: difficulty in obtaining adequate numbers of study patients, inability to standardize patient care throughout the study, inadequate randomization, blinding and lack of control of associated medications.

Conclusion - Outline for Prospective Randomized Trial

Guidelines for designing a prospective randomized controlled surgical trial were suggested and developed as the main product of the thesis. Although created as a result of and for the purpose of comparing heart valve substitutes, the format was designed for applications to any surgical trial and to serve as an easy to use reference for surgical investigators or their designates. A trial following the Canadian Institutes of Health Research guidelines and the findings of the thesis was proposed.

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LIST OF ABBREVIATIONS

AATS	American Association of Thoracic Surgeons
CCS	Canadian Cardiovascular Society
CASS	Coronary Artery Surgery Study
CIHR	Canadian Institutes of Health Research
EOA	Effective Orifice Area
ICU	Intensive Care Unit
LVH	Left Ventricular Hypertrophy
MRC	United Kingdom Medical Research Council
NOS	Newcastle Ottawa Scale
NYHA	New York Heart Association
RCT	Randomized Controlled Trial
TIA	Transient Ischemic Attack
VA	Veterans' Administration

CHAPTER 1

INTRODUCTION

1.1 OVERVIEW

There are few randomized controlled trials that evaluate the prosthetic heart valve substitutes used in the treatment of adult aortic valve disease. Obstacles encountered in designing and implementing surgical trials may be responsible for the paucity of such studies and the abundance of outcomes research with weaker study designs. The clinician is then faced with a wide assortment of commercially available devices that have not been tested in comparative studies. They have only been evaluated by a simple tabulation of outcomes. Each group of study patients may have distinct characteristics that result in systematic bias of the performance of the device being studied.

A comprehensive systematic review of the literature is necessary to understand better the design and implementation of surgical trials comparing heart valve substitutes. A better perspective of the quality of the available evidence will be obtained from such a review. Thereafter, a list of the obstacles encountered in past and more recent studies could be formulated. These obstacles can then be applied to the literature in cardiac surgery to examine the factors that have affected the quality and design of studies. Ultimately, it may be possible to produce a blueprint for developing studies that evaluate bioprosthetic heart valve substitutes.

1.2 STATEMENT OF THE PROBLEM

The smooth and unrestricted forward flow of blood through the pumping heart is governed by a series of valves. The mobility and competence of these valves is essential to normal cardiac function. The aortic valve serves an important role in the high-pressure

zone that anatomically divides the left ventricle and the aorta. Prosthetic heart valve substitutes are an essential modality of therapy for treating valvular heart disease. Several commercially available devices enable the surgeon to replace diseased heart valves. However, it is difficult to identify which are the best for durability, frequency of complications and ease of implantation.

A randomized controlled surgical study that compares the performance of two bioprosthetic heart valve substitutes used in the management of adult aortic valve disease is problematic. An effect modifier hindering the evaluation of heart valve substitutes is the concomitant treatment with anti-hypertensive agents. The major treatment benefit achieved by substituting a narrowed, diseased aortic valve as found in aortic stenosis, with a bioprosthetic valve substitute is a decrease in the pressure gradient across the left ventricular outflow tract. This results in a regression of the overall mass of the left ventricular chamber. Left ventricular mass regression is extremely important for the reduction of both sudden and unexpected death as well as congestive heart failure.[1] However, the rate and extent of mass regression are affected in a significant way by treatment with anti-hypertensive drugs. These medications achieve their effect by lowering blood pressure and decreasing the cardiac workload. Effective blood pressure control enhances the rate and degree of mass regression by further lowering the load against which the ventricle must work. Hence, treatment effect of a particular heart valve is subject to a significant interaction by an anti-hypertensive drug that may be administered postoperatively producing a synergistic effort. Although measuring the effective orifice area and the trans-prosthetic gradient for each valve often compares the hemodynamic efficiency of heart valves, such studies are weakened by the variable presence of anti-hypertensive agents and inadequate randomization. Hence, it is imperative to control for these effect modifiers. Ideally this would be done through a randomized controlled trial. There are no studies evaluating the impact of angiotensin converting enzyme inhibitors, angiotensin receptor blockers or other anti-hypertensive agents in patients that have undergone aortic valve replacement for aortic valve disease.

If anti-hypertensive agents can potentially yield such strong effects, comparison of prosthetic heart valves theoretically may only be appraised by randomized controlled trials.

In order to truly declare the superiority of one device over another, meticulous attention must be paid to protocol limitations and confounding factors in a surgical study. Non-randomized assessment of bioprosthetic valves in the surgical treatment of aortic valvular disease are common, whereas randomized clinical trials assessing heart valves are quite rare.[2,3,4] A study design that takes into account the effect modification of medication, patient heterogeneity, blinding, and a protocol that is responsive to changes in surgical practice is necessary to relate the hemodynamic performance of a prosthesis to clinical outcomes. In order to design, implement and conduct a successful study, obstacles in conducting randomized controlled trials in cardiac surgery must be clearly understood and accommodated.

1.3 OPERATIVE DEFINITION OF A SURGICAL TRIAL

Surgery is that branch of medicine, which treats diseases, injuries, and deformities of the body by manual or operative techniques. Surgical trials evaluate specific devices, procedures or manual treatments that are used in the management of disease. They do not include trials using medications in the operative therapy of such patients. Questionnaires, audits, quality of life assessments and surveys are examples of studies conducted with surgical patients, often by surgeons that are not assessing randomized groups of patients with respect to a device implanted or a technique. Entry of surgical patients into trials where a group is to receive an investigational medication does not constitute a surgical study for the purpose of this thesis. Examples of surgical trials include laparoscopic versus open cholecystectomies, videoscopic assisted thoracic versus open thoracotomy procedures and wide local excision versus mastectomy for breast cancer.

Surgical trials ideally have a control arm to serve as a comparison. A novel technique or new technology can often be compared with the standard or accepted approach. Sham operations where an incision is performed without any internal "corrective measures" are difficult to justify on legal, ethical or clinical grounds. They place patients at undue risk of harm and may violate the right to informed consent. Therefore, these procedures are generally not used in a control arm of a surgical trial.

1.4 CONTRIBUTION OF THE THESIS

This thesis contributes to the field of cardiac surgery in several ways.

1) By implementing a systematic review of the literature, it summarizes and consolidates the somewhat heterogeneous clinical evidence that has accumulated regarding the use of bioprosthetic heart valve substitutes in the management of aortic valve disease.
2) It contributes to the evidence available regarding the choice of a valve substitute for the management of aortic valve disease.
3) It evaluates the strength of the data available in the surgical literature by developing a system to assess the strength of surgical studies that have been conducted.
4) Through a comprehensive review of the literature, it identifies the obstacles that are encountered in conducting clinical trails in surgery, particularly cardiac surgery.
5) It develops a surgical study protocol that examines two bioprosthetic heart valves used in the treatment of adult aortic valvular disease. A methodological blueprint is created for future surgical studies on the effect of heart valve substitutes on the morbidity and mortality associated with aortic valvular disease.
6) It identifies strategies for dealing with the obstacles encountered in conducting clinical trials in surgery as well as evaluating surgical studies that have been conducted in the past.

1.5 OUTLINE OF THE THESIS

The overall aim of this thesis is to evaluate the performance of bioprosthetic heart valve substitutes in aortic valve surgery while taking into consideration the inherent bias and obstacles encountered in conducting cardiac surgical trials. This process also entails tackling the confounding treatment effects of commonly used anti-hypertensive agents in the management of such patients.

The thesis is comprised of three major studies. The first study entails performing a systematic review of randomized controlled trials, controlled clinical trials, non-randomized studies and large case series that evaluate the effect that the choice of bioprosthetic valve substitute has on the mortality and morbidity of adult patients undergoing aortic valve surgery. The systematic review is not merely a survey of the literature but rather uses an extensive electronic literature gathering strategy that follows well-developed guidelines.

The second part of the thesis entails the identification of obstacles that are encountered in conducting clinical trials in surgery, particularly cardiac surgery. This section deals with identifying the problems encountered in the systematic review of bioprosthetic valves as well as a comprehensive review of the literature to identify the obstacles that other authors have encountered when conducting surgical trials. This process will lead to the development of the third part of the thesis.

The third component involves the development of guidelines for a surgical study protocol to examine two bioprosthetic heart valves used in the treatment of adult aortic valvular disease. The study protocol will take into account the obstacles that are usually encountered in conducting surgical trials, consider solutions to these obstacles, and formulate a blueprint whereby other surgical trials may be developed with a strong methodological foundation. The guidelines were applied to develop a specific study protocol for evaluating two bioprosthetic stented heart valves (Carpentier-Edwards Perimount Magna versus Medtronic Mosaic Porcine)

CHAPTER 2

BACKGROUND

2.1 AORTIC VALVE DISEASE

2.1.1 Aortic Stenosis - Clinical Description of a Medical Condition

The normal adult human aortic valve has an orifice area of 2.6 to 3.5 cm^2, with a mild narrowing or stenosis defined as a valve area of greater than 1.5 cm^2, moderate being 0.75 to 1.5 cm^2 and severe as less than 0.75 cm^2.[5] The extreme ranges of body weight necessitate indexing the aortic valve area. Hence, an indexed area of greater than 0.9 cm^2/m^2 is defined as mild stenosis, moderate as between 0.6 to 0.9 cm^2/m^2 and severe as less than or equal to 0.6 cm^2/m^2. When symptoms develop, the aortic valve usually exhibits moderate stenosis. Despite having severe stenosis, some patients may have no symptoms while others may have moderate stenosis and have considerable symptoms. These may include chest discomfort or angina, light-headedness or presyncope, fainting spells, or heart failure. Heart failure may manifest as shortness of breath, fatigue, ankle swelling and difficulty breathing while in the supine position.

Aortic stenosis generally progresses with a gradual decrease in the valve area from 0.1 to 0.3 cm^2 per year and a mean increase in the pressure gradient of about 5 to 11 mmHg per year. The average valve area change per year is about 0.12 cm^2 per year. This is usually determined by cardiac catheterization or echocardiography, procedures that usually cannot distinguish the etiology of the condition. In order to follow the progression of aortic valve disease, serial evaluations by echocardiography at annual or semi-annual periods are necessary.[6]

2.1.2 Epidemiology

Unfortunately, the incidence of aortic valvular disease in the general population is undetermined but estimated to be around 2%.[7] This is predominantly due to lack of detection, as most people do not get examined regularly by a physician. In addition, many of the cases may not be identified unless the physician has a heightened awareness for such a heart murmur. Occasionally the transvalvular turbulence is inaudible. Often only echocardiography will identify the condition. Accurate diagnosis of the medical condition relies on the availability of cardiac ultrasonographers, which traditionally have tended to be concentrated in urban settings. There is also a prolonged period of low morbidity that may go on for years possibly decades before the condition becomes clinically apparent. The severity of the stenosis may also remain stable for decades and then get worse over a relatively shorter period as one to four years if serial echocardiography has been used to follow the condition. There has been a slight increase in the incidence over the past decade.[7] As senile degenerative changes in the valve account for the majority of cases in recent years, this has been attributed to the aging population and more careful clinical evaluation of the elderly. Secondly, the greater availability of echocardiography has increased the likelihood of detection. Following the development of heart failure, syncope or angina, average survival is about 2, 3 and 5 years respectively.[8]

2.1.3 Patient Population

Aortic valve disease does not appear to afflict one gender in favour of the other. The presence of both aortic insufficiency and stenosis in a valve usually occurs as a result of the same causes, which result in these conditions when they present in isolation. Patients with congenital bicuspid aortic valves may begin experiencing symptoms from their teenage years up to about 65 years of age.[9] In such patients, the normal three leaflets of the aortic valve are replaced by two abnormally shaped leaflets. When rheumatic fever has produced the aortic stenosis, patients may be symptom free for at least 40 years. In

this condition, the aortic valve leaflets become inflamed from an autoimmune process. Subsequent scar formation and cusp fusion leads to aortic stenosis. The incidence of rheumatic fever in Canada and the United States has declined to only rare and sporadic cases over the past several decades.

In the seventh and eighth decades of life, patients that present with aortic stenosis usually have valves that are severely calcified and demonstrate age-related degenerative changes. Most of these patients have been relatively asymptomatic for much of their lives until the most recent months or years.

2.1.4 Anatomy

The aortic valve may be described as a passive valve mechanism comprised of three leaflets having the texture and consistency of a rose petal. Its passive nature enables the valve to open and close with minimal pressure differences between the left ventricular chamber of the heart and the main outflow passage called the aorta, which distributes blood to the rest of the body.[10] Perfect alignment of the three leaflets or cusps occurs during closure of this mechanism, which must prevent backflow of blood during the relaxation phase of the heart also known as diastole. There must be sufficient structural integrity of the valve to withstand the tension generated by systemic blood pressures. The semi-lunar attachments of the aortic valve leaflets onto the junction between the left ventricular chamber and the aorta comprise the surgical annulus of the aortic valve. The valve leaflets are classically described as semi-lunar in shape because they take on a crescent shape as a result of the geometry of attachment to the aortic wall. The leaflets are composed of collagen, elastin and glycosaminoglycans. The outer layers of the leaflet form a continuum with the aortic endothelium or ventricular endocardium, which is the inner lining of the heart and great vessels.[11]

2.1.5 Physiology

The passive mechanism, which opens and closes the aortic valve, occurs in response to fluctuations in pressure during the cardiac cycle. In the non-diseased valve, the three leaflets offer little resistance to blood flow because the specific gravity of the leaflets is equal to that of blood. This means that the leaflets close rapidly in response to the minimal application of force. During the diastolic phase of cardiac function, the pressure difference between the aorta and the ventricle creates stresses on the valve leaflets that cause the base of the aortic root to constrict. The constriction enhances closure and coaptation of the leaflets. This action is aided by the elastic properties of the aortic root. As late diastole approaches, the left ventricle becomes filled with blood resulting in an expansion of the aortic root. This flattens the aortic valve leaflets to reduce their apposition to a minimum. As the pressure rises, the aortic root expands to allow the valve to open rapidly at the beginning of ejection. This expansion of the aortic root allows the valve to open quickly by changing the angle of the leaflets at their bases, thereby offering a minimum resistance.[12] Apposition of the valve leaflets occurs briskly during the phase of closure, which occurs when the pressure between the ventricular outflow tract and the aorta equalizes, producing a small reversal of flow and a deceleration of the ejected blood.

2.1.6 Natural History

Aortic stenosis is a condition, which occurs when the aortic valve restricts the ejection of blood from the left ventricular cavity into the aorta. In adult humans, the principle cause of aortic stenosis is the deposition of calcium within the aortic valve leaflet. This calcification is attributed to a lifetime of leaflet stress that occurs with each cardiac contraction and may be found on a normal trileaflet valve as degenerative aortic stenosis. Small deposits of calcium within the collagen framework increase with time as a result of these shearing stresses. The development of aortic stenosis may be accelerated by rheumatic fever. It may also be related to a congenital abnormality such as a bicuspid

valve that is present in about one to two percent of the general population.[13] These congenitally abnormal valve leaflets tend to calcify when patients are less than thirty years and may become symptomatic[13] at any time before the age of sixty years. The abnormal resistance of blood flow that occurs in aortic stenosis results in acceleration in the velocity of ejected blood. This produces turbulence within the aorta. A high degree of turbulence can cause deterioration of the valvular lining and induce changes within the aortic wall that weaken it.[14] This weakening can produce a life-threatening or even lethal aortic dissection or rupture.

Aortic stenosis is defined as a point of resistance between the left ventricular cavity and the aorta that prevents the proper ejection of blood from the heart to rest of the body. As a result of the resistance, there is an elevation of pressure within the left ventricular chamber. The elevated pressure produces structural changes over time and results in a thickening of the heart muscle called left ventricular hypertrophy (LVH). LVH may be induced by either pressure or volume overloading of the chamber.

LVH is an adaptive mechanism of the ventricular wall to the increased stress and allows the patient to remain symptom-free for many years. However, the continuing hypertrophy caused by progression of the aortic stenosis eventually leads to development of symptoms. An inability of coronary blood flow to meet the oxygen demands of the myocardium or heart muscle produces symptoms of chest discomfort, shortness of breath or upper extremity discomfort known as angina. Following the onset of angina, patients have an average survival of about four or five years.[15] Patients may also experience symptoms of light-headedness or dizziness and may faint. This condition is called syncope and is related to a drop in blood pressure, which may be caused by a rhythm disturbance. Sudden changes in left ventricular pressure may be created by a reflex, which produces arterial and venous dilatation in response to exertion even though ventricular function may be normal at that time without any decreased cardiac output. When the heart muscle starts to fail, symptoms of congestive heart failure begin to develop. The patient begins to complain of shortness of breath and fatigue as the pulmonary circulation becomes congested with blood. An inadequate perfusion of the

skeletal muscle with oxygen produces an accumulation of lactic acid and this creates a feeling of fatigue. On average, about fifty percent of patients survive less than two years when they have reached this stage.[16] A very small group of patients with untreated aortic stenosis die suddenly as a result of a rhythm disturbance although the majority of patients usually succumb to congestive heart failure.

Following aortic valve replacement, the stress placed on the myocardial wall is significantly reduced due to a major reduction in the gradient across the aortic valve. This produces a significant reduction in the degree of left ventricular hypertrophy with major changes occurring within the first six months and gradual improvements continuing for at least the next two years. Such changes include improvement in ventricular systolic and diastolic function, better compliance and relaxation of the chamber wall and a return to a more normal diameter by the coronary arteries.

2.1.7 Pathophysiology of Aortic Stenosis

As previously noted, the cross-sectional area of the normal adult human aortic valve is approximately 2.6 to 3.5 $cm.^2$. A pressure gradient develops across the annulus of the valve as stenosis progresses and sometimes results in an intra-ventricular chamber peak pressure of 300 mmHg. The peak pressure may be achieved while the systemic pressure and stroke volume may remain relatively normal. The compensatory left ventricular hypertrophy occurs as a result of increased muscle mass without any significant chamber dilatation. The development of symptoms often occurs when the orifice area has reduced to approximately 0.7 to 0.9 $cm.^2$. There may be a decrease in the ejection fraction as a result of impairment of the contractility of the left ventricular chamber.[17] Rhythm disturbances such as atrial fibrillation may occur reducing the cardiac output further as the atrial contraction contributes up to forty percent of the left ventricular filling during the diastolic phase for patients that have aortic stenosis. In the normal human heart, the atrial contribution is only about twenty percent of the stroke volume.

2.1.8 Aortic Insufficiency - Clinical Description of a Medical Condition

Occasionally the leaflets of the aortic valve fail to coapt accurately. This produces retrograde flow of recently ejected blood back into the left ventricular chamber. The retrograde flow occurs during the diastolic or relaxation phase of the left ventricular chamber. The left ventricular chamber becomes overloaded by the resultant increase in pressure and volume. The volume overload is created by the additional regurgitant flow of blood backwards into the ventricular chamber and the pressure overload occurs in response to the additional work required to eject this added volume of blood. The end result is not only a thickening of the heart muscle wall but also an enlargement of the chamber to accommodate the additional volume.

Although aortic insufficiency may be present in a variety of cases of aortic stenosis due to calcification of the valve and inflexibility that prevents adequate closure, there are other etiologic determinants. Some of these determinants may be collagen related diseases that produce degeneration of the annulus that supports the leaflets, rheumatoid disease or collagen vascular abnormalities. Incompetence of the valve may also occur as a result of loss of the commissural support from an aortic dissection or simply destruction of the valve leaflets due to infection, which occurs in bacterial endocarditis.

In untreated aortic insufficiency, the flow reversal of ejected blood back into the left ventricle increases the stress on the left ventricular chamber wall, which subsequently increases the internal diameter. At first the thickness of the ventricular chamber wall does not increase but as the pressure during systole gradually increases to normalize the stress on the ventricle, thickening of the chamber wall occurs. The left ventricle finally adapts to the increased volume demand by becoming thick and dilated. Although the effect of cardiac output remains approximately the same at rest, at about four to six litres per minute, the total cardiac output can reach as high as twenty litres per minute when there is good compensation for the aortic regurgitation. Eventually, however, fibrosis or scarring occurs within the myocardium and this produces a decrease in the compliance of the left ventricle. This is an important factor in determining the degree of reversibility of

the left ventricular dilatation following valve replacement.[18]

Patients who have no symptoms whatsoever are not recommended for aortic valve replacement even if the regurgitation is severe. This is because of the morbidity associated with anticoagulant therapy that is necessary for some valve substitutes or the relatively hastier degeneration of other types of valves. However, they should have normal ventricular function and a good exercise tolerance. When such patients have an ejection fraction that begins to decline by serial echocardiography or increase in the diastolic dimension of the left ventricular chamber in excess of 75 mm. or an end systolic dimension of 50 mm., they should then be considered for surgery. Surgery is also recommended if patients experience symptoms of congestive heart failure such as fatigue, shortness of breath or a decline in their exercise tolerance. It is quite likely in these cases that despite aortic valve replacement and good medical management, left ventricular dysfunction may not return to normal as a result of fibrosis. It may take up to three to four years for the regression of the left ventricular dilatation to occur. Much of the success from replacing the valve will depend on the pre-operative state of the left ventricular chamber.

2.1.9 Pathophysiology of Aortic Insufficiency

In order to meet the metabolic demands of the body, the cardiac output in the presence of a regurgitant valve adapts by increasing the stroke volume. The rate at which the insufficiency develops determines the physiologic response of the heart. When the size of the regurgitant jet varies between 0.5 to 1.0 cm^2 , blood volumes of up to 60 to 70% can be regurgitated back into the ventricular chamber[19]. Hence, the ejected volume must account for the normal outflow and the regurgitated blood. Over time, the left ventricle becomes enlarged and hypertrophied. This hypertrophy is eccentric as the increased wall thickness is proportionate to the increased diameter of the ventricle making the ratio between wall thickness and chamber radius approximately normal.

This is in contrast to the concentric hypertrophy that occurs in aortic stenosis where the wall thickness increases disproportionately to the radius of the chamber.

2.2 SURGICAL INTERVENTIONS

2.2.1 Cardiac Valve Substitutes and Their Characteristics

Although there have been major advances in the development of mechanical prosthetic and bioprosthetic heart valves, none of the commercially available devices are able to fulfill all the design characteristics sought in the ideal substitute. Mechanical prosthetic valves afford good hemodynamics and long-term durability but they require anticoagulation due to their thrombogenicity and this is often associated with anticoagulant related hemorrhage. Bioprosthetic valves do not require anticoagulation on a long-term basis as they are less thrombogenic but their durability is limited by structural degeneration, which is often seen in younger patients who have a greater metabolic rate. The ideal valve should decrease the work of the heart, function freely without any risk of structural failure for the duration of the patient's life, and should not produce destruction of any of the cellular elements of the blood or activate any protein systems.

2.2.2 Mechanical Valves

The three major categories of commercially available mechanical valves include the bi-leaflet, the tilting disc and the caged ball heart valves. They are frequently chosen for patients under the age of 65 years where the anticipated durability of the valve will be the determinate of the patient's longevity.[20] Patients without any history of increased bleeding tendencies or who are at lower risk of hemorrhage from trauma are generally selected. These patients, however, should be suitable from a geographic perspective with regards to the availability of accurate blood testing to ensure that the proper degree of

anticoagulation is maintained to prevent thromboembolic or hemorrhagic complications. As well, the patient should demonstrate a strong desire to stay compliant with the regimen necessary for accurate monitoring of the level of anticoagulation necessary in such valves. The low profile mechanical valves are suitable in patients that have a small aortic root or left ventricular chamber, which allows the device to function unimpeded by the surrounding soft tissues. Late deaths occur in such patients as a result of progressive heart failure, myocardial infarction, or rhythm disturbances due to the elevated outflow tract resistance to flow produced by the small root. These mechanical prostheses consist of an orifice through which blood flows, an occluder such as a disc or a ball and a structure to facilitate the opening and closing of this occluder to control the flow of blood.

In the caged ball valve, a ball that floats within a cage, which gives the structure a rather high profile, achieves occlusion. The tilting disc and bi-leaflet valves afford a lower profile as less space is occupied by the occlusion mechanisms in these two devices. It is the profile of the occluder mechanism that determines the degree of opening of the valve, the opening angle, the internal orifice, the overall size of the valve, and the degree of stenosis produced by the prosthesis. These in turn determine the amount of leakage regurgitation, which is the volume of blood regurgitated back across the prosthesis when the valve is attempting to occlude the backflow of blood. A small amount of regurgitation allows for backwashing of the valve to prevent the accumulation of micro-thrombi along the inner edges of the prosthesis. Surveillance echocardiography should be able to differentiate regurgitation associated with the normal motion of the occluding mechanism from peri-prosthetic leakages, which occur because of an inadequate seal between the sewing ring of the valve and the surrounding body tissues. As well, all mechanical valves produce some degree of destruction to the blood elements due to the abnormal flow characteristics associated with each valve shape and function. This hemolysis is usually sub-clinical in nature.[21]

Examples of commercially available mechanical substitutes are the mechanical bileaflet by St. Jude Medical Inc., Minneapolis, MN, the mechanical bileaflet by Sulzer

Carbomedics Inc., Austin, TX, the Edwards Tekna mechanical by Edwards Lifesciences LLC, Irvine, CA, the Bicarbon mechanical bileaflet by Sorin Biomedica, Saluggia, Italy, the Medtronic Hall tilting disc mechanical by Medtronics Inc., Minneapolis, MN, the Allcarbon monoleaflet by Sorin Biomedica, Saluggia, Italy, the Bjork-Shiley Monostrut mechanical by Shiley Inc., Irvine, CA, and the Omnicarbon mechanical prostheses by MedicalCV Inc., Inver Grove Heights, MN.

2.2.3 Bioprosthetic Heart Valves

There are five major types of valve substitutes that are composed of biologic tissue: glutaraldehyde-preserved porcine valves, bovine pericardial prostheses, stentless valves, homografts and pulmonary autografts. These valves are suitable for patients who are at an increased risk of hemorrhage associated with anticoagulation, for patients that are unable to have good monitoring of their anticoagulation levels, and young women who wish to become pregnant. The latter are unable to take oral anticoagulants due to the teratogenicity associated with these medications in pregnant women. These devices have a much lower incidence of thrombosis and generally do not require the use of long-term anticoagulation therapy. The major disadvantage with bioprosthetic heart valves is their limited long-term durability associated with structural degeneration, which is accelerated in younger patients. Structural degeneration is partly accelerated by the immune response of the recipient to the foreign biologic tissue.

2.2.4 Porcine Bioprosthetic Heart Valves

Porcine valves are treated with glutaraldehyde at a low pressure to maintain the pliability and leaflet structure and are then mounted on a cloth covered flexible wire or a plastic frame called a stent to maintain the occluding mechanism of the porcine leaflets. The flow characteristics and hemodynamic performance of these valves appear to be satisfactory in the aortic position when compared with mechanical valves of larger sizes

where there is also less sheer stress to the blood elements. In the aortic valve position, the smaller sizes (19 and 21 mm.) tend to be relatively stenotic producing some impedance to the outflow of blood from the left ventricular outflow tract.[22]

Examples include the Carpentier-Edwards Supra-annular porcine by Edwards Lifesciences LLC, Irvine, CA, the Hancock II porcine by Medtronics Inc., Minneapolis, MN, the Medtronic Intact porcine by Medtronics Inc., Minneapolis, MN, the Medtronic Mosaic porcine by Medtronics Inc., Minneapolis, MN, the Hancock modified orifice porcine by Medtronics Inc., Minneapolis, MN, the Biocor porcine by Biocor Industria e Pesquisas Ltd, Belo Horizonte, Brazil, the St. Jude Medical Bioimplant porcine by St. Jude Medical Inc., Minneapolis, MN, and the St. Jude X-Cell porcine bioprostheses by St. Jude Medical Inc., Minneapolis, MN.

2.2.5 Bovine Pericardial Heart Valves

This class of heart valve substitutes consists of stented valves where the leaflets are composed of pieces of the pericardium of bovine origin. The pericardium is the protective fibrous sac that surrounds the heart and parts of the origins of the great vessels in the chest. Several models made by a variety of manufacturers are available using similar engineering approaches. The three leaflets may be brought together either from three pieces of carefully cut pericardial tissue or from one strip. The orientation of the collagen fibres in the cusps is maintained by treatment with glutaraldehyde under conditions of zero pressure. A variety of chemical agents is used to treat the valve to inhibit calcium deposition, which results in loss of flexibility of the valve. The loss of flexibility can then lead to leaflet tearing resulting in stenosis or stiffness and fusion, which can produce stenosis in the long term.[23]

Examples of available pericardial substitutes are the Carpentier-Edwards Perimount pericardial by Edwards Lifesciences LLC, Irvine, CA, the Mitroflow pericardial by

Sulzer Carbomedics Inc., Austin, TX, and the Sorin Pericarbon pericardial bioprostheses by Sorin Biomedica, Saluggia, Italy.

2.2.6 Stentless Valves

Stentless porcine valves have been used for aortic valve replacement with increasing frequency over the past few years. The major benefit of these valves is their superior hemodynamic performance and low impedance to flow for any given size of valve. These valves are an attractive option for patients with a small aortic annulus that is commonly seen in patients with rheumatic aortic valve disease or non-bicuspid congenital aortic stenosis. Since mechanical heart valves and stented biologic valves have a fixed and rigid ring, they tend to be somewhat obstructive and in patients that require small prostheses residual high transvalvular gradients may exist. Persistent left ventricular hypertrophy as seen in patients with systemic hypertension has an adverse effect on long-term survival.

Examples of stentless porcine valves are the St. Jude Medical Toronto SPV stentless porcine, the Medtronic Freestyle stentless porcine, the Cryolife Bravo stentless porcine, the Baxter Prima stentless porcine, and the Biocor stentless porcine bioprostheses.

2.2.7 Homografts and Pulmonary Autografts

These two types of aortic valve substitutes are described only briefly for the sake of completeness, as they do not involve a significant part of this thesis. The mechanical characteristics of homografts are important as they produce superior hemodynamics and somewhat improved durability when compared to the above-mentioned devices. Homografts are obtained as part of the organ donation process under aseptic conditions and over the past decade only within hours after the death of the donor. A variety of preservation techniques involving antibiotics, cryopreservation and in some cases fresh

preservation within a nutrient medium are utilized. The storage time for those tissues treated with antibiotics may last from hours to days, with cryopreservation from months to years, and for fresh tissues for less than 72 hours. The pressure gradients measured in vivo after implantation are minimal and only slightly different from normal native aortic valves and are considerably better than those of the alternative devices noted above. Generally, these allografts are retrieved from heart beating cadavers that are deemed unsatisfactory cardiac donors but may have been satisfactory for other organ transplants. Generally, cadaveric hearts are currently used up to 12 hours after death. The limited availability of such donors has been the major drawback in the proliferation of this technique.

Pulmonary autografts, whereby the pulmonary artery and valve are substituted into the aortic position and a homograft is placed in the pulmonary position, have been used predominantly in children and adolescents since the valve autograft offers the potential for growth and continued adaptation to the patient's increasing size. These operations will not be discussed further in this thesis as the advantages of pulmonary autografts are not as pronounced in patients older than 40 years of age.

2.3 OUTCOMES

2.3.1 Survival

Survival refers to the proportion of patients that are alive after a period of time or interval often related to an event or intervention. A group of statistical procedures are involved in survival analysis to make inferences about the surgical intervention, associated risk factors and co-variates, and complications. Analysis of long-term survival is important for surgical trials as patients enter the study over a period with varying durations of follow-up. Hence, the full survival events during follow-up may be analyzed as time to specific dichotomous events such as death, stroke, hemorrhage and so on.

2.3.2 Late Mortality

To identify mortality related to delayed valvular dysfunction, one would need to exclude early mortality rates that are reported as either in-hospital or thirty-day mortality figures. These numbers tend to be reflective of operative factors such as patient selection, co-morbidities, operative complications, critical care complications, and issues unrelated to valve durability. Exclusion of such subjects that experience early morbidity or mortality events would attempt to control to some degree the extent of susceptibility bias. Beyond these factors, late mortality would be related to the natural mortality as a function of time and the impact of the surgical intervention on this function. This will be affected by variations in prosthetic function, the manufacturing process, and preservation techniques for such valves, and the immune reaction of patients implanted with prosthetic devices. Treatment of susceptibility bias would give more information about the long-term durability of bioprosthetic heart valves.

2.3.3 Thromboembolic and Hemorrhagic Complications

Thromboembolism is a condition that involves the formation of a solid mass comprised of the constituents of blood and its transmission downstream causing the sudden blockage of an artery. This is a complication associated with the presence of a foreign object such as a bioprosthetic valve within the blood stream. Data accumulated on the incidence of such events in patients over a course of time are related to the number of patients that have been followed and the number of years that they have been followed in this regard. This method of data gathering takes into account variations in the follow-up periods for different patients within a study. It then allows a comparison between studies of such event rates. Examples of thrombotic events include valve occlusion secondary to thrombosis, the development of thrombus on the valve leaflets and annulus, and fusion of valve leaflets related to thrombus. Strokes, kidney failure, and ischemia to the bowel and lower extremities are examples of embolic events where a clot has been proven as the cause of the ischemia.

Hemorrhagic complications that may also be measured in patient years may include external or internal bleeding and bruising related to the intake of anticoagulant therapy necessary for valve implants or rhythm disturbances.

2.3.4 Primary Tissue Valve Failure

Failure of the bioprosthetic valve to perform its function to the extent that surgical intervention is necessary can be documented as an event. A bioprosthetic valve may fail to function when it becomes stenotic in a fashion similar to what would occur with native heart valves. Destruction such as deformity or tearing of the prosthetic leaflets may lead to incompetence of the valve, progression or recurrence of symptoms, and subsequent surgical intervention. If the process of degeneration is very gradual, the patient may go on for years compensating for the inadequacies of the valve and may live on to an advanced age without the need for surgery. If the event is more acute with significant impairment of heart function, then the tissue valve failure may lead to fairly prompt surgery.

2.3.5 Bacterial Endocarditis

Endocarditis is an infection that initially involves the inner lining of the walls of the cardiac chambers known as endocardium or aortic root also known as endothelium. A bacteremia is the first of five components that are present in the propagation of the infection. Infections of an anal, urethral, or oral origin particularly related to instrumentation or endoscopy are often the initiating factor. Infected intravascular cannulas are another common etiology. Native valves that are abnormal in structure and function are prone to infection and this may be due to congenital, degenerative, inflammatory, traumatic, or autoimmune mediated changes.

This condition can occur as a complication of having a prosthetic valve succumbing to infection from an organism that may enter the blood stream from a variety of sources. Invasion by microorganisms may be early as part of the surgical procedure and manifest as an infection within the first few weeks. Monitoring devices implanted within the blood stream, such as catheters or electrodes because of surgery may serve as a portal of entry for bacteria. Infection may also occur later on as a result of a variety of endoscopic procedures or dental work. Due to the foreign nature of the materials used in the manufacture of prosthetic devices there is an elevated risk of these valves becoming infected or damaged by the bacteria. The third component related to initiating and developing infection is the turbulence of blood flow. This creates increases in the shear stress on the valve and surrounding tissues leading to activation and aggregation of platelets. These growths also accumulate bacteria leading to infected vegetations that may embolize, produce abscesses and lead to further valve damage. The ensuing infection is life threatening and requires treatment with antibiotics and/or surgery. Another feature important to the propagation of infection is the virulence of the infecting organism. While bacteremias from E. coli are common, infective endocarditis due to this organism is relatively infrequent due to its poor ability to cause platelet aggregation and inability to invade tissues. Finally, and important determinant of developing endocarditis is the immune status of the patient and ability to fight off infection. Cardiac procedures that utilize the heart-lung machine render the patient immunocompromised temporarily.

The incidence of this bacterial endocarditis as a complication of valve surgery should be measured in patient-years of follow-up.

2.3.6 Reoperation

Patients may undergo re-operative surgery for a variety of complications associated with valvular dysfunction. Re-replacement of the prosthesis does not always occur at re-operation after primary aortic valve replacement. Occasionally acute thrombectomy and simple re-suturing of the area of dehiscence may treat thrombosis and may successfully

treat a paravalvular leak associated with a bioprosthetic implant. Often, adjacent tissue ingrowth into the prosthetic ring is responsible for interference with the occlusion mechanism of mechanical substitutes. Fusion or tearing of the cusps in bioprosthetic substitutes may occur over a period of years. Prosthetic valve endocarditis induced degeneration producing a major central leakage or extensive paravalvular leakage generally requires re-replacement.

2.3.7 Structural Valve Degeneration

When valvular dysfunction occurs as the result of a breakdown in the materials that are used to manufacture the valve, the term structural valve degeneration is used. This may be an age related phenomenon of the valve that is caused by deposition of calcium, leaflet tearing, fusion, perforation, or breakdown in the struts and skirt of the valve. Non-structural valve degeneration is a condition that may necessitate re-operation for a paravalvular leak, encroachment on the normal valve leaflet function from pannus or scar formation or accumulation of thrombus surrounding the valve. It may also occur when other cardiac tissues either impair or impede the flow of blood across the valve.

2.3.8 Left Ventricular Mass Regression

As left ventricular enlargement develops due to hypertrophy from aortic valve disease there is an increase in the left ventricular mass and wall thickness, as well as in shape. The myocardial cell hypertrophy and increase in interstitial non-muscular tissue found in the pressure overloaded left ventricle of aortic stenosis is similar to that seen in the volume-overloaded ventricle of aortic insufficiency. When surgical intervention is appropriate and effective, there should be a regression in the left ventricular mass. This will occur if the rheology has been effectively returned to as close to normal as possible with the valve substitute. Echocardiography used pre-operatively and done at intervals post-operatively may be used to compare chamber dimensions and indirectly calculate

the extent of mass regression.[24] The degree of mass regression and the rate at which it is achieved is a good measure of the effect of treatment with surgical intervention. This may be correlated with survival.

2.3.9 New York Heart Association Classification of Heart Failure

The New York Heart Association (NYHA) system is used to document a patient's functional status and is based on symptoms of shortness of breath and fatigue.[25] These symptoms are a manifestation of clinical heart failure and the score assigned designates the presence and extent of these symptoms. The classification system is documented in Appendix A. Progression from Class I to Class IV implies worsening of symptoms while reversal implies improvement in symptomatology.

2.3.10 Canadian Cardiovascular Society Classification of Angina

The Canadian Cardiovascular Society has developed a classification of the severity of angina that is universally recognized. Angina is the term used to describe the clinical manifestations of inadequate coronary perfusion that creates a mismatch in the supply and demand of oxygen by the myocardium. The classification is documented in Appendix B. Progression from Class I to Class IV represents a worsening of the severity in symptoms. Improvement in a patient's symptom profile can be measured and compared to others in an objective fashion using this scale.

2.3.11 Effective Orifice Area

Effective orifice area (EOA) is the calculated area available for the passage of blood across the aortic valve prosthesis. There are variations between devices in the area available for the passage of blood. These variations may be related to the composition of

materials used, the width of the valvular skirt that is used to suture the valve in place, the position of the struts and how the leaflets are sewed on to the struts. In stentless valves, struts are not used which theoretically enables a larger effective orifice for the passage of blood. Hence, an efficient valve would require a relatively smaller aortic annulus but allow a relatively high proportion of blood to pass through due to the larger effective orifice area.

2.3.12 Regurgitation

Regurgitation refers to the presence of transvalvular leakage that may occur due to degeneration of the valve components or around the skirt of the valve.[26] Essentially blood travels in a retrograde fashion. Regurgitation may also occur in stentless valves due to improper implantation techniques. Adequate seating of an implanted prosthesis is a function of the difficulty of surgical exposure, technique, quality of tissues, extent of annular calcification, and presence of coexistent infection. Valvular regurgitation may occur early related to cusp tears, infection, distortion of the struts due to difficulty in seating the valve and manufacturing defects. Congestive heart failure occurs when the cardiac chambers fail to cope with volume overloading, leading to fatigue and shortness of breath.

Valvular regurgitation can be assessed visually by angiographic or echocardiographic studies. A grading system from I to IV (or mild to severe) has been used to describe the severity of regurgitation or valvular insufficiency both in the clinical setting of patient care as well as in scientific reporting.

2.4 CLINICAL TRIALS IN SURGERY

2.4.1 Introduction

A large body of knowledge has been developed through the management and from understanding the outcomes of heart disease in surgical trials and protocols. The vast majority of these studies have involved non-randomly assigned treatment groups. Specific exceptions where studies have been randomized are the Veterans' Administration (VA) study[27] of coronary artery bypass grafting, the coronary artery surgery study (CASS)[28] of coronary artery bypass grafting, and the European Cooperative Surgical Study (ECSS)[29] of surgical revascularization. The random assignment of patients to the two treatment groups allowed for similar prevalence of risk factors both known and unknown in these studies. There was also excellent follow-up evaluation of patients. Clinical studies with non-randomly assigned treatment add little to the body of knowledge when they are improperly designed, interpreted, or are uncontrolled for a variety of methodological biases. However, when such studies are performed with rigorous attention to methodology, they can provide a significant amount of reliable knowledge.[30] In fact, much of the information base for surgical trials and in particular, cardiac surgery would have to be abandoned if it was automatically assumed that a study that was not randomized was to be ignored. A poorly designed RCT will add little to our body of knowledge compared to a well constructed nonrandomized concurrent control design.[30,31,32] Since it is challenging to overcome the bias and confounding factors of non-randomized studies, it would be extremely beneficial to the field of cardiovascular surgery to identify and overcome the obstacles in designing and implementing a randomized control valve study. There is also a potential for significant patient heterogeneity when a variety of risk factors and co-morbidities associated with a particular cardiac condition are being evaluated. Stratification and subgroup analysis attempt to deal with these issues. The severity of the surgical illness will vary from patient to patient in terms of symptomatology and extent of pathology. These variables must be factored into the analysis. With a significant number of subsets, excessive

stratification will result in inadequate numbers of patients in each subgroup to produce a meaningful result. The major disadvantage of this is that the results of the study cannot be applied to a given patient that presents himself for surgical treatment. Hence, a clinical approach for this patient may not be derived from the available studies. Often, medical care must be individualized. Trials that address this issue by randomizing based on subsets or stratifying the data have subsequently reduced the power of the study and the resulting data, as is often the case with most techniques of stratification.[31]

When surgical studies are conducted on patients that are non-randomly assigned to a treatment group, one approach that has been used is to compare the patients assigned to the treatment group with a registry that contains a large number of patients with similar background or risk factors and characteristics.[33] In such a situation, multi-variable analyses may be performed with a hazard function regression model on the patients that are present in the registry. These may then be used to predict the now known outcomes of patients randomly assigned to the alternative treatment. Ideally the characteristics of the database should be well defined, but often this data is imprecise and not detailed because much of the information is obtained from the clinical record in a patient's chart. In outcomes research, the precision of the subsequent data is based solely on the gathered information from patient records and operative notes that constitute a database.

2.4.2 A Review of Obstacles in Conducting Surgical Trials

It is evident that there is a variety of obstacles that stand in the way of conducting well-designed, properly controlled surgical trials. Certainly, in the field of cardiac surgery, based on the author's experience, the major journals are mainly comprised of articles on case series and retrospective reviews of the surgical experience of an individual surgeon or group. Even large surgical experiences may produce results that cannot be applied to a given surgeon's practice or for that matter, these results may not guide the surgical decision-making involving a specific patient's care. This is often due to differences in patient characteristics, surgical techniques and resources available. Diversities in referral

patterns, regional variations in the incidence or diagnosis of disease, and inclusion or exclusion criteria in published studies make comparisons challenging. Although there has been a trend towards developing some degree of randomization, the majority of cardiac surgical scientific papers have been case series. The consecutive case series report has been the traditional method of recording cardiac surgical findings but the validity has only been addressed elsewhere.[34]

There are elemental differences between the characteristics of medical and surgical treatment. Medicines can be taken multiple times to treat a given condition. However, treatment of a disease condition by surgery usually involves a one-time operation although there are exceptions such as staged procedures for perforated bowel or gastrointestinal cancer. It is also difficult to obtain adequate follow-up in surgical trials as data is usually only accumulated prior to the patient's discharge from hospital or at one or two follow-up visits creating a rather short-term follow-up. Treatment visits are more easily tied with data recording visits in medically treated patients. Since ongoing therapy seen in medical trials is not present in surgical cases, it is more arduous to obtain follow-up data on a long-term basis unless it is specifically allocated as part of the study protocol. Hence, patients tend to get lost to follow-up resulting in a number of patient visits that cannot be standardized to any particular protocol. Medical trials on the other hand generally have clearly defined endpoints and follow-up appointments with associated specific testing planned as a part of these visits.

The endpoints chosen in the majority of medical trials are often clearly defined parameters related to death, composite end points, or a variety of physiological and or biochemical parameters. On the other hand, surgical trials tend to have endpoints related to a particular period for morbidity or mortality. In cardiac surgery, this may be the duration for structural valve degeneration and re-operation, freedom from thromboembolic or hemorrhagic complications and the interval for which these are measured, and loss to follow-up including death. Until the last few years, quality of life assessments following cardiac surgery were not well developed and morbidity events were the main factors used to follow such patients. The issues of morbidity and quality

of life in patients having undergone valvular heart surgery have become more distinct in terms of the long-term post-operative follow-up allowing a unique opportunity to assess bioprosthetic heart valves with respect to their impact on the quality of life of the recipients.

The outcomes in medical trials are often independent of the skills of the physician involved. In surgical studies, a procedure that may be commonly used by one surgeon may prove to be technically challenging for another surgeon due to a lack of expertise, thereby making it difficult to independently assess a particular technique or device. For example, in cardiac surgery implantation of stentless valves requires a certain degree of surgical expertise. The need for surgical experience perhaps makes this procedure operator dependent and produces results that are dependent on the volume of cases done by the surgeon.

A major stumbling block in establishing a randomized surgical trial is the creation of a control population and the ethics associated with this. Although more recently surgeons have begun to appreciate the importance of having a control population, the process of actually designing a suitable study is more complex. Sham operations are no longer considered an acceptable part of any surgical trial and are clearly unethical. Large banks of observational data have been used occasionally for control populations because some degree of matching of patient characteristics is possible.[35] Identifying specific subgroups with analysis of their characteristics may help identify certain significant features although this form of control is rather weak. Patients that turn down recommended surgical therapy can certainly be used as a 'no treatment' group but these patients are often distinctive in terms of their age or symptomatology that creates a systematic bias. An approach that has been used over the past ten years but is becoming less common is the comparison of new techniques or devices with other procedures performed about a decade ago. With the evolution of new techniques and a substantial decline in the morbidity and mortality associated with surgical therapy in general, a systematic bias is introduced that confounds the evaluation. In the past five years, more and more elderly and ill patients are undergoing cardiac surgery due to improved techniques and declining

morbidity and mortality as noted by internal audits at the author's centre. This makes it very difficult to compare the two patient populations from a perspective of time.

2.4.3 Summary List of Obstacles in Conducting Surgical Trials

An initial list of perceived obstacles has been created from personal observations, informal discussions with surgical research associates and the literature. These are summarized below.

1) Difficulty in obtaining two or more comparative groups of patients for assessment in a surgical study.
2) Inability to create a control population that is subjected to a sham surgical procedure.
3) Specific skills and qualifications for the surgeon or the group that actually performs the procedure are not standardized. This is further complicated by variations in experience, skills and techniques applied by other members of the surgical group including Anesthesia, Nursing, and Critical Care.
4) Using a specific surgeon or anaesthetist compared with using a group to treat the experimental arm of the study. An associated obstacle involves a surgeon performing a particular procedure out of preference or special aptitude for this technique.
5) Difficulty in blinding the surgeon and the patient.
6) Bias created by preferential use of one procedure over another based on a surgeon's experience, skill, or bias towards a particular procedure.
7) Failure to recruit an adequate sample size for the treatment arm of the study.
8) When a control group is possible, it needs to be clearly addressed as either a group of patients that are representative and similar to those that undergo surgery or they may be a completely healthy group of patients.

9) The surgeon's inadequate knowledge of study design protocols and inability in conducting controlled clinical trials is an important factor in determining how studies are conducted.

10) Insufficient source of funding may interfere with initiating good clinical trials with bias involvement when a proprietor supports a particular device being implanted and studied.

11) Advances in surgical techniques with changing standards over time as well as increasing complexity of patients found acceptable for undergoing surgical procedures confound complication rates.

The above list is not intended to be comprehensive. It is made up of factors that the author has collated through his own experience and that of surgical associates.

CHAPTER 3

METHODS

3.1 SYSTEMATIC REVIEW OF BIOPROSTHETIC VALVES

3.1.1 Objectives

The overall aim of this review was to perform a systematic search of the health care literature in order to gather randomized controlled trials, controlled clinical trials, non-randomized studies, and large case series that evaluated the relationship between the choice of bioprosthetic valve substitute and the mortality and morbidity of adult patients undergoing aortic valve surgery. The objectives were:

1) To assemble a comprehensive list of all published clinical studies based on electronic and manual search strategies;
2) To rank the level of evidence provided by these studies based on the methodological quality;
3) To summarize the general state of information currently available on the management of aortic valve disease in adults using bioprosthetic valves;
4) To formulate hypotheses regarding the obstacles encountered in conducting such research to guide the development of the second and third components of this thesis;
5) To identify factors that facilitate the design and implementation of surgical study protocols that examine bioprosthetic heart valves as delineated in the third part of this thesis.

3.1.2 Search Strategy

A combined electronic and manual search strategy was used consisting of the following avenues.

1) A systematic search of Medline (a computer-based, biomedical database developed and maintained by the United States National Library of Medicine) from 1966 to July 2004 using the Medical Subject Headings (MeSH) and text words (tw) listed in Appendix C. The search strategy was formulated by the information specialist based on guidelines developed by the reviewer. The search was then executed by the information specialist and updated by the reviewer.
2) A systematic search of CURRENT CONTENTS (a multi-disciplinary summary of current issues of journals formatted in a computer accessible table of contents) from week twenty-seven of 2000 to week number fifteen of 2004 using the search strategy described below. The strategy was confined to the English literature only and was set up and executed by the reviewer.
3) A search using Ad Referendum was executed by the reviewer to identify any major European publications that would have been omitted in the Medline search. Ad Referendum is a major pharmaceutical database provided by Searle with a strong emphasis on European publications.
4) A manual search of the reference lists of identified citations, texts, and related articles such as reviews, editorials, commentaries, letters and commercial monograms.
5) Written or telephone contact of content experts and authors for assistance in obtaining additional randomized controlled trials especially those that were not published.
6) A hand search of the most commonly subscribed cardiac surgical journals noted previously.

7) An EMBASE search was introduced as a strategy to complement the MEDLINE search. EMBASE is a computer based version of EXCERPTA MEDICA which is a European database consisting of health science literature with significant overlap with Medline. It was unclear whether the EMBASE search would be found to be complementary to the MEDLINE findings.
8) Certain literary pieces were subsequently retrieved through manual and bibliographic searches, personal communications, and interactions with representatives from the medical technology industries. These included research reports, product monograms, Cardiac Care Network statistical summaries and policy papers as well as abstracts from conferences and presentations. All of these would be considered to fulfill content criteria but possibly not methodological criteria.

The computer search strategy for the systematic review of bioprosthetic valves is provided in Appendix C.

3.1.3 Selection of Trials

A preliminary review of the literature suggested that predominantly non-randomized, unblinded studies have been conducted in this area of the health sciences. Using the search strategies described above, a collection of potentially relevant articles was obtained and then assessed independently by two reviewers using a predetermined screening format. Based on the inclusion and exclusion criteria, inter-observer agreement was assessed and the differences were resolved by consensus as well as through discussion with the thesis supervisor. Priority was given to prospective and retrospective concurrent cohort studies that evaluated bioprosthetic valve substitutes in terms of morbidity and mortality as well as hemodynamic performance of the prosthesis. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis was implemented. The two independent reviewers would use a Kappa coefficient of agreement to assess the variance in assessment. Before and after cohort studies were to be entertained in this systematic review.

3.1.4 Eligibility - Inclusion Criteria

Studies that were evaluated in the systematic review were retrieved electronically as well as through manual search strategies. The four general criteria of population, intervention, outcomes and study design were applied. The population that was studied was over the age of 18 years suffering from aortic valve disease. Surgical treatment for aortic valve stenosis and insufficiency disease in adult humans over the age of eighteen years was the subject matter sought after in these papers. Animal studies were excluded irrespective of the study design. The intervention of interest was surgical replacement of the aortic valve with a bioprosthetic substitute. All outcomes were included in the initial search and included mortality, morbidity, complications and clinical as well as diagnostic evaluations of response to therapy. Study designs included comparative work such as randomized controlled trials, controlled clinical trials, case-control studies, and cohort studies.

3.1.5 Eligibility - Exclusion Criteria

Studies were excluded based on their content or for methodological reasons. The former were:

(a) Studies where the data for aortic valve surgery was combined with other valvular procedures or where the data predominantly involved follow-up of other types of open heart procedures with inclusion of key words associated with aortic valve surgery that would have resulted in retrieval of such unrelated studies;

(b) Research papers where aortic valve replacement was part of a new or controversial procedure. Operations such as minimally invasive surgery and the pulmonary autografts (Ross Operation) were considered examples in this situation.

(c) Papers where highly selective study groups were used such as studies involving exclusively pregnant women, patients with infective endocarditis, or a cohort of patients greater than eighty years of age.

(d) Research papers involving other kinds of aortic valve substitutes, such as homografts and autograft procedures. These papers clearly represent a different hemodynamic situation and operative technique.

(e) Research papers involving modifications or variations of a standard aortic valve replacement such as aortic root enlargement procedures, root replacements, or autologous pericardial valve reconstructions. The rationale for such exclusions was based on two factors. Firstly, the pathology, surgical techniques, morbidity, mortality and long-term impact extended far beyond that for standard aortic valve replacement. Secondly, the thesis sought to develop a strategy for comparing commercially available heart valve substitutes in an objective and unbiased manner.

3.1.6 Information Extraction

Each article initially deemed eligible from the electronic library retrieval and hand search, was subjected to data extraction. This was done in an unblinded fashion and tabulated in a predetermined form. Clinical characteristics, results, conclusions, methodological details, and comments were extracted. The data extraction form used for cohort studies is provided in Appendix D. Guidelines for the performance of systematic reviews were used to elicit the pertinent data.[36,37,38,39] Details were extracted in an unbiased and reproducible fashion. Where quantitative data was not available, a detailed qualitative description was recorded. The original authors were contacted whenever any clarification was needed.

3.1.7 Quality Assessment of Study Methodology

In order to develop a meta-analysis from this systematic review, studies that were chosen from the literature search were to be submitted to a quality assessment of the methodology employed using the Newcastle Ottawa Scale (NOS). The NOS has been developed to assess methodological quality for cohort studies. The scale is provided in Appendix E.

The scale awarded points for study design based on subject selection, comparability, and outcome assessment in cohort studies. For cohort studies, points were awarded for representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at commencement of the study. In order to assess comparability of these studies, points were awarded based on design or analysis for the groups involved. The category of outcomes was awarded points based on the method of outcomes assessment, adequacy of long-term follow-up for outcomes, and the proficiency in cohort follow-up.

For randomized control trials, the Jadad Scoring System was used. The Jadad Scale, which is provided in Appendix F, assesses the quality of the randomization, blinding, and patient withdrawals from the study.

3.1.8 Data Analysis

Data from the chosen studies was to be analyzed using a random-effects model. The formulas developed by DerSimonian and Laird were to be used for summarizing studies in which the effects were measured as odds ratios with a formula prescribed as follows:

Software packages such as RevMan 3.0 (by Review Manager (RevMan) [Computer program] version 4.1 for Windows, Oxford, England: The Cochrane Collaboration, 2000) that have been developed for meta-analytical calculations, could only be used for

randomized control trials and not for case control or cohort studies. Hence, summary measures and critical values for Chi-Square tests of significance were to be computed using Microsoft Excel (by Microsoft Inc., Redmond, WA) with calculations based on the random effects model formulas developed by Fleiss.

$$\ln OR_{dl} = \frac{\sum_i (w_i^* \ln OR_i)}{\sum_i w_i^*}$$

where OR_{dl} is the DerSimonian-Laird summary estimate of the odds ratio, w_i^* is the DerSimonian-Laird weighting factor for the i^{th} study, and OR_i is the odds ratio from the i^{th} study.

The weighting factors w_i^* were to be estimated as

$$w_i^* = 1/ [D + (1/ w_i)]$$

where $w_i = 1/ \text{variance}_i$

The variance_i for each study utilized the Mantel-Haenszel method and

$$D = \frac{[Q - (S-1)] \sum_i w_i}{[(\sum_i w_i)^2 - \sum_i (w_i^2)]}$$

where S was the number of studies and

$$Q = \sum w_i (ln\ OR_i - ln\ OR_{mh})$$

The Mantel-Haenszel method was used for the odds ratio calculation and the OR_i were the odds ratios from the *i*th study.

A test of homogeneity was conducted to ensure that the studies to be combined for meta-analysis were similar with respect to outcomes and that observed variations were attributed to sampling. A chi-squared test of homogeneity would be used for the reported proportions. If the calculated chi-squared value was significant, then subgroup and sensitivity analyses would be then be conducted.

3.1.9 Sensitivity and Subgroup Analysis

A sensitivity analysis was intended to test how robust the conclusions were, based on the statistical assumptions made during the review. Looking at the presence or absence of the study in the statistical calculations and its impact on the summary estimate would assess uncertainty regarding study inclusion in the analysis.

In order to determine the impact the year of publication would have on the summary estimate, a cumulative meta-analysis would be conducted by adding studies single file into the calculations starting from the earliest year and proceeding to the present. The same approach would be used to evaluate trends in valve implantation techniques, perioperative techniques, and other time-related advances that could affect the outcomes of the study assessment. The cumulative meta-analysis technique for sensitivity would enable determination of study quality. Studies would be entered sequentially starting with those that were well designed and ending with less well-designed investigations.

In order to conduct a sensitivity analysis, the odds ratio or relative ratio would be entered in the analysis as the first summary estimate. Combining the summary estimate of the first and second studies would then be entered in the next study. A summary estimate that did not fluctuate would imply robustness across papers of different quality, or different eras.

3.1.10 Publication Bias

Publication bias refers to the tendency of journal editors and book authors to publish articles that report innovative results or positive conclusions, particularly if they refute previous work. Studies conducted in the fields of psychology and education[39] found bias to be related to the pressures of publishing journals that were both interesting and progressive. Publication bias is of great concern in data synthesis that involves systematic reviews and meta-analyses because it may skew the results in a negative fashion. This form of research may yield invalid or incorrect conclusions because of unchecked bias. This phenomenon is confirmed by meta-analytic conclusions that are subsequently overturned by well-designed trials. Statistical methods that deal with bias need to address the language of publication, preferential choice of journal for publication, positive studies, studies that contrast good and bad devices, identification of an adversely functioning device compared to another, and unclearly sponsored studies. These are issues of great importance in the cardiac surgical literature.

The funnel plot was to be used if successful at performing a meta-analysis to appraise the presence of bias. Treatment effects such as morbidity and mortality incidence would be plotted on the X-axis and study precision measured on the Y-axis. The funnel plot would endeavour to identify bias towards small treatment effects in the meta-analysis. Sample size or log sample size would be plotted on the vertical axis and ratio measures of effects on the horizontal axis. The resulting plot would take the shape of an inverted funnel.

3.2 REVIEW OF OBSTACLES IN CONDUCTING CARDIAC SURGICAL TRIALS

3.2.1 Objectives

A survey was conducted in a systematic fashion on representative journals to identify articles that raised issues on the obstacles of conducting cardiac surgical trials. The objectives of this systematic review were:

1) To identify the experiences of cardiac surgical researchers and to report their difficulties in executing surgical studies.
2) To document any steps taken by the researchers to avoid or to overcome these obstacles.
3) To obtain documentation in the form of an overview of the methodology and study designs currently used in published surgical trials.
4) To determine how obstacles encountered affect surgeons' subsequent choice of study design.

3.2.2 Search Strategy

The Journal of Thoracic and Cardiovascular Surgery and the Annals of Thoracic Surgery were the journals of choice for this survey. The search involved a one-year duration of publications utilizing a detailed hand search. These two journals are peer reviewed and were chosen for the following reasons:

(a) they are generally considered as main sources of publications in thoracic and cardiovascular surgery and they have the widest subscription of any journal in this particular field.
(b) they are published in English but receive articles submitted by authors from all countries performing tertiary care cardiovascular surgery.
(c) these publications date back to the commencement of cardiovascular surgery.
(d) the journals encompass a variety of study designs, commentaries, editorials, and literature reviews submitted by surgeons and other professionals in Cardiovascular Medicine, Pathology, Science, and Surgery.

Although clinical surgery trials may be published in other journals such as Family Medicine, Nursing, Science, and Epidemiology, the likelihood of this in such a highly specialized field as cardiac surgery would be minimal. The journal reviews in this case were restricted to focus on the potential obstacles of conducting surgical trials. They would also give a general impression of the studies submitted and accepted in peer-reviewed surgical journals. A one-year span of journal publication was deemed as an adequate snapshot for the investigation as sufficient papers were found.

3.2.3 Eligibility Criteria

Articles were included using the following criteria:

(a) the study was a clinically based, original surgical study published in one of the two selected journals;

(b) the article was published in English in one of the two selected journals;

(c) the article included patients who had undergone valvular heart surgery to receive any kind of prosthetic device whether it was mechanical or bioprosthetic; and

(d) the participants, methodology, outcomes and origin of the study were reported.

Although the selection criteria used for reviewing the articles was developed after an initial survey, the criteria were made explicit prior to actual retrieval of the articles. Retrospective, prospective studies and case series were included in anticipation of less than ideal study design, reporting and sample size.

Articles were excluded if:

(a) the study population was less than ten patients;

(b) the intervention did not involve any valve replacements;

(c) it was a pathologic review without any outcomes analysis; or

(d) the study population was a selected group of individuals with specific characteristics that were not generalizable.

3.2.4 Selection and Data Extraction Process

An unblinded individual, that is, the thesis candidate, conducted the review of the two clinical journals. The aim of the survey was to identify authors' concerns with regard to obstacles encountered in conducting such studies. Since the inclusion criteria were specific and the aim of the review was to identify the obstacles, blinding was not used in this survey.

The eligibility criteria were applied to all articles published in the years 2001 to 2002 in these two journals. During the article selection process if any concern arose due to uncertainty about the eligibility of a paper, it was reviewed with the thesis supervisor to arrive at a decision by consensus. The author, date of publication and location of origin were then used to identify the articles. Articles that were not accepted were not documented, as they did not contribute to the endpoint of this thesis section. For example, papers with less than ten patients were excluded as case series and case reports based on the same criteria documented previously in the thesis.

Following article selection, information was tabulated according to location and identification of the study author and the centre of origin, participants and types of operations performed. The methodology specifically examined included study design and purpose, outcomes, and discussions of obstacles encountered by the investigators. In addition, obstacles that may have not been reported but were obviously based on the study design were also recorded. If any obstacle was recorded, then the details relating to this obstacle was also documented. The information was then recorded in an analog data base format.

3.2.5 Data Analysis

The following items were enumerated, tabulated and described by the review of the two journals: Articles selected, author and date of publication, location, study groups, patient

populations, patient demographics, methodology, inclusion and exclusion criteria, method of randomization if any, outcomes and length of follow-up, complications, and obstacles. Information regarding financial sources and material contributions were documented separately and whether indeed they were disclosed.

Summary statistics were reported when appropriate. A narrative approach was used to describe obstacles encountered by the investigators. Conclusions were made from summaries of the appropriate studies. Although it was not anticipated that specific reasons would be given for the choice of study design in the majority of surgical papers, the reasons were recorded when documented in the articles (Appendix M).

3.2.6 Information Extraction

A single reviewer, that is, the student, subjected each article initially deemed eligible from the hand search to data extraction. This was done in an unblinded fashion and tabulated in a predetermined format. Clinical characteristics, results, conclusions, methodological details, and comments were abstracted. As for the first part of the thesis, guidelines for the performance of systematic reviews were used to elicit the pertinent data.[36,37,38,39] Details were extracted in an unbiased and reproducible fashion. Where quantitative data were not available, a detailed qualitative description was recorded. The extraction focussed on the difficulties encountered in proceeding with these studies. The hand search took advantage of any issues presenting as obstacles in studies not included in the selected list.

3.3 DESIGN OF A SURGICAL TRIAL: COMPARING TWO BIOPROSTHETIC HEART VALVES

3.3.1 Clinical Trial Guidelines

The guidelines for completing a full research proposal have been clearly set up by the Canadian Institutes of Health Research (CIHR). The information necessary for peer review has been subdivided into sections including the need for a trial, the proposed trial, trial management, and more specific issues related to health economics, quality of life, age, consumer and industrial involvement, and international collaboration.

The CIHR guidelines (www.cihr.ca) require a brief summary of answers to questions regarding the study design. These guidelines are based on the United Kingdom Medical Research Council (MRC) guidelines for grant proposals. The list includes: proposed trial design, planned control and experimental interventions, allocation of participants to the study groups, methods such as blinding or masking to protect against sources of bias, inclusion and exclusion criteria, proposed duration of treatment period, proposed frequency and duration of follow-up, proposed primary and secondary outcome measures, outcome measures assessed at follow-up, sample size, recruitment rate, assessment of compliance problems, rate of loss to follow-up, planned analyses, economic issues, and cost and duration of the trial.

3.3.2 Applying the Guidelines for Surgical Trials

From the background survey of the literature and the summary list of obstacles in conducting surgical trials, certain features that are unique to surgical trials need to be highlighted as key features in such a study. Issues such as surgical practice variation, difficulty in obtaining two or more comparative groups of patients, inability to create a control or sham population, difficulty in blinding the procedure, systematic bias from the preferential use of one procedure over another based on a surgeon's experience or skill, inadequate sample sizes, insufficient funding, and heterogeneity need to be accounted for

upon completion of the systematic review of bioprosthetic valves. This would also include an analysis of the data from a study by study comparison and a review of obstacles in conducting cardiac surgical trials. Doing this would achieve a better understanding of how to develop a surgical trial that overcomes as many of these pitfalls as possible. Development of the guidelines for design of a surgical trial will come from an understanding of the obstacles encountered and reported by surgeons that have published recent studies in major cardiac surgical journals, a systematic review of bioprosthetic valves, and the preliminary list of obstacles identified from the literature.

CHAPTER 4

RESULTS

4.1 SYSTEMATIC REVIEW OF BIOPROSTHETIC VALVES

4.1.1 Search Results

From the initial computer search, a total of 646 articles were found and a review of their abstracts was conducted to evaluate which studies to include. A summary of the article selection for the systematic review is provided in Appendix G. The articles were classified according to: a) randomized controlled trial, b) case control trial, c) cohort study, d) case series, e) case reports and editorials, and f) other (for example, product monographs, commentaries, economic evaluations, and policy papers). Some studies were eliminated due to the irrelevant purpose or type of study. A key word in the computer search may have retrieved an inappropriate topic and hence, policy papers, commentaries, industry sponsored monographs and economic evaluations would have found themselves in this category. A total of 173 articles were eliminated because they did not fit the criteria or the design of interest to this thesis. Several of the involved articles were related to coronary artery pathology or other valvular heart disease. Specifically, they included case reports, commentaries, editorial opinions and reviews. Some of these related to medico-legal, ethical, or epidemiologic concerns. Examples of unsuitable subject material included a) Brucella endocarditis, b) Marfan's syndrome, c) allografts, d) Ross procedure, e) tricuspid valve replacement, f) mitral valve replacement, g) studies examining valve safety, h) endocarditis, i) autologous tissue valves, j) unusual operative techniques, k) industrial monograms.

A further 309 articles were case series that were eliminated from further analysis. All of

the case series were removed from the analysis regardless of the number of patients that were followed. Of the remaining 164 articles, there were 67 studies that were of a cohort design comparing one group with at least another group. An additional nine studies that were labeled as case control did not fit the definition on closer examination and were actually identified as cohort studies. Hence, a total of 76 articles were of a cohort design. From this group, 54 articles were removed as they did not fit the definitions of the correct population of interest, intervention, outcomes, or because of incorrect design. Within these, 22 studies were submitted to close analysis. Examples of unsuitable matter included: a) prevention of thromboembolism, b) balloon dilatation of heart valves, c) valve studies involving young children, d) effects of pregnancy, e) allograft comparison, f) bioprosthetic versus mechanical valve studies, g) valve replacement versus valve preservation studies, h) comparisons of anticoagulation protocols, i) outcome studies in pregnancy. There were 31 studies that were excluded following close scrutiny and these have been documented in Appendix H.

As previously noted, case control studies were also identified from the master list of abstracts. Nine studies were classified in this category and eliminated. The nine studies were eliminated for several reasons in addition to being incorrectly designated as case control studies. Examples of reasons for their exclusion from further analysis were (a) minimally invasive versus conventional operative approach, (b) mitral valve replacement, (c) stented versus stentless valves, (d) mechanical valve, (e) Ross operation.

There were five randomized clinical controlled trials that were identified but two had to be excluded due to the subject material of the study. These were studies involving homografts and regression of left ventricular hypertrophy. After categorizing the studies based on their study methodology, they were then classified according to the type of aortic valve prosthesis used. The studies selected at this point were drawn from the RCT studies, the case-control studies, and the cohort studies. At the beginning of the literature review, the primary objective was to analyse papers that focussed on stented aortic valve prosthetic devices. However, the review was intended to be as comprehensive as possible to increase the generalizability of the findings and hence studies that used a

cohort of stentless aortic valve prosthetics were included as well.

The initial impression was that there were no comparative studies whatsoever and an arbitrary cut-off of ten cases or less was to be used to exclude case series. After extracting some comparative studies, it became evident that all case series could be excluded. The inclusion of comparative studies was initiated once at least 10 suitable studies were identified. It should be noted that 31 studies comparing mechanical versus bioprosthetic valve substitutes were excluded. These studies are detailed in Appendix H along with the reason for exclusion. Another ten studies involving comparison between stented and stentless valves were also identified and excluded. There were eight studies that involved the comparison of two different types of stentless valves and these were also excluded. Bioprosthetic valves were compared with homografts in four studies that were removed from the evaluation and there were another seven studies that involved a comparison between a particular stented valve versus homografts that were eliminated from further review.

Thirty studies were chosen for further consideration. Four were lost to language barriers. One was a commentary. One focussed on explanted valves. Another was lost due to the nature of the operative procedure and the prosthetic devices used. One paper was submitted to two different journals using a different title. Other miscellaneous studies that were excluded were unrelated to the specific topic of interest but were picked up by the initial literature search based on the inclusion of key words. Several of them were laboratory studies without any clinical data.

A total of 23 comparative papers, documented Appendix I, involved an evaluation between two different stented valves. These papers were then retrieved for the assessment as part of the included studies. From the remainder of studies that were excluded, most of these were unrelated to the specified topic of interest but were chosen by the initial literature search based on the inclusion of key words. Several of them were laboratory studies without any clinical data.

4.1.2 Description of Included Studies

The entire 23 full papers were selected for inclusion in this review. The data extracted from these papers were tabulated into eight categories, namely: study design, subject characteristics, study characteristics, study methodology, follow-up assessment times, results at follow-up assessment times, outcomes assessed, and specific outcomes (Table 4.1 to 4.8).

The studies included ranged in date of publication from 1986 to 2003. The majority were conducted and published between 1996 and 1999. A variety of comparative study designs was used. Three papers reported prospective randomized studies.[41,61,62] The first study by Bloomfield[41] was composed of three study groups, one group used a mechanical valve and the other two groups had bioprosthetic substitutes from two different manufacturers. The other two papers were randomized controlled studies comparing stentless valves with conventional stented valves. The remaining studies did not use or indicate randomization. Most investigators collected their data prospectively. There were seven prospective cohort studies, some specifically stating that the cohorts were not randomized and others making no mention of the presence or absence of randomization. In addition, there was one prospective randomized cohort study by F. Santini (1998) that compared one type of stented valve and a second group consisting of both stentless and another type of stented valve.[59] It was included in the list of analyzed papers. Of the remaining studies, some were retrospective cohort studies, others were conducted in a prospective fashion while yet others made no mention of the method of data extraction. A study by Del Rizzo (1998) used non-concurrent cohorts and a comparison was made with prospectively collected data.[44] Among the retrospective cohort studies, one study design used by J. Dumesnil (1998) compared a retrospective cohort and an external control group where data was obtained from previously published studies.[46]

Examining the sample size column in Table 4.1, it is apparent that there were many relatively small studies, using between 10 and 50 patients per group. There were no

Table 4.1: Design of Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 - 2004			
Study	***Study Groups***	***Sample Size (Total)***	***Design Type***
M. Achtelik, et al., 1996	Group 1: Biocor stentless prosthesis	22	Retrospective Cohort
	Group 2: Hancock porcine valve combined with aortic root enlargement	10 (published data)	
P. Bloomfield, et al., 1986	Group 1: Bjork-Shiley mechanical	273	Randomized
	Group 2: Hancock	107	
	Group 3: Carpentier-Edwards	160	
R. Casabona, et al., 1992	Group 1: Stentless porcine	27	Prospective Cohort
	Group 2: Stentless pericardial	30	
	Group 3: Stented porcine	30	
	Group 4: Mechanical	30	
T. David, et al., 1998	Group 1: Custom-made Stentless	29	Prospective Cohort
	Group 2: Toronto SPV	213	
D. Del Rizzo, et al., 1998	Group 1: Medtronic Freestyle	849	Prospective Non-concurrent Cohort
	Group 2: Toronto SPV	263	
R. De Paulis, et al., 1998	Group 1: Stentless valve	10	Retrospective Cohort, followed Prospectively, Internal Cohorts
	Group 2: Stented valve	10	
	Group 3: Bileaflet mechanical valve	10	
J. Dumesnil, et al., 1998	Group 1: Freestyle stentless bioprosthesis	157 (79 used for comparison)	Retrospective Cohort with External Control group data obtained from previously published studies
	Group 2: Stented bioprosthesis	79 stented at 20 months & 78 stented at 12 months	
W. Eichinger, et al., 1998	Group 1: Mosaic bioprosthesis Group 2: Hancock Modified Orifice II	55	Retrospective Cohort with Internal Cohorts
	Group 2: Hancock Modified Orifice II	52	
B. Goldman, et al., 1988	Group 1: Ionescu-Shiley	320 (41 combined)	Retrospective Cohort with Internal Cohorts
	Group 2: Hancock	81 (7 combined)	
R. Houel, et al., 1999	Group 1: Carpentier-Edwards Perimount bioprosthesis	94	Retrospective Cohort with Internal Cohorts
	Group 2: Mitroflow pericardial bioprosthesis	118	
W.R. Jamieson, et al., 1999	Group 1: Carpentier-Edwards	567	Retrospective Internal Cohort
	Group 2: Supra-annular bioprosthesis	1670	
Y. Kobayashi, et al., 1998	Group 1: Carpentier-Edwards bioprosthesis	30 (4 combined)	Retrospective Cohort
	Group 2: Ionescu-Shiley	40 (15 combined)	
J. Legare, et al., 1998	Group 1: St. Jude SPV	69	Prospective Cohort
	Group 2: Medtronic Freestyle	43	
C. Mullany, et al., 1994	Group 1: Intact Porcine bioprosthesis	89	Prospective Cohort
	Group 2: Carpentier-Edwards porcine bioprosthesis	130	
F. Nistal, et al., 1986	Group 1: Hancock	221	Retrospective Cohort, Internal Cohort
	Group 2: Ionescu-Shiley	133	
J. Oury, et al., 1998	Group 1: Hancock I	119	Retrospective Cohort
	Group 2: Hancock II	104	

Table 4.1: Design of Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 - 2004			
Study	***Study Groups***	***Sample Size***	***Design Type***
L. Pelletier, et al., 1989	Group 1:Carpentier-Edwards bioprosthesis	878	Retrospective Cohort, followed prospectively, Internal Cohorts
	Group 2: Pericardial bioprosthesis (3 different models)	715	
D. Pupello, et al., 2001	Group 1: Medtronic Intact	(includes aortic, mitral, tricuspid and pulmonic positions) 64	Retrospective Cohort with Internal Cohorts
	Group 2: Carpentier-Edwards	1428	
	Group 3: Medtronic Hancock	448	
	Group 4: Medtronic Hancock Modified Orifice	270	
R. Riley, et al., 2000	Group 1: Freestyle stentless bioprosthesis	44	Prospective Cohort
	Group 2: Toronto SPV	14	
F. Santini, et al., 1998	Group 1: Hancock II	40	Prospective Randomized Cohort
	Group 2: Toronto SPV or Biocor stentless	37 (17 Biocor, 20 Toronto SPV)	
G. Van Nooten, et al., 1999	Group 1: Toronto SPV	103	Retrospective Non-randomized with Internal Cohorts
	Group 2: Carpentier-Edwards supra-annular porcine	51	
T. Walther, et al., 1999	Group 1: Stentless aortic valve	106	Randomized Control Study
	Group 2: Conventional stented valve	74	
R. Williams, et al, 1999	Group 1: Carpentier-Edwards	19	Randomized Control Study
	Group 2: Toronto SPV	20	

sample size justifications done for any of these studies. The studies by Del Rizzo (1998), Jamieson (1999) and Pupello (2001) had substantial differences in the number of patients between groups.[44,50,57] On the other hand, the studies by R. Casabona (1992) and R. De Paulis (1998) and Williams (1999) had equal numbers of patients divided into all groups examined.[42,45,62] In Casabona's study, there was an additional group with fewer patients (27) compared to 30 which they chose to use in order to study the stentless porcine valve.

In Table 4.2, subject characteristics were documented in detail using data extracted from the retrieved articles. Substantial differences in the mean age of patients were identified with Nistal's study (1986) having a mean age of 38 and 39 years for each of the two groups in this study compared with Santini (1998) where the mean age of cohorts were 77 and 76 years, respectively.[54,59] The mean ages of patients admitted to other study groups ranged between the fifth and seventh decades of life. Although in more recently conducted research, patients tend to be older as age is no longer considered a barrier to operative intervention. The studies by Kobayashi (1998) and Oury (1998) showed that even as recently as 1998 relatively younger cohorts of patients were admitted into these studies.[51,55]

The gender ratio of the included studies did not demonstrate any particular pattern. While aortic valve disease and aortic valve surgery generally do not favour one gender over the other, it is interesting to note that some studies had many more women and others had far more men. An example of the former would be the study by Eichinger (1998) with more women being included in both arms of the study, while examples of the latter would include the studies by Bloomfield (1986) and David (1998).[41,43,47] One could speculate that in the latter study, the stentless valve is technically more challenging to implant. Therefore, it would require a larger annulus and hence David (1998) would have used this more in men and less frequently in women who have a much smaller aortic annulus.

Table 4.2: Characteristics of Subjects in Comparative Studies of Bioprosthetic Valves – Systematic Review 1986 -2004

Study	*Group*	Mean Age	Gender M/F	NYHA Class Before Surgery I, II, III, IV	NYHA Class Post Surgery I, II, III, IV
M. Achtelik, et al., 1996	Group 1: Biocor	63.9	8/14	III or IV: 22	I or II: 22
	Group 2: Root Enlargement	Not Stated	Not Stated	Not Stated	Not Stated
P. Bloomfield, et al., 1986	Group 1: Mechanical Group 2: Hancock & CE	<50: 29.5% 50-65: 53.3% >65: 17.1%	150/60	I & II: 111 III & IV: 99	Mean: 1.53
R. Casabona, et al., 1992	Group 1: Porcine & Bovine	63.1	Not Stated	Not Stated	43, _, _, _
	Group 2: Stented & Mechanical	55.7	Not Stated	Not Stated	47, _, _, _
T. David, et al., 1998	Group 1: Custom Stentless Group 2: Toronto SPV	58	165/77	16, 102, 95, 29	180, 39, 5, _
D. Del Rizzo, et al., 1998	Group 1: Freestyle	70.7	455/352	_, _, 115, 24	Not Stated
	Group 2: Toronto SPV	61.8	110/78	_, 335, 360, _	Not Stated
R. De Paulis, et al., 1998	Group 1: Stentless	70.7	7/3	Not Stated	23, 9, _, _
	Group 2: Stented	73.6	3/7		
	Group 3: Mechanical	64.8	6/4		
	Group 4: Control	61.3	4/6		
J. Dumesnil, et al., 1998	Group 1: Stentless	69	69/88	Not Stated	Not Stated
	Group 2: Stented	Not Stated	Not Stated		
W. Eichinger, et al., 1998	Group 1: Mosaic	72	24/48	Not Stated	Not Stated
	Group 2: Hancock MO II	76.8	20/32		
B. Goldman, et al., 1988	Group 1: Ionescu	58.6	53/47	85% III or IV	65% I or II
	Group 2: Hancock I	56	65/35		
R. Houel, et al., 1999	Group 1: Carpentier-Edwards	Not Stated	61/33	8, 21, 51, 14	Not Stated
	Group 2: Mitroflow	66.5	73/45	8, 47, 47, 47	
W.R. Jamieson, et al., 1999	Group 1: CE-S	59.6	Not Stated	Not Stated	Not Stated
	Group 2: CE-SAV	67.4			
Y. Kobayashi, et al., 1998	Group 1: Carpentier-Edwards	56	28/52	_, _, 18	Not Stated
	Group 2: Ionescu	50.1	51/60	_, _, 15	
J. Legare, et al., 1998	Group 1: SPV	70.8	43/26	III or IV: 85%	All I or II
	Group 2: Freestyle	67	28/15		
C. Mullany, et al., 1994	Intact Porcine	74.6	56/33	I & II: 12 III & IV: 75	Not Stated
F. Nistal, et al., 1986	Group 1: Hancock I	38	150/71	13, 53, 115, 40	Not Stated
	Group 2: Ionescu	39	57/76	9, 18, 67, 39	
J. Oury, et al., 1998	Group 1: Hancock I	58	56/48	Not Stated	Not Stated
	Group 2: Hancock II	67	64/55		
L. Pelletier, et al., 1989	Group 1: Porcine	54	0.93/1	Not Stated	Not Stated
	Group 2: Pericardial	57	1.16/1		

Table 4.2: Characteristics of Subjects in Comparative Studies of Bioprosthetic Valves – Systematic Review 1986 -2004					
Study	***Group***	***Mean Age***	***Gender*** **M/F**	**NYHA Class Before Surgery I, II, III, IV**	**NYHA Class Post Surgery I, II, III, IV**
D. Pupello, et al., 2001	Bioprostheses	73.9	1126/949	_, _, 1994	1998, _, _
R. Riley, et al., 2000	Group 1: Freestyle	72	21/23	0, 8, 34, 2	44, _, _, _
	Group 2: Toronto SPV	74	11/3	0, 2, 9, 3	_, _, 9, 5
F. Santini, et al., 1998	Group 1: Hancock	77	16/24	4, 17, 16,3	All I or II
	Group 2: Stentless	76	12/25	3, 12, 16, 6	
G. Van Nooten, et al., 1999	Stentless SPV	75.2	43/60	Mean: 3.3	Mean: 1.3
	Stented CE	74.4	30/21	Mean: 3.2	
T. Walther, et al., 1999	Group 1: Stentless	72.3	53/53	2.6	All I or II
	Group 2: Stented	74.8	34/40	2.6	
R. Williams, et al., 1999	Group 1: Carpentier-Edwards	72	9/10	Not Stated	All I or II
	Group 2: Toronto SPV	73.2	7/13		

The New York Heart Association Classification prior to and following surgery is considered an important subject characteristic determining whether or not surgery proved to be beneficial for patients and in particular, whether there was a significant improvement in symptoms based on the kind of prosthesis used. Ten studies did not state the NYHA Class before operative intervention. Casabona (1992) did, however, combine the two stentless valves together as one group and assigned the functional class for 43 out of the 57 patients from these two groups as being Class I.[42] They also subsequently combined, for unspecified reasons, the stented porcine and mechanical valve groups and stated that 47 out of these 60 patients had Class I functional symptoms post-operatively. Five of the remaining groups that described the NYHA Class prior to surgery failed to do so post-operatively. It is unclear whether this was related to inadequate follow-up or perhaps due to the lack of understanding of unsatisfactory results. Van Nooten (1999) decided to calculate the average NYHA Class before and after surgery for all groups of patients in the study.[60]

In several studies, the authors attempted to cluster whatever follow-up data was available into groups showing a general tendency of improvement in symptoms post-operatively. Achtelik (1996) showed that all 22 patients in the Biocor valve group treated with a stented valve belonged to NYHA Class III or IV symptomatology pre-operatively, and were all improved to either in Class I or II post-operatively.[40] Unfortunately, they had no symptoms to compare with in the group undergoing aortic root enlargement.

Goldman (1988) compared two stented bioprosthetic valves and was unable to record a significant difference between the two groups pre-operatively or post-operatively.[48] He did, however, combine all the patients from the two groups showing that 85% of them both belonged to Class III or IV pre-operatively and 65% of them belonged to Class I or II after surgery. This confirmed that the valve surgery helped both groups post-operatively from a heart failure perspective, but failed to show a significant difference between the two groups of valves being tested. Similarly, Legare (1998) showed that 85% of all patients from both group 1 and 2 belonged to NYHA Class III or IV and all patients post-operatively belonged to NYHA Class I or II.[52] Once again, a comparison of

the two groups for benefit of one valve versus another was not apparent in this study. Pupello (2001) showed that 1,994 patients were in NYHA Classes III and IV pre-operatively and 1,998 patients were in NYHA Classes II and I post-operatively.[57] A variety of porcine bioprosthetic valves were used in this study, namely: Medtronic Intact, Carpentier-Edwards, Hancock Standard and Hancock Modified Orifice valves.

An interesting twist to the analysis was performed by Van Nooten (1999) and Walther (1999).[60,61] They both recorded the average NYHA Class for their patients pre-operatively. There was no distribution of patients amongst the four classes. The post-operative average NYHA Class was improved in both studies with Van Nooten's study showing a mean of 1.3 and Walther's study showing all patients to be in Class I or II. In both studies, there was no post-operative comparison between the two valves being evaluated. It is important to note that the authors incorrectly use mean class to compare preoperative and postoperative functional status when it is not possible to do this for the NYHA classification system as this is an ordinal scale.

Table 4.3 illustrates the characteristics of the studies that were included in the analysis. The characteristics included the time frame of the study, location, the surgeons involved and whether standardization of surgical technique was documented. A broad range of time lines for the initiation of the studies was apparent. Some studies were conducted over a 2 year period while others spanned anywhere from 10 to 15 years. In the latter studies there were no subgroups based on the era when the operation was performed. No specific reference was made in these studies with regard to changes in surgical techniques, post-operative management, technologic advances, or changes in the members of the surgical team. Only four studies did not state whether a single centre group of surgeons was involved or whether a single surgeon or multiple centres performed the technique. Three out of the four studies, Del Rizzo (1998), De Paulis (1998), and Jamieson (1999) were from Canadian centres.[44,45,50] The fourth study was from France.

Table 4.3: Time, Site and Surgical Technique in Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 - 2004					
Study	**Group**	**Time**	**Place**	**Single Centre Group of Surgeons Yes/No/Not Stated**	**Surgical Technique Standardized Yes/No/Not Stated**
M. Achtelik, et al., 1996	Group 1: Biocor Group 2: Root Enlargement	1993-1995	Hamburg, Germany	Yes	Yes
P. Bloomfield, et al., 1986	Group 1: Mechanical Group 2: Hancock & CE	1975-1979	Edinburgh, Scotland	Yes	Yes
R. Casabona, et al., 1992	Group 1: Porcine & Bovine Group 2: Stented & Mechanical	Time frame not documented	Torino, Italy	Yes	Yes
T. David, et al., 1998	Group 1: Custom Stentless Group 2: Toronto SPV	1987-1989 1991-1997	Toronto, Canada	Not Stated	Not Stated
D. Del Rizzo, et al., 1998	Group 1: Freestyle Group 2: Toronto SPV	1991-1997	Winnipeg, Canada	Not Stated	Yes
R. De Paulis, et al., 1998	Group 1: Stentless Group 2: Stented Group 3: Mechanical Group 4: Control	1994-1996	Rome, Italy	Yes	Not Stated
J. Dumesnil, et al., 1998	Group 1: Stentless Group 2: Stented	1993-1995	Quebec City, Canada	Yes	Not Stated
W. Eichinger, et al., 1998	Group 1: Mosaic Group 2: Hancock MO II	1994-1997	Munich, Germany	Yes	Yes
B. Goldman, et al., 1988	Group 1: Ionescu Group 2: Hancock I	1979-1985 1982-1983	Toronto, Canada	Yes	Not Stated
R. Houel, et al., 1999	Group 1: Carpentier-Edwards Group 2: Mitroflow	1980-1987	Creteil, France	Not Stated	Yes
W.R. Jamieson, et al., 1999	Group 1: CE-S Group 2: CE-SAV	1976-1988 1981-1997	Vancouver, Canada	Not Stated	No
Y. Kobayashi, et al., 1998	Group 1: Carpentier-Edwards Group 2: Ionescu	1984-1993 1983-1985	Osaka, Japan	Yes	Not Stated
J. Legare, et al., 1998	Group 1: SPV Group 2: Freestyle	1993-1997	Halifax, Canada	Yes	Yes
C. Mullany, et al., 1994	Intact Porcine	1990-1992	Rochester, Minnesota, USA	Yes	Yes
F. Nistal, et al., 1986	Group 1: Hancock I Group 2: Ionescu	1977-1981	Santander, Spain	Yes	Yes
J. Oury, et al., 1998	Group 1: Hancock I Group 2: Hancock II	1975-1983 1983-1987	La Jolla, USA	Yes	Not Stated

Table 4.3: Time, Site and Surgical Technique in Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 – 2004					
Study	**Group**	**Time**	**Place**	**Single Centre Group of Surgeons Yes/No/Not Stated**	**Surgical Technique Standardized Yes/No/Not Stated**
L. Pelletier, et al., 1989	Group 1: Porcine Group 2: Pericardial	1976-1988	Montreal, Canada	Yes	No
D. Pupello, et al., 2001	Bioprostheses	1974-1998	Tampa, Florida, USA	Yes	Not Stated
R. Riley, et al., 2000	Group 1: Freestyle Group 2: Toronto SPV	1997-1999	Winston-Salem, North Carolina, USA	Yes	Yes
F. Santini, et al., 1998	Group 1: Hancock Group 2: Stentless	1993-1996	Verona, Italy	Yes	Yes
G. Van Nooten, et al., 1999	Stentless SPV Stented CE	1992-1997	Ghent, Belgium	Yes	Yes
T. Walther, et al., 1999	Group 1: Stentless Group 2: Stented	1996-1998	Leipzig, Germany	Yes	Yes
R. Williams, et al, 1999	Group 1: Carpentier-Edwards Group 2: Toronto SPV	1996-1999	Glasgow, Scotland	Yes	Yes

Surgical technique was standardized in all but seven studies. In these seven studies, it was not stated whether the technique was standardized. In those studies where the surgical technique was standardized, a brief description was given with regard to the procedure. No accountability for changes in surgical technique over the duration of the study was made. The studies by Kobayashi (1998), Oury (1998) and Pupello (2001) extended over many years and did not clarify whether there were changes in technique during these time periods.[51,55,57]

Group selection, comparability, statistics, and the outcomes assessed are tabulated in Table 4.4 as study methodology. Eight of the studies utilized direct measurement in selecting both of the patient groups. Achtelik (1996), Dumesnil (1998), Jamieson (1999), Pelletier (1989) and Santini (1998) used a combination of direct measurement and secure records in selecting the study populations.[40,46,50,59] De Paulis (1998), Oury (1998), Walther (1999) and Williams (1999) used a combination of the structured interview and direct measurement to select their groups.[45,55,61,62] In general, when a structured interview was used, there were also very specific inclusion and exclusion criteria defined in these studies. In six studies, records were secured for the purpose of group selection. In another six studies, records were used to select one or part of both groups of patients entered in the study. In the latter studies, inclusion and exclusion criteria were either not defined or not clearly stated. In general, the same method of measurement was used at both the baseline and the postoperative interval for the outcome of interest. An example of this was echocardiography. Those studies that used a structured interview in group selection, however, did not conduct an interview during the post-operative follow-up and resorted to direct measurement techniques. There were four studies that utilized self-reporting to assess the outcomes post-operatively. Bloomfield (1996), Del Rizzo (1998), Jamieson (1999), and Riley (2000) used data obtained from self-reporting for one or possibly both groups that were followed during the study.[41,44,50,58] Details of the self-reporting were not explicit and the amount of data retrieved using this technique were not documented.

Table 4.4: Methodology of Comparative Studies of Bioprosthetic Valves – Systematic Review 1986 -2004				
Study	**Group**	**Group Selection**	**Comparability/Statistics**	**Outcomes Assessed**
M. Achtelik, et al., 1996	Group 1: Biocor Group 2: Root Enlargement	Direct Measurement Secure records	Inclusion/exclusion criteria not defined No randomization defined Regression of left ventricular hypertrophy	Direct Measurement
P. Bloomfield, et al., 1986	Group 1: Mechanical Group 2: Hancock & CE	Direct Measurement	Inclusion/exclusion & randomization criteria defined T-test, Fischer exact test & Pearson chi-square analysis	Direct Measurement & Self Report
R. Casabona, et al., 1992	Group 1: Porcine & Bovine Group 2: Stented & Mechanical	Direct Measurement	No randomization defined Exclusion criteria defined Mean +/- standard deviation, chi-squared test	Direct Measurement
T. David, et al., 1998	Group 1: Custom Stentless Group 2: Toronto SPV	Direct Measurement	No randomization defined Little inclusion/exclusion criteria Life-table method, means, standard deviation, Student's t-tests	Direct Measurement
D. Del Rizzo, et al., 1998	Group 1: Freestyle Group 2: Toronto SPV	Direct Measurement	No randomization defined Inclusion/exclusion criteria defined Nonconcurrent cohort study design T-test, Nann-Whitney U test, chi-square test, Fischer's exact test	Direct Measurement & Self Report
R. De Paulis, et al., 1998	Group 1: Stentless Group 2: Stented Group 3: Mechanical Group 4: Control	Structured Interview & Direct Measurement	Well defined inclusion criteria No randomization defined Subjects chosen consecutively from one group Defined control group Sheffe F-test, Student's t-test, chi-square, ANOVA, two factor repeated measures	Direct Measurement
J. Dumesnil, et al., 1998	Group 1: Stentless Group 2: Stented	Direct Measurement Secure Records	Inclusion/exclusion criteria not defined Student's T test, Pearson linear coefficient, linear regression equation	Direct Measurement Secure Records
W. Eichinger, et al., 1998	Group 1: Mosaic Group 2: Hancock MO II	Secure Records	Inclusion criteria defined Exclusion criteria not defined Randomization method not defined Mann-Whitney U test, mean gradient, orifice area	Direct Measurement
B. Goldman, et al., 1988	Group 1: Ionescu Group 2: Hancock I	Secure records	Inclusion criteria: time frame for patients referred for valve replacement Actuarial curves	Secure Records & Direct Measurement
R. Houel, et al., 1999	Group 1: Carpentier-Edwards Group 2: Mitroflow	Secure records	Inclusion/exclusion criteria not defined Included all prospective patients within defined time Chi-square test, Kaplan-Meier method, Cox model	Secure Records
W.R. Jamieson, et al., 1999	Group 1: CE-S Group 2: CE-SAV	Secure Records Direct Measurement	Inclusion/exclusion criteria not defined No randomization defined Kaplan-Meier method, log rank test, Wilcoxon rank-sum test	Secure Records, Direct Measurement & Self Report

Table 4.4: Methodology of Comparative Studies of Bioprosthetic Valves – Systematic Review 1986 -2004				
Study	**Group**	**Group Selection**	**Comparability/Statistics**	**Outcomes Assessed**
Y. Kobayashi, et al., 1998	Group 1: Carpentier-Edwards Group 2: Ionescu	Direct Measurement	Inclusion/exclusion criteria defined No randomization defined Both cohorts chosen from single source Mean +/-standard deviation, Kaplan-Meier event-free curves	Direct Measurement
J. Legare, et al., 1998	Group 1: SPV Group 2: Freestyle	Direct Measurement	No randomization defined Inclusion criteria defined Two tailed t-test, chi-squared analysis, Fischer's exact test	Direct Measurement
C. Mullany, et al., 1994	Intact Porcine	Secure Records & Direct Measurement	Inclusion/exclusion criteria not defined Comparison cohort obtained by retrospective review No randomization defined Mean gradient, effective orifice area	Secure Records & Direct Measurement
F. Nistal, et al., 1986	Group 1: Hancock I Group 2: Ionescu	Secure records	Inclusion/exclusion criteria not defined Both cohorts chosen from single source Standard error, mean, actuarial curve	Secure Records & Direct Measurement
J. Oury, et al., 1998	Group 1: Hancock I	Secure Records	Inclusion/exclusion criteria not defined	Secure records
	Group 2: Hancock II	Structured Interview & Direct Measurement		Direct Measurement
L. Pelletier, et al., 1989	Group 1: Porcine Group 2: Pericardial	Secure Records & Direct Measurement	Inclusion/exclusion criteria not defined Chi-squared test used for data analysis Retrospective cohorts followed prospectively	Secure Records & Direct Measurement
D. Pupello, et al., 2001	Bioprostheses	Secure Records	Inclusion criteria defined Exclusion criteria not defined No randomization defined Mean/standard deviation, chi-squared analysis, two-tailed Fisher's exact test, student's t test	Secure Records & Direct Measurement
R. Riley, et al., 2000	Group 1: Freestyle Group 2: Toronto SPV	Direct Measurement	Inclusion/exclusion criteria not clearly defined No randomization	Direct Measurement & Self Report
F. Santini, et al., 1998	Group 1: Hancock Group 2: Stentless	Secure Records & Direct Measurement	Inclusion/exclusion criteria not clearly defined Prospectively randomized T-test, one way ANOVA & survival analysis used	Direct Measurement
G. Van Nooten, et al., 1999	Stentless SPV Stented CE	Secure Records	No randomization defined Inclusion/exclusion criteria not defined Chi-square test, Fischer's exact test, Mann-Whitney test, Kaplan-Meier analysis, unpaired Student t-test	Secure Records

Table 4.4: Methodology of Comparative Studies of Bioprosthetic Valves – Systematic Review 1986 -2004				
Study	**Group**	**Group Selection**	**Comparability/Statistics**	**Outcomes Assessed**
T. Walther, et al., 1999	Group 1: Stentless	Structured Interview & Direct Measurement	Prospective randomized control study Inclusion & exclusion criteria defined Mean +/-standard deviation, Student's t-test, chi-square test	Direct Measurement
	Group 2: Stented			
R. Williams, et al, 1999	Group 1: Carpentier Edwards	Structured Interview & Direct Measurement	Prospective randomized control study Inclusion & exclusion criteria defined Student's t-test, chi-squared test, ANOVA was used for the hemodynamic data	Direct Measurement
	Group 2: Toronto SPV			

Follow-up assessment times are summarized in Tables 4.5 and 4.6. Table 4.5 categorizes assessment times into early, interim, and late time frames. All studies included in the analysis categorized early assessments as less than a year post-operatively. Interim assessment was defined as between one and five years and late assessment as more than five years. All studies recorded early follow-up assessments of their patients. Only three studies did not have interim assessments between one to five years post-operatively. Six studies had late assessments of at least five years or more. The total follow-up and time course column shows that there was significant variability in the duration of follow-up for some groups in the included studies. While some studies had follow-up time frames of a few months, there were also studies that had patients followed up for 15 years or more.

The results at the follow-up for the three different time frames are provided in Table 4.6. David (1998) measured overall actuarial survival at one, five and at nine years, respectively, showing a gradual decline with time.[43] However, the two groups in the study were not compared with each other. Bloomfield (1986) showed no difference in survival at one year or between one and five years.[41] An actuarial survival of seven years was recorded for all patients at seven years. Houel (1999) showed no differences in survival at one year but differences in actuarial survival during the interim and late periods.[49]

Table 4.5: Follow-up Assessment Times for Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 – 2004						
Study	**Group**	**Initial Number of Patients**	**Total Follow Up Time Course**	**0 - 1 Year Assessment**	**1 - 5 Years Assessment**	**5 + Years Assessment**
M. Achtelik, et al., 1996	Group 1: Biocor	22	1-25 months	X	X	-
	Group 2: Root Enlargement	10				
P. Bloomfield, et al., 1986	Group 1: Mechanical	273	2.8-8.3 years Mean: 5.6 years	X	X	X
	Group 2: Hancock & CE	267				
R. Casabona, et al., 1992	Group 1: Porcine & Bovine	57	Mean: 11.5 months	X	X	-
	Group 2: Stented & Mechanical	60	Mean: 23 months			
T. David, et al., 1998	Group 1: Custom Stentless	29	3-120 months Mean: 43 months	X	X	-
	Group 2: Toronto SPV	213				
D. Del Rizzo, et al., 1998	Group 1: Freestyle	849	3 years	X	X	-
	Group 2: Toronto SPV	263				
R. De Paulis, et al., 1998	Group 1: Stentless	10	15 months	X	X	-
	Group 2: Stented	10				
	Group 3: Mechanical	10				
	Group 4: Control	10				
J. Dumesnil, et al., 1998	Group 1: Stentless	157	129: 3-6 months 79: 1 year 21: 2 years	X	X	-
	Group 2: Stented	106	78: 12 months 28: 20 months			
W. Eichinger, et al., 1998	Group 1: Mosaic	55	2 years	X	X	-
	Group 2: Hancock MO II	52				
B. Goldman, et al., 1988	Group 1: Ionescu	41	Mean: 38 months	X	X	-
	Group 2: Hancock I	81				
R. Houel, et al., 1999	Group 1: Carpentier-Edwards	94	0.14-17.4 years Mean: 9.85	X	X	X
	Group 2: Mitroflow	118	0.26-14.8 years Mean: 8.15			
W.R. Jamieson, et al., 1999	Group 1: CE-S	567	15 years	X	X	X
	Group 2: CE-SAV	1670				
Y. Kobayashi, et al., 1998	Group 1: Carpentier-Edwards	30	Mean: 6.1 years	X	X	X
	Group 2: Ionescu	40	Mean: 7.2 years			
J. Legare, et al., 1998	Group 1: SPV	69	Mean: 15.9 months	X	X	-
	Group 2: Freestyle	43	Mean: 28.9 months			

Table 4.5: Follow-up Assessment Times for Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 – 2004						
Study	**Group**	**Initial Number of Patients**	**Total Follow Up Time Course**	**0 - 1 Year Assessment**	**1 - 5 Years Assessment**	**5 + Years Assessment**
C. Mullany, et al., 1994	Intact Porcine	89	12 months	X	-	-
F. Nistal, et al., 1986	Group 1: Hancock I	221	4-83 months Mean: 59	X	X	-
	Group 2: Ionescu	133	1-83 months Mean: 48			
J. Oury, et al., 1998	Group 1: Hancock I	58	5-13 years	X	X	X
	Group 2: Hancock II	67	2-5 years			-
L. Pelletier, et al., 1989	Group 1: Porcine	331	Mean: 74 months	X	X	X
	Group 2: Pericardial	370	Mean: 34 months			
D. Pupello, et al., 2001	Bioprostheses	1402	1 month-23 years Mean: 60.8 months	X	X	-
R. Riley, et al., 2000	Group 1: Freestyle	44	6-9 months (6 months for all patients)	X	-	-
	Group 2: Toronto SPV	14				
F. Santini, et al., 1998	Group 1: Hancock	40	5-51 months Mean: 14.5 months	X	X	-
	Group 2: Stentless	37	6-51 months Mean: 18.5 months			
G. Van Nooten, et al., 1999	Stentless SPV	103	6-66 months Mean: 32-34 months	X	X	-
	Stented CE	51				
T. Walther, et al., 1999	Group 1: Stentless	106	6 months	X	-	-
	Group 2: Stented	74				
R. Williams, et al, 1999	Group 1: Carpentier-Edwards	16	3 years	X	X	-
	Group 2: Toronto SPV	18				

Table 4.6: Results at Follow-up Assessment Time for Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 – 2004						
Study	**Group**	**Initial Number of Patients**	**Total Follow Up Time Course**	**0 - 1 Year Assessment**	**1 - 5 Years Assessment**	**5 + Years Assessment**
M. Achtelik, et al., 1996	Group 1: Biocor	22	1-25 months	3 deaths within 30 days	Signif. diff. in LV mass regression and valve gradients	-
	Group 2: Root Enlargement	10		None		
P. Bloomfield, et al., 1986	Group 1: Mechanical	273	2.8-8.3 years Mean: 5.6 years	No significant differences seen in survival at 1 year	No significant differences seen between 1-5 years	Actuarial survival at 7 years: 69.6 % all patients
	Group 2: Hancock & CE	267				
R. Casabona, et al., 1992	Group 1: Porcine & Bovine	57	Mean: 11.5 months	13.4 % early death	Mild aortic regurgitation: 43.3 %	-
	Group 2: Stented & Mechanical	60	Mean: 23 months	3.3 % early death	Mild aortic regurgitation: 18.5 %	
T. David, et al., 1998	Group 1: Custom Stentless	29	3-120 months Mean: 43 months	Overall actuarial survival: 97 % at 1 year	Overall actuarial survival: 93 % at 5 years	Overall actuarial survival: 89 % at 9 years
	Group 2: Toronto SPV	213				
D. Del Rizzo, et al., 1998	Group 1: Freestyle	849	3 years	Early deaths: 1.9 %	Late deaths: 1.2 %	-
	Group 2: Toronto SPV	263		Early deaths: 0 %	Late deaths: 1.6%	
R. De Paulis, et al., 1998	Group 1: Stentless	10	15 months	Significant reduction in left ventricular mass for all patients but remained above normal values found in controls	-	-
	Group 2: Stented	10				
	Group 3: Mechanical	10				
	Group 4: Control	10				
J. Dumesnil, et al., 1998	Group 1: Stentless	157	129: 3-6 months 79: 1 year 21: 2 years	3-6 months: significant increase in EOA	1 year: 1.86 cm2 EOA	-
	Group 2: Stented	106	78: 12 months 28: 20 months	No significant increase in EOA	1 year: 1.73 cm2 EOA	
W. Eichinger, et al., 1998	Group 1: Mosaic	55	2 years	Early mortality: 3.6 % (within 30 days)	Differences in pressure gradients & effective orifice areas not significant between 2 valves	Overall mortality: 12.7 %
	Group 2: Hancock MO II	52		Early mortality: 3.8 %		Overall mortality: 13.5 %
B. Goldman, et al., 1988	Group 1: Ionescu	41	Mean: 38 months	7 % died within 30 days	-	Actuarial survival: 73 % at 6 years
	Group 2: Hancock I	81		6 % died within 30 days	Actuarial survival: 65 % at 5 years	-

Table 4.6: Results at Follow-up Assessment Time for Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 – 2004						
Study	**Group**	**Initial Number of Patients**	**Total Follow-up Time Course**	**0 – 1 Year Assessment**	**1 – 5 Years Assessment**	**5 + Years Assessment**
R. Houel, et al., 1999	Group 1: Carpentier-Edwards	94	0.14-17.4 years Mean: 9.85	No significant differences seen in survival at 1 year	Actuarial survival: 86.9 %	Actuarial survival: 66.3 % 10 years 45.1 15 years
	Group 2: Mitroflow	118	0.26-14.8 years Mean: 8.15		Actuarial survival: 81 %	Actuarial survival: 59.8 % 10 years 39.9 % 15 years
W.R. Jamieson, et al., 1999	Group 1: CE-S	567	15 years	No significant differences seen in survival at 1 year	No significant differences seen in survival at 5 years	No clinically relevant differences between valves with regard to freedom from structural valve deterioration
	Group 2: CE-SAV	1670				
Y. Kobayashi, et al., 1998	Group 1: Carpentier-Edwards	30	Mean: 6.1 years	Not Stated	Late deaths: 4	-
	Group 2: Ionescu	40	Mean: 7.2 years		Late deaths: 5	
J. Legare, et al., 1998	Group 1: SPV	69	Mean: 15.9 months	1 year aortic insufficiency: 26.2 %	No evidence of structural deterioration with either valve	-
	Group 2: Freestyle	43	Mean: 28.9 months	1 year aortic insufficiency: 5.9 %		
C. Mullany, et al., 1994	Intact Porcine	89	12 months	4 hospital deaths 3 late deaths (between 6-25 wks postoperatively)	-	-
F. Nistal, et al., 1986	Group 1: Hancock I	221	4-83 months Mean: 59	No significant differences seen in survival at 1 year	No significant differences seen between 1-5 years	93.1 % freedom from primary dysfunction at 7 years
	Group 2: Ionescu	133	1-83 months Mean: 48			79.6 % freedom from primary dysfunction at 7 years
J. Oury, et al., 1998	Group 1: Hancock I	58	5-13 years	No significant difference in survival up to 4 yrs	84 % alive at 5 yrs	56 % alive at 10.6 yrs
	Group 2: Hancock II	67	2-5 years			
L. Pelletier, et al., 1989	Group 1: Porcine	331	Mean: 74 months	30 day mortality: 6.6 %	80 % survival	62 % survival at 10 years
	Group 2: Pericardial	370	Mean: 34 months	30 day mortality: 3.8 %	79 % survival	-
D. Pupello, et al., 2001	Bioprostheses	1402	1 month-23 years Mean: 60.8 months	Overall hospital mortality rate: 10.2 %	Late mortality: 9.5 % per patient year	At completion of last follow up: 49.6 % alive
R. Riley, et al., 2000	Group 1: Freestyle	44	6-9 months (6 months for all patients)	6 months: EOA: 1.83 cm2	-	-
	Group 2: Toronto SPV	14		6 months: EOA: 1.80 cm2		

Table 4.6: Results at Follow-up Assessment Time for Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 – 2004						
Study	**Group**	**Initial Number of Patients**	**Total Follow-up Time Course**	**0 – 1 Year Assessment**	**1 – 5 Years Assessment**	**5 + Years Assessment**
F. Santini, et al., 1998	Group 1: Hancock	40	5-51 months Mean: 14.5 months	No significant differences seen in survival at 1 year	Probability of survival at 36 months: 92 %	-
	Group 2: Stentless	37	6-51 months Mean: 18.5 months		Probability of survival at 36 months: 81 %	
G. Van Nooten, et al., 1999	Stentless SPV	103	6-66 months Mean: 32-34 months	6 late deaths	Freedom from thromboembolism at 5 years: 83 %	-
	Stented CE	51		12 late deaths	Freedom from thromboembolism at 5 years: 94 %	
T. Walther, et al., 1999	Group 1: Stentless	106	6 months	At early follow up (not defined) 1 death in each group. At 6 months 1 in each group had paravalvular incompetence.	-	-
	Group 2: Stented	74				
R. Williams, et al, 1999	Group 1: Carpentier-Edwards	19	3 years	MRI at 6 months showed improvements in left ventricular volume & end-diastolic & endsystolic muscle mass indices in both groups but these trends did not reach statistical significance.	Repeat studies at 3 years did not show any further improvements in stroke volume & ejection fraction in either group.	-
	Group 2: Toronto SPV	20				

Table 4.7 illustrates the various outcomes assessed by the studies included in the analysis. Eleven different outcomes were sought in the studies for extraction: survival, late mortality, thromboembolism, primary tissue valve failure, bacterial endocarditis, re-operation, structural valve degeneration, left ventricular mass regression, NYHA classification, effective orifice area, and regurgitation. Most studies reported on late mortality, re-operation, and NYHA classification. There were two studies that documented only one outcome; Achtelik (1996) reported on NYHA classification[40] and Jamieson (1999) reported on structural valve deterioration.[50] Objective endpoints such as late mortality and re-operation were much more likely to be assessed with only seven studies neglecting to present late mortality and nine studies not reporting on re-operative rates. Left ventricular mass regression, an important outcome of valve replacement, was documented in only five studies. Similarly, survival was recorded by only four studies.

Table 4.7: Outcomes Assessed in Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 - 2004											
Study	**Survival**	**Late Mortality**	**Thromboembolic**	**Primary Tissue Valve Failure**	**Bacterial Endocarditis**	**Reoperation**	**Structural Valve Deterioration**	**LV Mass Regression**	**NYHA Class**	**Effective Orifice Area**	**Regurgitation**
M. Achtelik, et al., 1996	-	-	-	-	-	-	-	-	X	-	-
P. Bloomfield, et al., 1986	X	X	X	X	X	X	-	-	X	-	-
R. Casabona, et al., 1992	-	-	-	-	-	-	-	-	X	-	X
T. David, et al., 1998	X	X	X	-	X	X	-	-	X	X	-
D. Del Rizzo, et al., 1998	-	X	-	X	-	X	-	X	-	X	X
R. De Paulis, et al., 1998	-	-	-	-	-	-	-	X	X	-	-
J. Dumesnil, et al., 1998	-	-	-	-	-	-	-	-	-	X	X
W. Eichinger, et al., 1998	-	X	-	-	X	X	-	-	-	X	X
B. Goldman, et al., 1988	-	X	X	X	X	X	-	-	X	-	-
R. Houel, et al., 1999	X	X	X	-	X	X	X	-	-	-	-
W.R. Jamieson, et al., 1999	-	-	-	-	-	-	X	-	-	-	-
Y. Kobayashi, et al., 1998	-	X	-	-	X	X	X	-	-	-	X
J. Legare, et al., 1998	-	X	-	-	X	-	-	-	X	X	-
C. Mullany, et al., 1994	-	X	-	-	-	X	-	-	-	X	X
F. Nistal, et al., 1986	-	X	-	X	-	-	-	-	-	-	-
J. Oury, et al., 1998	X	X	X	X	X	X	-	-	-	-	-
L. Pelletier, et al., 1989	-	X	X	X	X	X	X	-	X	-	-
D. Pupello, et al., 2001	-	X	-	X	-	X	X	-	X	-	-
R. Riley, et al., 2000	-	X	-	-	-	X	X	-	X	X	X
F. Santini, et al., 1998	-	X	-	-	-	-	-	X	X	-	X
G. Van Nooten, et al., 1999	-	X	-	X	-	X	-	-	X	-	-
T. Walther, et al., 1999	-	-	-	-	-	X	-	X	X	-	-
R. Williams, et al, 1999	-	-	X	-	-	-	-	X	X	X	X

4.1.3 A Study by Study Comparison

4.1.3.1 Outcomes and Conclusions

The results of the study outcomes obtained in the analysis are recorded in Tables 4.8a and 4.8b. There is a wide disparity in the methods of data reporting as well as in the amount of information that could be extracted from each study. Endpoints in survival were usually not stated and varied between 7 and 15 years. Late mortality was measured using a percentage in many of the studies although some studies recorded it as per patient year while others gave a specific endpoint although this was between 2 to 5 years or 5 to 13 years. Thromboembolic complications did not adhere to the same guidelines for reporting complications of anticoagulant use and only some studies recorded the percentage of complications per patient year. This approach was also used for other endpoints such as primary tissue valve failure, bacterial endocarditis, structural valve degeneration, and re-operation. Left ventricular mass regression was reported either as a percentage or as an actual mass reduction by the few studies that actually reported it. There was no standardized definition for regurgitation and a variety of endpoints was used to record this phenomenon. Only a subset of studies reported on the findings of left ventricular mass regression and hemodynamics. The conclusion of each study evaluated in the systematic review is provided in Table 4.9. This table documents the style in which findings from valve studies are reported. The conclusions are presented in a descriptive format that shows trends and tendencies rather than statistically significant findings. Most studies describe acceptable morbidity and mortality statistics for the valves studied as deemed by the authors of the studies.

Table 4.8a: Results of the Outcomes of Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 - 2004					
Study	**Group**	**Survival**	**Late Mortality**	**Thromboembolism**	**Primary Tissue Valve Failure**
M. Achtelik, et al., 1996	Group 1: Biocor	-	-	-	-
	Group 2: Root Enlargement	-	-	-	-
P. Bloomfield, et al., 1986	Group 1: Mechanical	63.2 % at 7 years	20.9 % overall	3 %	3 %
	Group 2: Hancock & CE	overall	overall	0 %	4 %
R. Casabona, et al., 1992	Group 1: Porcine & Bovine	-	-	-	-
	Group 2: Stented & Mechanical	-	-	-	-
T. David, et al., 1998	Group 1: Custom Stentless	89 % over 9 years	4.5 % overall	8 % over 9 years	-
	Group 2: Toronto SPV	-	-	-	-
D. Del Rizzo, et al., 1998	Group 1: Freestyle	-	1.2 %	-	-
	Group 2: Toronto SPV	-	1.6 %	-	-
R. De Paulis, et al., 1998	Group 1: Stentless	-	-	-	-
	Group 2: Stented	-	-	-	-
	Group 3: Mechanical	-	-	-	-
	Group 4: Control	-	-	-	-
J. Dumesnil, et al., 1998	Group 1: Stentless	-	-	-	-
	Group 2: Stented	-	-	-	-
W. Eichinger, et al., 1998	Group 1: Mosaic	-	12.7 %	-	-
	Group 2: Hancock MO II	-	13.5 %	-	-
B. Goldman, et al., 1988	Group 1: Ionescu	-	15 %	1 %	1.1 % per patient yr
	Group 2: Hancock I	-	17 %	1.6%	5.9 % per patient yr
R. Houel, et al., 1999	Group 1: Carpentier-Edwards	45 % at 15 years	41.5 %	7 %	-
	Group 2: Mitroflow	39.9 % at 15 years	28 %	6 %	-
W.R. Jamieson, et al., 1999	Group 1: CE-S	-	-	-	-
	Group 2: CE-SAV	-	-	-	-
Y. Kobayashi, et al., 1998	Group 1: Carpentier-Edwards	-	13 %	-	-
	Group 2: Ionescu	-	13 %	-	-
J. Legare, et al., 1998	Group 1: SPV	-	8.7 %	-	-
	Group 2: Freestyle	-	14 %	-	-

Table 4.8a: Results of the Outcomes of Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 - 2004					
Study	**Group**	**Survival**	**Late Mortality**	**Thromboembolism**	**Primary Tissue Valve Failure**
C. Mullany, et al., 1994	Intact Porcine	-	3 %	-	-
	Group 2: Ionescu	-	12 %	-	6 % 36-70 months
J. Oury, et al., 1998	Group 1: Hancock I	50 % at 12 years	31 % - 5 -13 yrs	1.49 % per patient yr	2.34 % per patient yr
	Group 2: Hancock II	-	8 % - 2 -5 yrs	2.33 % per patient yr	1.30 % per patient yr
L. Pelletier, et al., 1989	Group 1: Porcine	-	2.9 % per patient yr	96 % at 10 yrs	1 %
	Group 2: Pericardial	-	3.5 % per patient yr	94 % at 10 yrs	2 %
D. Pupello, et al., 2001	Bioprostheses	-	9.5 % per patient yr	-	16.3 % at 18 years
R. Riley, et al., 2000	Group 1: Freestyle	-	3.6 % overall	-	-
	Group 2: Toronto SPV	-	-	-	-
F. Santini, et al., 1998	Group 1: Hancock	-	3 % overall	-	-
	Group 2: Stentless	-	-	-	-
G. Van Nooten, et al., 1999	Stentless SPV	-	24 %	-	17 %
	Stented CE	-	6 %	-	6 %
T. Walther, et al., 1999	Group 1: Stentless	-	-	-	-
	Group 2: Stented	-	-	-	-
R. Williams, et al, 1999	Group 1: Carpentier-Edwards	-	-	No thromboembolic complications	-
	Group 2: Toronto SPV	-	-	-	-

Table 4.8b: Results of the Outcomes of Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 - 2004								
Study	**Group**	**Bacterial Endocarditis**	**Reoperation**	**Structural Valve Deterioration**	**LV Mass Regression**	**NYHA Class I, II, III, IV**	**Effective Orifice Area**	**Regurgitation**
M. Achtelik, et al., 1996	Group 1: Biocor	Not Stated	Not Stated	Not Stated	Not Stated	I or II: 22	Not Stated	Not Stated
	Group 2: Root Enlargement					Not Stated		
P. Bloomfield, et al., 1986	Group 1: Mechanical	2 patients	4 patients	Not Stated	Not Stated	Mean: 1.53	Not Stated	Not Stated
	Group 2: Hancock & CE	2 patients	7 patients					
R. Casabona, et al., 1992	Group 1: Porcine & Bovine	Not Stated	Not Stated	Not Stated	Not Stated	43, _, _, _	Not Stated	31.6 %
	Group 2: Stented & Mechanical					47, _, _, _		Not Stated
T. David, et al., 1998	Group 1: Custom Stentless	2 % at 9 years	18 % at 9 years	Not Stated	Not Stated	180, 39, 5, _	Statistically significant	Not Stated
	Group 2: Toronto SPV							
D. Del Rizzo, et al., 1998	Group 1: Freestyle	0 %	Not Stated	Not Stated	Decreased by 10 %	Not Stated	EOA increased as a function of time for all valve sizes	Moderate: Negligible both groups
	Group 2: Toronto SPV	0.5 %						
R. De Paulis, et al., 1998	Group 1: Stentless	Not Stated	Not Stated	Not Stated	198>135	23, 9, _, _	Not Stated	Not Stated
	Group 2: Stented				185>144			
	Group 3: Mechanical				216>139			
	Group 4: Control				107			
J. Dumesnil, et al., 1998	Group 1: Stentless	Not Stated	Not Stated	Not Stated	Not Stated	Not Stated	Not Stated	34 %
	Group 2: Stented							29 %
W. Eichinger, et al., 1998	Group 1: Mosaic	None in either group	1 patient	Not Stated	Not Stated	Not Stated	Better hemodynamics after 2 years	Moderate: 1
	Group 2: Hancock MO II		0 patients				Differences not significant	Moderate: 0
B. Goldman, et al., 1988	Group 1: Ionescu	1.1 % per patient yr	0.8 %	6 %	Not Stated	I or II: 437	Not Stated	Not Stated
	Group 2: Hancock I	5.9 % per patient yr	1.3 %	20 %				
R. Houel, et al., 1999	Group 1: Carpentier-Edwards	4 %	15 %	3 patients	Not Stated	Not Stated	Not Stated	Not Stated
	Group 2: Mitroflow	6 %	31 %	5 patients				
W.R. Jamieson, et al., 1999	Group 1: CE-S	Not Stated	Not Stated	15 yrs: 75.6 %	Not Stated	Not Stated	Not Stated	Not Stated
	Group 2: CE-SAV			15 yrs: 79.6 %				
Y. Kobayashi, et al., 1998	Group 1: Carpentier-Edwards	1 patient	14 %	1 patient	10 % at 10 yrs	Not Stated	Not Stated	14 % at 10 yrs
	Group 2: Ionescu		46 %	23 patients	46 % at 10 yrs			46 % at 10 yrs
J. Legare, et al., 1998	Group 1: SPV	2 patients	Not Stated	Not Stated	Not Stated	I or II: All	Increased EOA in all patients except one	Not Stated
	Group 2: Freestyle							

Table 4.8b: Results of the Outcomes of Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 - 2004								
Study	**Group**	**Bacterial Endocarditis**	**Reoperation**	**Structural Valve Deterioration**	**LV Mass Regression**	**NYHA Class I, II, III, IV**	**Effective Orifice Area**	**Regurgitation**
C. Mullany, et al., 1994	Intact Porcine	Not Stated	1 patient	Not Stated	Not Stated	Not Stated	No significant difference between valves	9 patients
F. Nistal, et al., 1986	Group 1: Hancock I	Not Stated	Not Stated	Not Stated	Not Stated	Not Stated	Not Stated	Not Stated
	Group 2: Ionescu							
J. Oury, et al., 1998	Group 1: Hancock I	0.93 % per patient yr	0 patients	Not Stated	Not Stated	Not Stated	Not Stated	Not Stated
	Group 2: Hancock II	0.46 % per patient yr	1 patient					
L. Pelletier, et al., 1989	Group 1: Porcine	95 % at 10 yrs	4 % at 6 yrs	2 % at 6 yrs	Not Stated	I or II::94 %	Not Stated	Not Stated
	Group 2: Pericardial	92 % at 10 yrs	9 % at 6 yrs	6 % at 6 yrs		I or II: 98 %		
D. Pupello, et al., 2001	Bioprostheses	Not Stated	8.2 %	44.6 %	Not Stated	1998, _, _	Not Stated	Not Stated
R. Riley, et al., 2000	Group 1: Freestyle	Not Stated	2 patients	77 % of all failures	Not Stated	44, _, _	1.95 +/- 0.58	None
	Group 2: Toronto SPV		0 patients			_, _, 9, 5	1.59 +/- 0.36	14 % mild aortic insufficiency
F. Santini, et al., 1998	Group 1: Hancock	Not Stated	Not Stated	Not Stated	10.5 % +/- 18 % decrease	I or II: All	Not Stated	Not Stated
	Group 2: Stentless				19 % +/- 23 % decrease			12 % mild regurgitation
G. Van Nooten, et al., 1999	Stentless SPV	Not Stated	2 patients	Not Stated	Not Stated	Mean: 1.3	Not Stated	Not Stated
	Stented CE		3 patients					
T. Walther, et al., 1999	Group 1: Stentless	Not Stated	1 patient	Not Stated	141 +/- 41 at 6 mos.	I or II: All	Not Stated	Not Stated
	Group 2: Stented		1 patient		170 +/- 43 at 6mos.			
R. Williams, et al, 1999	Group 1: Carpentier-Edwards	Not Stated	Not Stated	Not Stated	Improvement in both groups but differences did not reach statistical significance.	I or II: All	3 years: 1.9 +/- 0.6	None
	Group 2: Toronto SPV						3 years: 2.2+/- 0.2	12.5 % mild aortic regurgitation

Table 4.9: Conclusions of Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 – 2004		
Study	**Group**	**Study Conclusions**
M. Achtelik, et al., 1996	Group 1: Biocor Group 2: Root Enlargement	Over a follow up period of 25 months the Biocor prosthesis demonstrated excellent hemodynamic data. When compared with published reference valves of standard bioprosthetic valve replacement the mean and peak gradients for the different root diameters were significantly lower. More follow up is required to determine the durability of the valve.
P. Bloomfield, et al., 1986	Group 1: Mechanical Group 2: Hancock & CE	No significant beneficial effect of anticoagulants found in the patients undergoing mitral or aortic valve replacement with porcine prostheses. No significant advantage of any three of the prostheses (Bjork-Shiley, Hancock and Carpentier-Edwards) has been observed. However a longer follow-up may reveal differences.
R. Casabona, et al., 1992	Group 1: Porcine & Bovine Group 2: Stented & Mechanical	Stentless valves showed a higher incidence of complete atrioventricular block when compared with stented valves. Long-term studies are necessary to determine the durability of both types of stentless valves. This study demonstrated that stentless valves permit a significantly lower gradient when compared with either biological stented valves or mechanical valves.
T. David, et al., 1998	Group 1: Custom Stentless Group 2: Toronto SPV	The clinical results using stentless porcine valves were excellent in this study. Our results suggest that the custom-made stentless valves may fail at a similar rate to stented porcine aortic valves. However, the stentless valves have better hemodynamic features which permit complete regression of left ventricular hypertrophy in most patients.
D. Del Rizzo, et al., 1998	Group 1: Freestyle Group 2: Toronto SPV	This study found no meaningful differences in the hemodynamic performance of the Toronto SPV and Medtronic Freestyle valves. The operative mortality of AVR with a stentless valve appears to be lower than the mortality associated with the use of a conventional device. The long-term performance and durability of these valves is not yet known.
R. De Paulis, et al., 1998	Group 1: Stentless Group 2: Stented Group 3: Mechanical Group 4: Control	In this study the assessment of left ventricular hypertrophy did not discriminate between patients with different types of valves after an intermediate length of follow up. Once the beneficial effect of stentless valves on left ventricular mass regression become apparent, it will be important to demonstrate that the incomplete regression is sufficient to determine differences in clinical status or in overall survival.
J. Dumesnil, et al., 1998	Group 1: Stentless Group 2: Stented	The hemodynamic performance of the Freestyle prosthesis is very satisfactory and represents an improvement in comparison to pervious observations in stented bioprostheses. The lower gradients observed in the Freestyle prosthesis are a marked improvement in comparison to the stented prostheses.
W. Eichinger, et al., 1998	Group 1: Mosaic Group 2: Hancock MO II	The mosaic valve has low pressure gradients for all sewing ring diameters. When compared with the Hancock Modified Orifice valve, there was no statistically gradient difference but there was a tendency for better hemodynamics noted in the Mosaic group after 2 years.
B. Goldman, et al., 1988	Group 1: Ionescu Group 2: Hancock I	All Hancock valves were replaced due to structural valve failure. The Ionescu-Shiley valve provided good functional results in low incidence of major valve related complications in patients followed up to 104 months. Primary tissue failure in the Hancock valve appears design dependent.
R. Houel, et al., 1999	Group 1: Carpentier-Edwards Group 2: Mitroflow	In patients less than 75 years, the Carpentier-Edwards valve performs better than the Mitroflow valve in valve replacement. However, in patients greater than 75 years, pericardial and porcine bioprostheses showed equivalent durability.

Table 4.9: Conclusions of Comparative Studies of Bioprosthetic Valves - Systematic Review 1986 – 2004		
Study	**Group**	**Conclusion**
W.R. Jamieson, et al., 1999	Group 1: CE-S Group 2: CE-SAV	The technologic changes to reduce fatigue lesions and calcification in the second-generation CE-SAV porcine bioprosthesis have not improved the structural integrity when compared to the first-generation porcine bioprosthesis over the 15-year interval, particularly in the mitral position versus the aortic position.
Y. Kobayashi, et al., 1998	Group 1: Carpentier-Edwards Group 2: Ionescu	The Carpentier-Edwards bioprosthetic valve has long-term durability following aortic valve replacement. However, the durability is poor after mitral valve replacement. Doppler echocardiography is useful in detecting bioprosthetic valve dysfunction.
J. Legare, et al., 1998	Group 1: SPV Group 2: Freestyle	From our study we determined that there has been slightly more mild aortic insufficiency with the SPV valve than with the Freestyle valve at our institution. Long-term follow up is necessary to determine if the aortic insufficiency progresses or becomes clinically important.
C. Mullany, et al., 1994	Intact Porcine	When the Intact porcine bioprosthesis is compared with the Carpentier-Edwards porcine bioprosthesis the effective orifice area and effective orifice area index were the same. Satisfactory hemodynamics were achieved in the smaller prostheses when valves are matched for body surface area and when annular enlargement is performed when necessary.
F. Nistal, et al., 1986	Group 1: Hancock I Group 2: Ionescu	Calcium and collagen degeneration was present on failing bioprostheses. The outcomes suggest that a greater tendency to primary tissue valve failure will be found with bovine pericardial than with porcine bioprostheses up to seven years following operation.
J. Oury, et al., 1998	Group 1: Hancock I Group 2: Hancock II	In theory the Hancock II has advantages in stent design, fixation pressure and anticalcification potential over the Hancock I bioprosthesis. An unusual thrombotic process was found in aortic valve replacements that was not observed in the Hancock I group or in our experience with other porcine xenografts. We believe there should be further documentation that this process is not related to the T6 anticalcification treatment of the Hancock II porcine xenograft.
J. Pelletier, et al., 1989	Group 1: Porcine Group 2: Pericardial	The Carpentier-Edwards porcine bioprosthesis appears to perform better than pericardial valves after the third to fourth year. The differences between the two types of bioprostheses appear to be mostly due to early tissue degeneration of the Ionescu-Shiley pericardial valve. A more detailed analysis of each type of pericardial valve should be undertaken to clarify its specific performance individually.
D. Pupello, et al., 2001	Bioprostheses	Valve replacement in older patients provides excellent functional improvement, reduces late cardiac events and enhances quality of life. The SF-36 can provide increased sensitivity in assessing the outcomes of treatment alternatives in older patients requiring heart valve replacement.
R. Riley, et al., 2000	Group 1: Freestyle Group 2: Toronto SPV	Aortic valve replacement with the Freestyle and Toronto SPV required equal time for implantation and had equal effective orifice areas. Freestyle had lower transvalvular gradient and less aortic insufficiency without increasing morbidity and mortality
F. Santini, et al., 1998	Group 1: Hancock Group 2: Stentless	Stentless valves are a valuable alternative to conventional prostheses in patients older than 75 years, although no great advantages with their use are apparent from this study. It would be beneficial to have continued evaluation particularly with regard to evidence of left ventricular remodeling and valve degeneration in the long term.
G. Van Nooten, et al., 1999	Stentless SPV Stented CE	Although the implantation technique is much more demanding for stentless procedures when compared with stented, elderly small-sized patients do very well with the large, non-obstructive prostheses.
T. Walther, et al., 1999	Group 1: Stentless Group 2: Stented	Regression of left ventricular hypertrophy occurs in all patients after aortic valve replacement. However, the use of stentless bioprostheses results in a significant improvement, which may result in a reduction of the cardiac risk profile for the patient.

4.1.3.2 Study Limitations

There were several factors that limited the quality of the studies. From a design perspective, the majority of studies were comparative cohort studies. Blinding was not a prominent feature of these studies and patients were often entered in a selective manner rather than a consecutive fashion. The studies were small in sample size and selection bias of patients appeared to contribute to major differences in the mean age, gender, and pre-operative health status of the comparative groups of patients entered into the studies. This was more apparent in some studies[44,49,57] than others.[45,52,54] For some cases,[40,46,49] comparison groups were not ideal; groups were lacking in similarities and occasionally were retrieved from a different population source or database. Difficulties were encountered in comparing studies as basic information as NYHA classification was not present,[40,46,47,50,55,56] and if it was stated prior to surgery, it was often not stated post-operatively.[44,49,51,53,54,62] There have been substantial changes in technology, perioperative care, surgical technique, and patient characteristics over the past 15 years. Studies included in the analysis may have been published in different surgical eras, or spanned several eras not taking into account surgical advances, the surgeons' experience, or the types of patients entered into such studies. Surgical techniques appeared to be standardized in over half of the studies presented but were either not present or not stated in the remainder. Study methodology including group selection did not follow any particular consensus with great variations in the statistical approach to the data. Limitations in following patients post-operatively appeared to be dependent on the size of the centre or volume of patients treated and in particular, the initial number of patients entered in the study. In general, large volume centres entered greater numbers of patients into the studies and tended to be more complete in their data, both in the short and long term follow-up. It was not clear from the studies what the specific resources were available that each centre dedicated to follow-up clinical and diagnostic assessment of post-operative patients.

Following exclusion of the case reports, case series and editorials, the vast majority of remaining papers were of a descriptive nature with respect to study design. A serious

limitation of the small number of studies that were included in the analysis was their lack of representation of the total body of literature available to the clinician. Another limitation encountered was the lack of clarity in the description of the study design. This left a substantial amount of the extraction of data open to interpretation bias. Another issue related to the lack of details recorded regarding the difficulty in designing or conducting particular surgical studies. The reasons for choosing a particular study design were not expressed by the investigators.

The Jadad and NOS scales were initially chosen for the systematic review as it was expected that reasonably well designed randomized controlled RCTs and cohort studies would be extracted from the literature search. However, it was difficult to apply these scales due to the extremely poor nature of the studies retrieved and all studies were simply classified as poor.

4.1.3.3 Standardization of Surgical Technique

A limitation in the analysis of study demographics was failure to discuss the type and standardization of surgical technique used. It was not clear in many studies whether all surgeons strictly adhered to the protocol in place at their respective institutions. This probably accounted for the fact that many papers did not state whether there was any standardization of the surgical technique. Other studies claimed to have standardized their technique, although, it was not clear how feasible that was or whether it was simply one surgeon who was the primary contributor to the study. The limited comparison of the operative technique used in the various groups of patients reduced the ability to generalize the results. Due to the lack of standardization, it was not possible to determine the true period of a patient's illness by using the date of surgery as a reference point as no details were recorded as to the duration of illness prior to surgery. Although information was provided about preoperative CCS or NYHA classification, this would not give insight into the rate of progression of symptoms and the general debility of patients that may have been living with the medical condition for many years. Hence, systematic bias

could have occurred from one centre to the next if one surgical group decided to intervene earlier in the natural history of aortic valvular disease compared to another centre. This would enable the results of the early intervention group to be possibly much better and hence, have a better prognosis as the patients would not be as ill. Limitations in the documentation of co-morbidities, concurrent therapy, and severity of aortic stenosis also prevented adequate comparison of studies.

The type of comparisons between the studies varied widely. Most authors used Student's t-test, however the Kaplan-Meier method, chi-square and the Fisher's exact test were commonly used tests. Variability in the statistical approach depended on the outcomes measured. The Student's t-test was the preferred method of analysis by most authors.

Blinding was not a prominent feature of the included studies. Due to the fact that it was always difficult to blind the patient and the surgeon from the surgical treatment in question, there were no further discussions in the studies about blinding other members of the investigative team including the individuals recording the data, statisticians, and the study nurse entering patients into the trial. Selection bias would be an important issue in many of the studies and could explain the major variations in patients' ages or the prevalence of one gender over the other in some studies. As well, without blinding, a substantial amount of bias might have been introduced so that certain patients would receive one therapy over another.

4.1.4 Performing a Meta-analysis and its Implications

A formal meta-analysis was not conducted. The lack of completeness of data and the presence of bias that is inherent to unblinded, nonrandomized and often uncontrolled trials especially seen in studies that evaluate heart valve substitutes preclude valid statistical pooling of data.

4.2 REVIEW OF OBSTACLES IN CONDUCTING CARDIAC SURGICAL TRIALS

4.2.1 Revised List of Obstacles

Based on the initial list of obstacles identified (***section 2.4.3***) and taking into consideration the experience of the systematic review of bioprosthetic valves, a revised list of obstacles was formulated. The new list is given below:

1) Difficulty with obtaining adequate numbers of patients for both treatment arms such that each treatment arm has a balanced proportion of patients with comparable co-morbidities and risk factors.
2) Inability to recognize sources of bias including patient selection, surgeon's preference, patient's self-selection, that is, referral bias.
3) Selection bias often due to lack of concealment of allocation resulting from inadequate randomization or knowledge of the nature of the disease process and surgical management of such diseases that could again lead to selection bias.
4) Inability to standardize patient care pre-operatively, intra-operatively and post-operatively which, for example, could be related to surgeon selection and preference, competence, critical care technique, anesthetic technique, and centre-specific resource availability.
5) Inability to include blinding as part of the study design.
6) Heterogeneity in the outcome assessment such as assessing valve hemodynamics with regard to echocardiographic protocol, technique, and timing.
7) Lack of training of the surgeon with regard to study design and methodology.
8) Difficulty in implementing a full randomized controlled trial beyond the stage of a pilot study.
9) Variability in patient compliance with regard to follow-up therapy and clinical evaluation.
10) Adequacy of funding for detailed follow-up on a long-term basis.

11) Absence of a consensus as to a standard protocol for extended follow-up of patients undergoing surgery.

12) Lack of control of associated medications including anti-hypertensive agents as well as anticoagulants and their interaction with the treatment effect of heart valve replacement.

4.2.2 Selection Results

A total of twelve papers were selected, four of which were from the Journal of Thoracic and Cardiovascular Surgery and the remainder were from the Annals of Thoracic Surgery. The details of the referenced papers are in Appendix J.

Fifteen other papers were excluded either because they were case series with less than fifteen subjects, or because they did not present any specific methodology comparing two or more groups of subjects. The balance of studies was on unrelated topics of a cardiovascular or thoracic nature. There were no other papers comparing heart valve substitutes in two or more groups of patients. There was a variety of case reports related to unusual or novel surgical techniques of heart valves, anecdotal reports, and editorials.

4.2.3 Description of Studies

As the objective of the search was to identify obstacles encountered by investigators comparing heart valve substitutes, any comparative study involving bioprosthetic valves as well as mechanical valves were included for analysis. Banbury carried out a study of 267 patients with non-random allocation of patients to echocardiographic analysis of the hemodynamics of aortic valve replacements using a bioprosthetic substitute.[67,68] The groups were not homogeneous as only patients with clinical indications underwent echocardiography. A "Premarket Approval Cohort" was used for comparison. No control was made for concomitant procedures performed in the experimental patient

population. No accurate comparative data were reported for comparison of the transvalvular gradient that was measured although the study did analyse patients for up to 17 years. There were no identifiable characteristics given for the comparison or control group. Study results focussed only on 85 of the 267 patients. Of the 267 patients followed, only 85 patients received the total of 168 echocardiographic studies over the 17 year follow-up period. The extent of follow-up for each of the 85 subjects was transparent enough to determine whether some patients received several studies and others only one study. The patients being assessed were followed annually during an office or hospital visit, or by means of a detailed questionnaire by mail or phone.

Butchert studied 1,766 valve replacements in the aortic, mitral and both positions with mechanical valve substitutes.[63] This study was not randomized and the authors did not comment on any limitations of their study. There were no controls, matching of patient populations, and randomization. Follow-up was based on clinical evaluation and those patients that did not attend were contacted by telephone. Results were compared with the literature from previous studies.

Cohen performed a comparative study with more attention being paid to randomization in the operating room and specific criteria being assigned to allow patients to be matched for suitability for both stented and stentless valve substitutes.[69] They did measure effective orifice areas, left ventricular mass regression, and controlled for concomitant cardiac procedures. As well, patient willingness to cooperative in post-operative follow-up was also taken into account prior to randomization and inclusion into the study. Although this study was quite detailed, long-term follow-up was considered to be the major drawback to assess late patient outcome and valve durability. A possible obstacle in the study, although not stated, was a lack of resources to conduct such a detailed study on a long-term basis. Goldsmith studied aortic, mitral and double valve replacements for a total of eight years.[70] Randomization was not discussed and follow-up was only 46.1 months on average. The authors felt that an increased evaluation time course was necessary to determine the long term durability of this bioprosthesis, although there were no explanations provided as to what obstacles were encountered in preventing such a

long term evaluation. Jamieson performed a comparative study without randomization with three treatment arms.[71] Data was retrospectively collected with comparison of effective orifice area and mean gradients between the prosthetic devices. Once again, these authors commented on the lack of significance of major differences between the devices and in particular, the need for intermediate long-term survival data. No obstacles were identified in this study. Khan evaluated mechanical valve substitutes in the aortic, mitral and combined positions.[64] As with other studies that were retrieved, this one was not randomized. Follow-up data were mostly achieved by annual questionnaires and reported by contact with a research nurse. No obstacles were identified although the authors commented that the study could not be randomized for comparison and admitted this was a possible source of bias. No reasons were provided. Mechanical valve recipients tended to be younger than the tissue valve recipients and were more often female in gender. This was not corrected for in the assignment to treatment.

Lim conducted a comparative study that was randomized and performed by five surgeons.[65] Although exclusion criteria were established in the selection of patients for mechanical valve substitutes, these authors identified clinical heterogeneity as being a major problem in balancing the two groups of randomized patients. They believed that a more sophisticated method of randomization including stratification, block randomization, or minimization could have been used although they did not identify any obstacles that would have prevented these techniques from being employed. In the study, the St. Jude mechanical bileaflet and the Carbomedics mechanical bileaflet substitutes were compared. These rather similar prosthetic devices were compared with respect to valve-related mortality, major thromboembolism, hemorrhage, and non-structural valve degeneration. Although the groups were similar in terms of demographics, preoperative clinical status and operative strategy according to the authors, they did not address the substantial variables introduced by the changes in operative and perioperative or anesthetic technique over a four year period, subgroup analysis of the aortic and mitral valve replacement group and the surgeons of groups assigned. The results of the study were disclosed at four years although initially the enrolment was to be over a ten year duration. The method of randomization was not specified.

The studies by Milano and Silberman were all retrospective.[72,73,74] Although these studies comprised less than 25% of this particular group of retrieved papers, they are representative of much of the literature of comparative studies done as noted in the systematic review of bioprosthetic heart valves. Once again the authors comment on heterogeneity of the study groups and the need for prospective studies as well as long-term follow-up. They do not give specific reasons as to what obstacles were preventing them from obtaining these facets in the methodology. Finally, the study by Vitale was performed as a randomized control study with enrolment being achieved through the multi-centre approach of eight academic cardiac surgical units.[66] The enrolment period lasted only about one year and all patients had a requisite six month follow-up. A double-blind method of randomization was carried out in this study. The authors admit that the major drawback was the rather short follow-up of six months. Patients that refused to undergo evaluation at six months were censored. The authors were actually able to identify differences in hemodynamics between the two valves that were studied. The authors were quite specific in determining how a cross-section area of the valve was measured and described the edge-to-edge method by echocardiography. Although this group addressed many of the barriers to randomized control trials, they implied that such a study could not assess long-term follow-up possibly related to inadequate resources.

4.2.4 Application of the Revised List to the Journal Review

Twelve obstacles were identified from the literature and refined using the systematic review of recent papers (section 4.2.1). A 12 X 12 table summarizing the assessment of the 12 obstacles for the 12 articles retrieved is given in section 4.2.4.5.

4.2.4.1 Participant Selection

Although patient selection was noted to be present in comparing different studies and

patient groups, this was not noted by the authors of the studies or not recognized as a factor in possibly biasing the study groups. Lim identified in their study a baseline imbalance in the two groups of randomized patients with more patients in the CarboMedics group being treated for infective endocarditis and congenital valve pathologic conditions.[65] These authors did admit that a more sophisticated method of randomization including strategic stratification, block randomization, or minimization could have been used. Furthermore, from the studies that were evaluated, several studies did not identify any method of randomization whatsoever.[63,64,67,68,70,72,73,74] Exclusion criteria varied from study to study with some studies excluding re-operation and others excluding the type of operation. Some of the studies included multiple valve replacements while others only involved replacements of the aortic valve.

4.2.4.2 Study Design

Some of the studies retrieved were retrospective in design. Many of these were database in origin with the major obstacle being the extent of detail of information entered into the database. No randomization was present and no details given as to the extent of follow-up, patient contact by telephone or clinical evaluation, or the duration and distribution of follow-up amongst various patients. As the follow-up was evaluated in patient-years, it was not clear as to whether the majority of patients were followed for extended periods or whether much of the follow-up years were measured as a result of a large number of patients being followed up for a relatively small amount of time. This would impact greatly on the incidence of complications, valve durability, prognosis, and co-morbid events that are often time related. Several authors commented on the need for long term follow-up but no reason was given for this. There were no comments provided to suggest whether inadequate financial resources, patient loss to follow-up or incomplete documentation were causative factors of the problem. Inconsistencies, quality of data collection and the ability of the investigators to maintain adequate follow-up on patients were apparent in the results although the details of assessment were lacking in the studies but, apparently, this was not recognized by most of the authors.

4.2.4.3 Heterogeneity of Measured Relevant Outcomes

Heterogeneity in the measured outcomes both primary and secondary, precluded adequate comparison of the studies, as there were as many measured factors as there were studies retrieved. Even clearly defined outcomes such as mortality and hemorrhage were variably defined from one study to the next. For example, mortality was reported as in-hospital mortality, 30-day mortality, valve-related mortality or long-term mortality at various durations. Hemorrhage could vary from a minor nasal, tracheal or rectal bleeding, to hemorrhage with or without hospitalization potentially needing transfusion. Variability was also identified in the time frames that were reported for follow-up and the morbidity or mortality that was measured at these points in time. Some studies reported early morbidity as complications while the patients were in hospital, events occurring at thirty days, or at six months. Long-term follow-up was measured at one year, eight years, ten years, or seventeen years. Most studies felt that long-term follow-up was a necessary factor to assess late patient outcome and valve durability. There were no specific reasons as to why this was not conducted, although there appeared to be a trend to publish interim data. The reasons were not given for this.

4.2.4.4 Assessment of Hemodynamic Function

Several studies evaluated regression of left ventricular mass index, transvalvular gradient, effective orifice area, and/or left ventricular outflow tract diameter. None of the studies measured all of these factors. Cohen (2002) identified over-sizing of valves as a cause of bias but did not report it as an obstacle to producing a suitable comparative study.[69] This study did, however, randomize patients in the operating room and attempted to standardize both patient populations by ensuring that surgical and technical requirements for implantation of both stented and stentless valves were met by specific criteria prior to randomization and entry into the study. Patients in this study were also screened to ensure a willingness to return for follow-up echocardiography post-operatively.

4.2.4.5 Obstacles Identified from Journal Review Appraisal

A summary of the results on assessing the obstacles in the journal review is provided in Table 4.10. Many of these listed problems were not explicitly stated by the authors. Recruitment, sources of bias, heterogeneity in outcomes assessment, and difficulty in implementing an RCT were the commonest problems cited by these authors. Lack of training and funding were not cited by any of the authors.

4.2.5 Financial Information Reported

The impact of financial contributions on the results of sponsored research may lead the surgical investigator to favour one valve substitute over another either consciously or not. Full disclosure of the sponsor on published research work allows the reader the opportunity to validate the credibility of the work. A search for sponsorship in published research will reveal information that the authors have chosen to disclose. Authors have not been contacted to obtain their financial agreements with valve manufacturers or granting institutions.

Appendix K summarizes the financial information extracted from two mainstream heart surgical journals. Six of the 12 studies did not report financial support for conducting the studies. Four provided details of the sources of funding. The sources were all from valve manufacturers. Two studies were not specific about the details for funding as the source may be institutionally based.

Table 4.10 Summary of Obstacles Assessed in the Journal Review													
Obstacles													
	Difficulty in adequate enrolment to balance comorbidities	Sources of bias recognized such as referral or surgeon's preference	Selection bias	Inability to standardize	Blinding issues	Heterogeneity in outcome assessment	Lack of training in methodology of surgeons	Difficulty in implementing RCT	Patient compliance	Funding problems for follow-up	No Standard Follow-up Protocol	No control of associated medications	Comments
Article													
E. Butchart (2001)	X	X	X	X					X				Funding by valve sponsor
S. Khan (2001)		X	X		X	X		X			X		
K. Lim (2002)	X			X		X		X					
N. Vitale (2001)		X											
M. Banbury (2002)	X	X	X	X		X		X			X		Funding by valve sponsor
M. Banbury (2001)													Funding by valve sponsor
G. Cohen (2002)	X	?	?	X		X		X				X	
I. Goldsmith (2001)													
E. Jamieson (2001)													
A. Milano (2001)	X			X		X							
A. Milano (2002)	X							X					
S. Silberman (2001)	X			X									

4.3 DESIGN OF A RANDOMIZED CONTROL TRIAL

Hemodynamic and Clinical Comparison of Two Bioprosthetic Stented Heart Valve Substitutes

4.3.1 Summary

In constructing a surgical trial comparing two bioprosthetic heart valve substitutes, the CIHR guidelines have been used. The information gathered in the first two steps of the thesis has been allowed a set of guidelines to be created that are recorded in Appendix N.

4.3.1.1 Background

Aortic stenosis occurs when the mobility and competence of the aortic valve that is essential to normal cardiac function becomes restricted resulting in resistance to the forward flow of blood through the pumping heart. The aortic valve serves an important role in the high pressure zone that anatomically divides the left ventricle and the aorta. Prosthetic heart valve substitutes are an essential modality of therapy for treating valvular heart disease. Several commercially available devices enable a surgeon to replace diseased heart valves. However, it is difficult to identify which is the best for durability, frequency of complications, and ease of implantation. The overall cardiovascular morbidity, mortality and life span of patients are affected by hypertrophy of the left ventricle. Resistance to the natural flow of blood across the aortic valve occurs as a result of a smaller orifice area and hence, produces an increase in the left ventricular mass. Maximizing the degree of reduction of left ventricular hypertrophy reduces the likelihood of incomplete left ventricular mass regression and lowers the ongoing cardiovascular morbidity and mortality.

The cardiovascular literature that reports on the performance of heart valve substitutes is

extremely inconsistent and consists essentially of case reports, case series observational studies and retrospective reviews. As such, the strength of these data is limited by study design and inherent bias. Population epidemiology studies estimate aortic valve disease to be about two percent. This is predominantly due to lack of detection as most people do not get examined regularly by a physician. Accurate diagnosis of the medical condition relies on the availability of cardiac ultrasonographers in addition to careful evaluation by a physician for an audible heart murmur. The goal of this research protocol is to perform a randomized control trial with specific attention to obstacles that would allow bias to be introduced into the analysis.

4.3.1.2 Objective

The objective of this proposal is to compare the hemodynamic performance between Valve A and Valve B in a randomized controlled patient population through assessment of transvalvular gradient, left ventricular mass regression at selected intervals, morbidity and mortality in adult patients with aortic valve disease.

4.3.1.3 Methods

This is a double-blinded, randomized, control trial. The objective of this trial is to determine if the choice between two bioprosthetic valve substitutes used for treatment of aortic valve disease in adults has an effect in the rate and extent of left ventricular mass regression, gradient and as well morbidity and mortality of such patients.

The two surgeons selected at each center would receive the usual method of practice at that center for operative and peri-operative care. Each center would be required to have two teams of physicians and staff. The blinded team would have no knowledge of the treatment allocation for the duration of the trial. They would be responsible for the pre-operative, anesthetic and post-operative care of the patients including assessment of the

patients for outcome measures such as echocardiographic follow-up, morbidity and mortality. The blinded team would be responsible for implantation of the device following randomization. The follow-up procedure for both treatment groups would be the same. Every effort will be made to conceal treatment allocation from the patient and the staff. Surgeons that are selected to implant the bioprosthetic valves should endure a learning phase so that she or he may familiarize themselves with implantation of the valve. Once the surgeon is comfortable with implanting the device, she or he may then start officially enrolling patients in the trial. A pre-operative echocardiogram will provide the baseline systolic aortic gradient, effective orifice area, and left ventricular mass. The hemodynamic parameters including cardiac index, right and left-sided filling pressures and degree of regurgitation will be collected.

Patients will be recruited over a five year period and followed for a minimum of 24 months. The average follow-up will be seven years. Each center would be required to have two teams of physicians and staff. The blinded team would have no knowledge of the treatment allocation for the duration of the trial. They would be responsible for the pre-operative, anesthetic and post-operative care of the patients including assessment of the patients for outcome measures such as echocardiographic follow-up, morbidity and mortality.

4.3.2 Background and Rationale

4.3.2.1 Epidemiology and Natural History

Unfortunately the incidence of aortic valve disease in the general population is undetermined but estimated to be around two percent. This is predominantly due to a lack of detection, as most people do not get examined regularly by a physician. In addition, many of the cases may not be identified unless the physician has a heightened awareness for such a murmur. Occasionally the transvalvular turbulence is inaudible.

Often only echocardiography will identify the condition. Accurate diagnosis of the medical condition relies on the availability of cardiac ultrasonographers which traditionally have tended to be concentrated in urban settings. There is also a fairly prolonged period of low morbidity that may go on for years possibly decades before the condition becomes clinically apparent. The severity of the stenosis may also remain stable for decades and then get worse over a relatively short period as one to four years of serial echocardiography has been used to follow the condition. There has been a slight increase in the incidence over the past decade. As senile degenerative changes in the valve account for the majority of cases in recent years this has been attributed to the aging population and more careful clinical evaluation of the elderly. Secondly, the greater availability of echocardiography has increased the likelihood of detection. Following the development of heart failure, syncope or angina, average survival is about two, three and five years respectively[8].

4.3.2.2 Treatment of Aortic Valve Disease

Although there have been major advances in the development of mechanical prosthetic and bioprosthetic heart valves, none of the commercially available devices are able to fulfill all the design characteristics sought in the ideal substitute. Mechanical prosthetic valves afford good hemodynamics and long term durability but they require anticoagulation due to their thrombogenicity and this is often associated with anticoagulant related hemorrhage. Bioprosthetic valves do not require anticoagulation on a long term basis as they are less thrombogenic but their durability is limited by structural degeneration, which is often seen in younger patients who have a greater metabolic rate and higher activity in their immune system. The ideal valve should decrease the work of the heart, function freely without any risk of structural failure for the duration of the patient's life, and should not produce destruction of any of the cellular elements of the blood or activate any protein systems.

There are five major types of valve substitutes that are composed of biologic tissue:

glutaraldehyde-preserved porcine valves, bovine pericardial prostheses, stentless valves, homografts and pulmonary autografts. These valves are suitable for patients who are at an increased risk of hemorrhage associated with anticoagulation, for patients that are unable to have good monitoring of their anticoagulation levels, and young women who wish to become pregnant. The latter are unable to take oral anticoagulants due to the teratogenicity associated with these medications in pregnant women. These devices have a much lower incidence of thrombosis and generally do not require the use of long term anticoagulant therapy. The major disadvantage with bioprosthetic heart valves is their limited long term durability associated with structural valve degeneration, which is accelerated in younger patients.

4.3.3.1 Description of Devices

4.3.3.2 Porcine Bioprosthetic Heart Valves

Porcine valves are treated with glutaraldehyde at a low pressure to maintain the pliability and leaflet structure and are then mounted on a cloth covered flexible wire or a plastic frame called a stent to maintain the occluding mechanism of the porcine leaflets. The flow characteristics and hemodynamic performance of these valves appear to be satisfactory in the aortic position when compared with the mechanical valves of larger sizes where there is also less shear stress to the blood elements. In the aortic valve position, the smaller sizes (19 and 21 mm) tend to be relatively stenotic producing some impedance of the outflow of blood from the left ventricular outflow tract.

Examples include the Carpentier-Edwards supra-annular porcine, the Hancock II porcine, the Medtronic Intact porcine, the Medtronic Mosaic porcine, the Hancock modified orifice porcine, the Biocor porcine, the St. Jude Medical Bioimplant porcine and the St. Jude X-Cell porcine bioprostheses.

4.3.3.3 Bovine Pericardial Heart Valves

This class of heart valve substitutes consists of stented valves where the leaflets are composed of pieces of the pericardium of bovine origin. The pericardium is the protective fibrous sack that surrounds the heart and parts of the origins of the great vessels in the chest. Several models made by a variety of manufacturers are available using similar engineering approaches. The three leaflets may be brought together either from three pieces of carefully cut pericardial tissue or from one strip. The orientation of the collagen fibers in the cusps is maintained by treatment with glutaraldehyde under conditions of zero pressure. A variety of chemical agents are used to treat the valve to inhibit calcium deposition, which results in loss of flexibility of the valve and tearing. The loss of flexibility can then lead to the leaflet tearing resulting in stenosis or stiffness and fusion, which can produce stenosis in the long term.

Examples of available pericardial substitutes are the Carpentier-Edwards Perimount pericardial, the Mitroflow Pericardial and the Sorin Pericarbon Pericardial prostheses.

4.3.3.4 Limitations of the Current Literature

There is a large volume of published material on aortic valve surgery, but it is not possible to overlook the limitations of this material. The limitation in the current literature makes it difficult to generate significant and concise conclusions regarding the hemodynamic performance, durability, and morbidity of biologic substitutes. Much of the published work on aortic valve surgery is found in case reports and series, observational studies of a retrospective nature, or prospectively conducted pilot studies of one or more types of prosthetic devices in a small patient population. Often information has been retrieved retrospectively from the medical records and suffers from limitations as patient selection bias, small sample size, interpretation of the data, incomplete charts, and inaccurately recorded signs, symptoms, complications and measurements. Comparisons and generalizations regarding valve performance and durability are made

with unmatched data obtained from studies with different methodology and different time frames, and occasionally compared with a data base. Also, patient selection criteria, patients' demographics, pre-operative and post-operative parameters, prosthetic devices, operative, anesthetic and post-operative techniques are inconsistently reported across the literature. In a comprehensive systematic review a total of four randomized clinical control trials were identified but two had to be excluded due to the subject material. These were studies involving homografts and the regression of left ventricular hypertrophy. After categorizing the studies based on the study methodology they were then classified according to the type of aortic valve prosthesis used. Due to the paucity of available literature the review was expanded to consider studies that used a cohort of stentless aortic valve prosthetics as well. Other trials have been conducted in a somewhat randomized fashion, one comparing two different types of porcine valves, another comparing pericardial and porcine valves in patients with aortic and mitral valve disease and a third study comparing the hemodynamic performances of different types of stentless and stented bioprostheses. The former studies essentially discussed structural valve degeneration, re-operation, durability and mortality.

Choosing the best bioprosthetic substitute is problematic to surgeons as it is difficult to find direct comparative data on hemodynamic performances. There is a lack of standardization in the hemodynamic parameters that are measured, sizes for the aortic valve substitutes, surgical technique, peri-operative management, and the details of follow-up data.

Accurate measurement of the annulus of the aortic valve and hemodynamic performance should be based on the specific internal diameter of the valve or effective orifice area. Hence there is a need for a methodologically sound, well designed prospective randomized controlled trial to assess the clinical outcomes after aortic valve surgery and as well to evaluate the best predictors of clinical hemodynamics. This study should also take into account the obstacles encountered by surgical trialists that hinder the implementation of such trials.

4.3.4 Device Descriptions

The Medtronic Mosaic® and the Carpentier-Edwards Magna® bioprostheses are both approved and marketed for the same patient population, including patients who have been diagnosed with aortic valve disease and require placement of a natural or previously implanted prosthetic or bioprosthetic valve.

4.3.4.1 Medtronic Mosaic® Porcine Bioprosthesis (Aortic Model 305)

The Medtronic Mosaic® is the latest generation of stented porcine aortic valve that is cross-linked and preserved in glutaraldehyde using a tissue fixation method unique to Medtronic called Physiological Fixation™ in which the aortic root is pressurized to its natural dimensions while the leaflets float freely at a zero net differential pressure. This method allows the valves to maintain their natural leaflet structure to help reduce cyclic fatigue. In addition, Physiological Fixation™ preserves the natural geometry of the aortic root, which allows the leaflets to open more fully, resulting in superior hemodynamics. The valve is then sewn into a Hancock II stent and treated with alpha amino oleic acid as an anti-mineralization agent to improve the durability further. The Mosaic® valve is designed and sized so that no part of the valve goes into the annulus (supra-annular) and the sizing technique should be done such that no part of the stent obstructs the flow area. It is aligned with the inside diameter to approximately match the annulus diameter by having the valve itself sit supra-annular.

4.3.4.2 Carpentier-Edwards Perimount Magna® Pericardial Valve (Model 3000)

The Carpentier-Edwards Perimount Magna® Bioprosthesis is the latest generation of stented valve constructed from glutaraldehyde-fixed bovine pericardial tissue. It is biomechanically engineered as a mechanical valve but with a biologic component and

designed using computer design techniques to determine the leaflet shape and stent configuration that produces a uniform stress distribution across the valve. The CE Perimount Magna® is a supra-annular prosthesis with tissue fixation with glutaraldehyde at approximately 60 mmHg. pressure. Each leaflet has a tab at each end. The three leaflets are then joined by wrapping and stitching the tissue tabs around a cloth covered plastic plug. The supra-annular construction ensures unobstructed flow maximizing the benefits of a large orifice resulting in better hemodynamics. The smaller sewing ring diameter allows a larger valve to be placed in a given patient's annulus with either the supra-annular or intra-annular placement. The scalloped shape of the sewing ring allows an optimal anatomic fit.

4.3.4.3 Contribution to Informing Clinical Decision-Making/Improved Understanding

The ultimate goal of this research is to assess the effectiveness of two types of stented bioprosthetic heart valve substitutes to help improve the clinical outcomes of patients who have undergone aortic valve replacement surgery. In a randomized control trial to identify the hemodynamic parameters that maximize left ventricular mass regression this study will determine the effect on the morbidity and mortality of aortic valve replacement using bioprosthetic substitutes in adult patients with aortic valve disease. The design and the results of the study will aid and encourage the development of future trials that accurately identify valves with superior qualities. This will allow the surgeon as well as hospitals to choose the valve design that best benefits their patients.

4.3.5 Objectives

4.3.5.1 Primary Objectives

The primary objective of this study is to compare the indexed left ventricular mass

regression between stented porcine and pericardial bioprostheses in a randomized patient population at six months, one and two years following implantation.

4.3.5.2 Secondary Objectives

1) To compare the systolic gradient across the aortic valve between two valve substitutes controlling for the annulus size at six months, one and two years post implantation.
2) To explore the correlation between the aortic valve gradient and left ventricular mass regression at six months, one and two years post implantation.
3) To identify differences in morbidity and mortality between two aortic bioprosthetic valve substitutes.

4.3.5.3 Study Hypothesis

The objective of this trial is to determine if the choice between two bioprosthetic valve substitutes used for treatment of aortic valve disease in adults has an effect in the rate and extent of left ventricular mass regression, gradient and as well morbidity and mortality of such patients.

4.3.5.4 Hypothesis

In adult patients with aortic valve disease there is a difference in the transvalvular gradient and the extent of left ventricular mass regression that occurs post implantation based on the choice of the aortic valve substitute used and this determines the morbidity and mortality.

4.3.6 Outcome Events

4.3.6.1 Primary Outcome Measures

The primary outcome is the indexed left ventricular mass regression at six months, one and two years post implantation measured by precordial echocardiography. Transvalvular gradients are obtained as part of the echocardiographic assessment.

4.3.6.2 Secondary Outcome Measures

Total mortality, cardiovascular mortality, survival, and complications.

4.3.6.3 Other Outcome Measures

CCS Class, NYHA Class, survival.

4.3.7 Study Structure

4.3.7.1 Study Design

This trial is a multi-center randomized double-blinded controlled trial of two treatment groups. The patients, the anesthetists, the post-operative caregivers, and statisticians will be blinded to the treatment allocation. The surgeon cannot be blinded to the device being implanted.

4.3.7.2 Trial Interventions

This trial will have two treatment groups. Eligible and consenting patients will be randomized in a 1:1 proportion to either of the two bioprosthetic aortic valve substitutes. All devices used in this trial will be the most up-to-date Medtronic market released valve substitutes obtained from the company.

4.3.7.3 Study Setting

The study will be conducted at the Hamilton General Hospital, Department of Cardiac Surgery in collaboration with the site coordinators at other centers involved.

4.3.7.4 Patient Population

The patient population 19 years and older who are in need of aortic valve replacement surgery and are candidates for a biologic valve. Eligible patients will be informed of the aspects of this study. After full discussion, the patient agrees to take part in the study, s/he will be asked to sign the consent form. The patient population must be geographically stable and able to attend follow-up examination at the study centre. Patients who are not willing to fully participate in the follow-up will not be entered in the study.

4.3.8 Study Population

4.3.8.1 Inclusion Criteria

Inclusion criteria for enrolling patients include the following:

- Adults 19 years and over with aortic valve disease undergoing first time replacement of the aortic valve
- A bioprosthetic valve substitute is the chosen option for the patient
- Patients undergoing aortic valve replacement and concomitant coronary artery bypass grafting
- Patients undergoing aortic valve replacement with or without coronary artery bypass grafting who have undergone previous bypass surgery

4.3.8.2 Exclusion Criteria

- Patients less than 19 years of age
- Have refused consent (refusal is from the patient or the surgeon)
- Patient suffering from a terminal illness with a life expectancy of less than six months
- Patients that have previously been enrolled in the study
- Patients currently enrolled in another surgical intervention study
- Patients who are unable to receive blood products (such as patients who are of the Jehovah's Witness faith, inability to receive a blood product, previous severe transfusion reaction, cross-matching technical difficulties)
- Patients undergoing primary or re-operative surgery for adult congenital heart procedures
- Patients who would be unable to return for clinical or echocardiographic follow-up

4.3.9 Methodology

4.3.9.1 Baseline Information and Pre-randomization Procedure

At the screening visit, patients will be provided with an information booklet describing the study. Prior to the study and randomization the surgeon will ensure that the patient is

eligible for the study. Informed consent will be sought for the surgery, post-operative care and follow-up visits. A study number will be given to the consenting patients. The patients will have a brief physical examination including weight, height, blood pressure and heart rate. A brief questionnaire will be completed regarding demographics (age, gender, smoking history, height, weight, etc.) and related risk factors such as alcohol consumption, dietary habits, and physical activity will be noted. Surgical and medical history as well as New York Heart Association (NYHA) functional Class, Canadian Cardiovascular Society angina (CCS angina) Class, hyperlipidemia, hypertension, diabetes, previous cardiac surgery, prior myocardial infarction, pulmonary disease, renal and hepatic dysfunction, peripheral thromboembolism and hemorrhagic events will be collected. A pre-operative echocardiogram will provide the baseline systolic aortic gradient, effective orifice area, and left ventricular mass. The hemodynamic parameters including cardiac index, right and left-sided filling pressures and degree of regurgitation will be collected.

4.3.9.2 Randomization and Allocation of Surgical Device

Eligible and consenting patients will be equally randomized to the porcine and pericardial bioprosthetic substitutes. Within each centre two surgeons will be chosen with an interest in aortic valve surgery. To reduce the heterogeneity of technique and experience, stratification will be performed to ensure that each surgeon has the opportunity to implant either of the two valves. To account for surgical experience, wherever possible, the surgeons selected will be with either five years of practice or less or greater than five years of practice.

Randomization will occur in the Operating Room. Patients will be randomized to receive one of the valves using the sealed envelopes. After the sealed envelope is opened the device type is revealed to the surgeon who will then use the respective product specific sizing device as per usual practice.

Central randomization will occur from the Hamilton General Hospital Coordinating Center. A telephone number will be available for randomization and study concerns. A set of envelopes will be delivered to each center in preparation for patients entered into the study.

4.3.9.3 Protecting Against Sources of Bias

To minimize the differences between the two study arms, standardization of anesthetic protocol, operative technique, surgical protocol and critical care support would be arranged through each Site Coordinator. The two surgeons selected at each center would receive the usual method of practice at that center for operative and peri-operative care. Each center would be required to have two teams of physicians and staff. The blinded team would have no knowledge of the treatment allocation for the duration of the trial. They would be responsible for the pre-operative, anesthetic and post-operative care of the patients including assessment of the patients for outcome measures such as echocardiographic follow-up, morbidity and mortality. The blinded team would be responsible for implantation of the device following randomization. The follow-up procedure for both treatment groups would be the same. Every effort will be made to conceal treatment allocation from the patient and the staff. Surgeons that are selected to implant the bioprosthetic valves should endure a learning phase so that she or he may familiarize themselves with implantation of the valve. Once the surgeon is comfortable with implanting the device, she or he may then start officially enrolling patients in the trial.

4.3.9.4 Generalizability

Steps have been taken to minimize the referral filter as well as understand its effects and the generalizability of study results. Patients will be recruited from large and small communities to each of the participating centers in the trial. Surgeons with particular

preferences for one valve over another or with special aptitude will not be selected as implanting surgeons. Hence, the surgeons that are recruited will have to go through a learning phase to familiarize themselves with these valves.

4.3.9.5 Ascertainment Bias

An adjudication process will be instituted to minimize ascertainment bias in primary and in the more subjective outcome measures. The Clinical and Valve Adjudication Committee will not have knowledge of the patients' treatment allocation.

4.3.10 Follow-up

4.3.10.1 Duration of Treatment Follow-up

Patients will be recruited over a five year period and followed for a minimum of 24 months. The average follow-up will be seven years.

4.3.10.2 Frequency and Duration of Follow-up

All patients will be seen in clinic follow-up visits at six weeks, six months, one year, two years and five year intervals. To maintain the blinding process, a separate file and data base will be kept for each patient for the follow-up visits. At each follow-up visit, the following information will be collected: echocardiographic assessment of transvalvular gradient, effective orifice area, left ventricular mass, left ventricular function, CCS Class, NYHA Class, clinical events, and complications. For patients missing LV mass assessment at six months' follow-up a slope will be calculated from the available measured data.

4.3.10.3 Complications

Valve related deaths, prosthetic regurgitation, prosthetic thrombosis/embolism, bleeding, endocarditis, thrombotic or embolic events, structural valve failure, re-operation and non-valve related deaths will be documented peri-operatively, post-operatively and at the interval time noted above. The reporting of mortality and morbidity occurring in patients after valve replacement will follow the guidelines of the American Association of Thoracic Surgeons (AATS). Definitions for peri-operative risk factors, NYHA functional class, CCS angina class, cardiac rhythms and complications are provided.

4.3.11 Statistical Considerations

4.3.11.1 Sample Size Determination

Anticipated LV mass indexed regression 120 g/meter^2
Anticipated between groups difference 15 g/meter^2 (approximately 10% difference)
Level of power 90%
Statistical significance 0.05

This calculation is based on a Student's t-test comparison of the change in indexed left ventricular mass. Analysis by slope would likely be more sensitive resulting in an even higher power. The anticipated volume of aortic valve surgery based on the Hamilton Health Sciences Cardiac Surgery data base shows that at least 200 patients and up to 275 patients per year undergo aortic valve surgery. A conservative estimate of at least 80% will be eligible for bioprosthetic valve substitutes as this would be the over 65 year age group. If the assumption is that 50% of patients agree to be enrolled in the study then the anticipated recruitment rate will be about 100 patients per year. To complete a one year

follow-up, the study would probably require about two to three years to enroll at least 200 patients and include the follow-up. The expected loss to follow-up is about 3%, possibly a maximum of 5% with crossovers generally considered not possible.

Annual Recruitment = N/ (1- 0.05) = 200/ 0.95 = 210 to account for loss to follow-up

The majority of the participating centers are referral centers. The referral base is well established for all of the centers. All of the centers have participated in the past in clinical trials including device trials. All participating centers will have an established valve clinic follow-up unit. The investigators recruited from each center will be chosen as those who regularly participate in Continuing Medical Education at the local and national level as well as having had experience in previous valve research. Recruitment will be enhanced through education. If patient recruitment has not been as anticipated from a particular center then satellite centers in those regions will be sought after to obtain recruitment of patients. If recruitment is still less than anticipated, recruitment can then be extended to non-Canadian sites.

4.3.11.2 Compliance

Compliance of the device therapy is considered to be near 100% as the patient does not administer the therapy. Once implanted however, compliance with anticoagulant therapy will be essential and is generally very good due to the close interaction of the patient and physician secondary to monitoring of the INR.

4.3.11.3 Loss to Follow-up

Patients may occasionally refuse to participate in follow-up and wish to drop out after initially consenting. They may change their mind or expire following implantation of the device. Imbalance in the two groups is less likely to occur as randomization occurs intra-

operatively just prior to device implantation. It is conceivable that due to technical difficulties that may be encountered by the surgeon cross-over from one arm to the other arm of the study may be possible intra-operatively and this is anticipated to be much less than 5%. Each center will be required to perform a minimum of five implants of each valve in the study prior to entry into the trial. It is anticipated that the learning curve should be relatively short as surgeons implanting the valves will have had experience with other bioprosthetic substitutes previously.

4.3.12 Data Analysis

As the valve technique is essentially similar to that which has been used for previous bioprosthetic substitutes interim analysis will not be performed and a principal analysis will be conducted at the end of the trial. The principal analyses of primary and secondary outcomes will use the intent-to-treat approach in which all patients who have a slope calculated for left ventricular mass regression in the randomly assigned treatment group will be included. Descriptive statistics will be employed to report patient characteristics, pre-operative and operative data. Comparison between categorical variables will be made using the Chi-square or Fisher's exact test as appropriate and continuous variables will be compared using the Student's t-test. Hemodynamic data will be summarized as mean and standard deviation and will be compared controlling for annulus size and valve type using paired and unpaired Student's t-test with corresponding 95% confidence intervals being calculated. The primary analysis will be comparison of left ventricular mass regression slopes using the t-test; also if required controlling for annulus size, age, gender, and surgeon using ANCOVA. As a secondary analysis, patients who did not have a slope calculated due to death will be excluded. Actuarial estimates of survival and freedom from morbidity events will be calculated using the Kaplan-Meier survival analysis method and will be compared using the log rank test for the two valve types. Multivariate proportional-hazards regression analysis will be used to assess which pre-operative risk factors such as demographics, NYHA functional class, annular size, and valve type are the best predictors of a composite endpoint of valve related or non-valve

related morbidity or mortality. A p value of 0.05 or less will be considered statistically significant for all the comparisons.

4.3.13 Committees

4.3.13.1 Executive Committee

The applicant, co-principle applicants and co-applicants form the Executive Committee (EC). It is the responsibility of the EC to act as the administrative and executive arm of the Steering Committee (SC), making decisions on behalf of the SC and prioritizing activities of the trial. The EC will be responsible for the conduct of the trial from conception to termination, interpretation of the result and final publication of the result. The principle applicant, Dr. Lloyd Semelhago, will serve as principle spokesman for the study, chair the Steering Committee and maintain communication within the study and with the industry partners. The co-principle applicants and co-applicants are to be nominated. They will be responsible for the collation and standardization of the echocardiographic follow-up data and methodology of the trial. The co-applicants are yet to be nominated. Surgeons at the respective centers have yet to be decided. The EC has met on several occasions to develop this trial proposal.

4.3.13.2 Steering Committee

The SC is the main leadership committee of the study and is the body which is responsible for the overall conduct and design of the study. They will appoint sub-committees and review the progress of the study in achieving its main goal. The members of this committee are yet to be nominated.

4.3.13.3 Safety and Monitoring Committee

This committee will direct the analyses needed for assessing treatment defects during the trial. Interim reports will be reviewed on a periodic basis such as every three months for evidence of adverse or beneficial treatment effects and accordingly will advise the committee regarding safety. This advice would be based on changes that are required for the treatment protocol. They will also provide advice to the SC on procedures affecting the quality of the trial. The members of this committee are yet to be nominated.

4.3.13.4 Adjudication Committee

This committee will be responsible for reviewing reports prepared by the Data Co-ordinating Center to detect deficiencies in data collection or intake processes and recommend alternate actions if required. They will advise the SC on important policy issues and review and approve recommendations from the Safety and Monitoring Committee. The committee will be also responsible to review the data of two outcome events, namely (1) cardiac deaths, (2) non-cardiac deaths.

4.3.13.5 Echocardiographic Sub-committee

This committee will be responsible for establishing protocols and guidelines for standardization of echocardiographic technique, measurements related to hemodynamics, effective orifice area, and left ventricular mass regression. These will all follow guidelines established in the echocardiographic and cardiologic literature regarding assessment of bioprosthetic heart valve substitutes.

4.3.14 Ethics Review

4.3.14.1 Institutional Review Board/Ethics Committee

This protocol will be approved by the Institutional Review Board of each of the participating clinical centers.

4.3.14.2 Informed Consent

Before any study related procedures are performed patients will be approached for informed consent by the investigator or research nurse and explain the potential advantages and disadvantages related to the study in detail. The principles and the protocol objectives will also be explained in a simplified manner to obtain a signed and dated declaration. This will be stored in the patient's file. Informed consent also implies individual discussion with the patient about the nature of the valve option and explanations that are specifically conducted in a language that is easy to comprehend. The patient will be also notified that if she/he refuses to participate in the study the quality of their subsequent medical care will not be affected. Should a protocol amendment be made, the patient consent form and information sheet may be revised to reflect the change in the protocol. It is the responsibility of the investigator to ensure that the amended consent is approved or reviewed by the Institutional Review Board and that it is signed by all patients subsequently entered into the study as well as those currently in the study if affected by the amendments.

4.3.14.3 Risks to the Participants Involved in the Trial

The two valves that have been chosen for the study have been in use throughout Europe

and North America for at least the past five to ten years. The valve that the patients will receive hence does not pose any additional risks to the patients as the study serves to compare the two valves in a methodologically sound trial.

CHAPTER 5

DISCUSSION

5.1 BRIEF SUMMARY OF THE THESIS

There were three objectives proposed in this thesis. The first objective entailed a comprehensive and systematic review of the literature on survival benefits, morbidity and mortality associated with the surgical treatment of aortic valve disease in adults. A major facet of this related to the limitations in developing a systematic review and a meta-analysis. The intent in the initial proposal was to come up with a meta-analysis and it was expected that much of the surgical practice of cardiac surgery is substantiated by double-blinded randomized controlled trials. This was clearly not the case even though the thesis design took into account the possibility of a statistical analysis including quality assessment of the studies that would be retrieved. Limitations of the method of the systematic review are provided in section 5.1. The second objective proposed in the thesis entailed a literature review of surgical journals to identify obstacles in conducting a clinical trial in cardiac surgery. This was not intended to be a systematic review or meta-analysis. It was simply a search for obstacles to identify why most of the scientific literature in cardiac surgery consists of case series, case reports, and retrospective reviews. Only small pilot studies have been identified as a comparative group in substantial numbers. Hence, the difficulties in conducting surgical trials or the obstacles that prevent the completion of randomized controlled trials are provided in section 5.5. The third objective of the thesis was to create a framework for the design and implementation of a surgical trial. A framework has been created as described in Appendix N and a full CIHR protocol prepared in section 4.3 of this thesis.

5.2 *LIMITATIONS OF THE METHOD OF THIS SYSTEMATIC REVIEW*

The **first objective** proposed in the thesis entailed a comprehensive and systematic review of the literature on survival benefits, morbidity and mortality associated with the surgical treatment of aortic valve disease in adults. Although it was the initial impression that most of the literature consisted of case series, it was unexpected that so few RCTs would be available to subject to a meta-analysis. Extreme heterogeneity was encountered in the structure and content of the few studies encountered. The literature search, study selection, extraction of data, and evaluation of this systematic review was subject to several limitations. Although the computer search was performed with the assistance of an experienced information specialist, retrieval of articles was subject to the limitations of the key words used. An extremely wide net was cast, both in the time frame and in the use of databases such as EMBASE, bibliographies, manual searches through texts, monograms, and journals. There was considerable overlap between the EMBASE and MEDLINE searches and this was possibly related to the fact that much of the cardiac surgical clinical valve research is published is a small number of journals that reflect the experience of a wide span of countries. This specialty has traditionally been restricted to tertiary care centres particularly outside North America, Europe, and Japan. These centres have been academic and tended to publish their results in the few journals dedicated to this specialty. Time constraints reduced the comprehensiveness of the search of grey literature and unpublished manuscripts. Non-English studies were not automatically excluded and an attempt was made to obtain translators for those abstracts that could not easily be excluded by the English translation. The assistance of an information specialist was necessary to retrieve full articles appearing to meet the inclusion criteria and this was not a blinded process. Articles that were unclear and which did not follow the systematic criteria for inclusion were referred back to the thesis supervisor for assessment. Overall, the criteria were clearly defined and this made the decision relatively easy for inclusion in the analysis.

Another limitation encountered with the methodology related to the quality assessment of the retrieved articles. The Jadad Scoring System and NOS were selected over other

quality appraisal instruments as the former is the most widely used with some validation and the latter has been validated but not published as yet. In addition, the National Health Service published a monograph on non-randomized studies identifying the NOS as one of six instruments selected for assessing quality. All articles were of such low quality that their inclusion in the analysis would not be able to yield additional information. Specifically, these articles were all the same, low in quality and nongradable. Hence, they were not assessed formally but agreed upon within our committee. The quality of the studies was considered poor enough that the studies included could not be graded at scores of more than zero or one, and hence an inter-observer agreement was not attempted. It should be noted that although these were the issues considered during the design of the thesis, it was not quite expected that the studies retrieved would be so few and not amenable to scoring.

The two journals of interest were the Journal of Thoracic and Cardiovascular Surgery and the Annals of Thoracic Surgery. These journals were not part of a systematic review but rather were used to test the hypothesized obstacles on publications to determine whether the authors of these studies encountered any such obstacles and whether any other was identified. Although only two journals were used, the majority of peer-reviewed articles were to be found in them for this specialty. Although the initial proposal did state that a two year period would be reviewed, only a single year period was necessary for these two journals as an adequate number of publications were available to test the obstacles.

5.3 UNIQUE FEATURES OF SURGICAL TRIALS

Surgical trials present features that distinguish them from a variety of other scientific studies but in particular, comparative studies of medical treatments. Surgical trials tend to compare single event procedures that irreversibly alter the human body and only occasionally multiple procedures may be part of the clinical treatment. Alternatively, medical treatments tend to be ongoing therapy with repeated administration of a pharmaceutical agent.

The methods by which patients are followed up in surgical and medical trials also are quite different. In general, patients after surgery are assessed primarily with regard to pre-discharge symptoms, complications, and improvement. Major studies may include a post-operative visit prior to being discharged from the care of the surgeon. As there are often no ongoing procedures that are necessary for the patient, these along with improved symptomatology make adequate follow-up difficult. The patient and/or the surgeon may find it unnecessary to meet with regard to clinical evaluation. As well, the patient may not cooperate, move to another location, or become lost to follow-up for other reasons and this may be more prominent as these types of trials tend to have a one-time therapy. Hence, there is a major shortfall in the details of post-operative follow-up. In contrast, medical trials tend to have clearly defined endpoints and follow-up assessments, and following termination of the trial the patients could be entered into other protocols.

The upfront risk of a surgical intervention is much more substantial than the risks of treatment with medications, particularly since the latter tend to have undergone extensive animal studies prior to administration in human beings. The attendant risks of a surgical procedure, including the associated anaesthetic and post-operative complications, tend to be endured by the patient as a single event compared with the ongoing risk of long-term therapy from a medication. This creates the added problem of identifying suitable controls in developing a comparative study. Control group individuals may not want to undergo operative intervention with the attendant anaesthetic risks or pain if there is no substantial personal gain to them. Associated risks of the procedure to vessels, nerves, and muscles, including post-operative complications, as well as pain are all included as the initial event that an experimental surgical group is exposed.

A major factor that precludes comparative studies involving surgical procedures lies in the technical expertise of the surgeon or group involved. There are substantial differences in surgical techniques, experience, perioperative support, and surgical preferences that introduce a considerable degree of heterogeneity in dispensation of a procedure, and which interfere in the comparison with other procedures. A sensitivity

analysis by surgeon may address this problem. Randomized control trials involving medications do not require any standardization of the technical skill of the study investigators. Hence, prolonged training periods for research personnel are not necessary in the latter studies.

5.4 AORTIC VALVE SURGERY AS A SUBJECT OF STUDY

Aortic valve surgery has been chosen by the author as a subject of study due to familiarity with the disease condition, techniques, and most importantly from the paucity of strong evidence available in guiding its practice. Aortic valve surgery is quite representative of many other surgical specialties in that much of the evidence has been based on poorly structured outcome evaluation, case series, and relatively few comparative studies, particularly randomized controlled trials. Choosing one prosthetic valve over another has been based largely on non-comparative work published by the manufacturers of such devices. It has become evident early in the review of the literature that a meta-analysis would not be possible because of the quality of data present. As part of the thesis, a system to assess previously conducted surgical studies was necessary. A comprehensive search of two major journals, specific to the surgical specialty, was able to identify some of the obstacles but, more importantly, as will be discussed later, failed to reveal obstacles that are normally encountered by surgical trialists. This work would potentially lead to a methodological blueprint for future surgical studies involving aortic valve substitutes. The thesis evaluated bioprosthetic heart valves with exclusion of a variety of other classifications of substitutes to reduce the heterogeneity that is inherent in surgical trials.

There are several limitations in this subject as a choice of study. Firstly, the methodological quality of the studies retrieved was exceedingly poor precluding the adequate use of a scaling system to rate the papers. As randomization is not a feature of reported surgical publications, a variety of biases is introduced into the analyses and these cannot completely be extricated from the findings of the thesis. Secondly, clinical

heterogeneity of the patient populations found in the studies prevents any comparison of the outcomes. Meta-analysis is also not possible due to the different variables measured by each study. Thirdly, the topic chosen is a somewhat esoteric part of the surgical specialties and not all issues may be applicable to other surgical fields. Certainly, the challenges encountered in the systematic review and the identification of obstacles are novel and not seen in medical trials. Although the goal of designing a surgical trial is to assist in the assessment of prosthetic heart valves, the principles would be applicable to all surgical studies.

5.5 MEASURED OUTCOMES

In the post-operative evaluation of patients, a variety of outcomes have been measured and reported in previously published works. Morbidity and mortality rates, as well as survival, are considered to be important outcome determinants of success. The primary outcome of left ventricular mass regression was selected as the most important factor that leads to the long-term survival of patients with regards to death, and freedom from recurrence of angina, congestive heart failure or syncope. The proportion of survivors in a group followed over a period of time that are alive at the beginning and those who survive to the end of this particular interval have been frequently used as a method of reporting survival rates. A variety of statistical procedures has been involved in reporting survival. Complete standardization of reporting has not yet become widespread in the reported surgical literature. Nevertheless, late mortality, and complications such as thrombosis, embolism, hemorrhage, primary tissue valve failure, bacterial endocarditis, re-operative rates, structural valve degeneration, left ventricular mass regression, functional classification, effective orifice area, and regurgitation are measures that are repeatedly reported in the literature. These events tend to be less likely to be affected by subjective evaluation. They do, however, depend on the comprehensiveness of the follow-up.

The length of hospital stay, total cost of hospitalization, quality of life, and subjective feeling of wellness are usually affected by multiple factors that may be subjected to bias. This bias may originate from the reporter, institutional costs, and efficacy of the general delivery of health care at a particular site. Such variations may be substantial and would interfere in the identification of small clinically important differences in the functioning of two comparable prosthetic devices.

5.6 OBSTACLES IN CONDUCTING SURGICAL TRIALS

The **second objective** proposed in the thesis entailed a literature review of surgical journals to identify obstacles to conducting a clinical trial in cardiac surgery. This objective was fulfilled with completion of a summary list of identified obstacles. The author sought out obstacles prior to conducting the formal search by discussions with surgical trialists and research assistants. Some obstacles were identified prior to the literature search, but only a few were clearly reported by surgical authors. Often only pilot studies were conducted and subsequently presented at specialty conferences with the conclusions of such projects citing the need for a large multi-centre RCT. There would be no detailed evaluation of the feasibility of a larger study.

There were several points that did not manifest themselves through the literature search. Firstly, the journal review only looked at obstacles encountered by investigators that were successful in conducting and publishing surgical studies. Obstacles encountered by surgical trialists that failed to publish their work would never have become known. As a corollary to this remark, works that have failed to meet acceptance criteria to the editors of peer-reviewed journals could quite easily have found their way into publications and circulations that are not conventional or possibly journals produced by professional associations or private health care facilities.

Secondly, the clinical heterogeneity of the patient populations enrolled in any comparative study were difficult to overcome and only occasionally recognized as a

problem by the investigators. Hence, it was quite common to retrieve studies where two valve substitutes would not have comparable results. This resulted in discrepancies between centres when one centre would identify a comparable performance by two substitutes while another centre would find a difference between the same two substitutes. Since these prosthetic valve devices are quite costly, only small comparative studies could be conducted, generally funded by the manufacturer that would be supplying the devices. This could potentially lead to conflict of interest in reporting data. Generally, randomized controlled trials have been funded by industry but case series, outcomes analysis, and retrospective reviews tend to be university or clinician sponsored. Disclosure rules have been more rigorously applied in medical journals and presentations and, although financial reporting is necessary for surgical trials including outcomes evaluations, this was not apparent in the review of journals for obstacles and financial reporting. In fact, batches of valves supplied to hospitals as a part of any budgetary agreement were never documented in the methods section of any of the extracted papers.

Another important factor that does not become apparent in the review for obstacles in preventing clinical trials is the difference in the extent of regulations in designing protocols for medical devices. There are far more pharmaceutical firms than there are companies that manufacture implantable medical devices partly because the history of pharmacology dates back to the earliest years of the health care professions. Regulations for the introduction of medicines to human subjects have been very well developed over the past century and the widespread consumption of therapeutics has made available adequate financial resources to such firms to have the capability of conducting large, well-designed studies to evaluate drugs.

As it has been unethical to use a placebo treatment group in the evaluation of a device, the literature on the clinical evaluation of medical devices reflects the absence of placebos. Similarly, device manufacturers often do not wish to compare directly their product with a prosthetic valve that may be currently in use belonging to a competitor. Hence, when open label trials are conducted where there are no blinding strategies, objective measures such as mortality, survival, stroke, hemorrhage, and so on are more

likely to be relied on compared with more subjective factors either actual or perceived such as quality of life, symptom improvement, and degree of valve degeneration.

Traditionally patients have always had a right to full disclosure about what operation is being performed on them. For example, if a patient undergoes a resection of the colon, the type of operation that is performed is of value to the patient as well as subsequent physicians involved in treatment of that patient years later. Similarly, if a device is implanted such as a pacemaker or a heart valve, it is of importance to know the specific device that is used as this would affect programmability and lifespan of the device if it were a pacemaker or anticipated degeneration of a bioprosthetic substitute. Another example could be that if a coronary stent is placed, patients and subsequent physicians may wish to know when the device was implanted and whether investigation such as magnetic resonance imaging could be performed with such a device in place. It could be potentially unethical for a patient not to be made aware of therapeutic procedures being conducted and possibly quite dangerous. The effect of a device or a procedure tends to be permanent. Medications tend to produce an effect as long as they are taken and this effect washes out when discontinued. The right of a patient to be aware of what medication is being used in a medical trial may be more of importance if concomitant drugs are being administered to deal with interactions. It may be less important to the patient to be aware of the drug after it has been discontinued. Full information can be provided to the patient except the specific device being implanted and he or she can be informed of their right to know only if requested. While it would be ideal for the surgeon to be not aware of what specific device is implanted, it is impractical as the surgeon that is doing the procedure is usually aware of the model of valve or the pacemaker that is being implanted for example. More importantly, it is not possible for a surgeon to be not aware of what is being done to the organ in question. From a practical standpoint, the independent assessors that are analyzing primary outcomes should be blinded so as they are not aware of which device was implanted into which patient.

5.7 TRADITIONAL TYPES OF CARDIAC SURGICAL RESEARCH

Well in excess of 90-95% of all publications in the cardiac surgical literature have been non-randomized and non-comparative studies. There has been an abundance of pilot projects, case reviews and case series, editorials, opinions, retrospective studies, and database reports. The majority of the studies were not controlled and comparative. Very few authors provided an explanation for the choice of design and there are several possible explanations for this. Prior to initiation of this thesis, I believed there would be a sufficient number of randomized studies to enable a meta-analysis to be performed.

The first major factor implicated has been the ethical concerns associated with randomizing patients to a treatment that has been considered beneficial in the treatment of a surgical illness. It is inappropriate for a patient not to know what is being performed on them, what are the long term implications of such treatment, its complications, and most importantly, of not having it done. Similarly, it is also very important for the surgeon to know whether the therapy that is provided is working, the kind of post-operative treatment that is necessary, and the follow-up of that patient. This has created a problem with enrollment of adequate numbers of patients to provide a comparative study with an adequate sample size.

A second major factor in determining the type of studies conducted relates to the availability of resources and knowledge of study designs. Surgeons have been late entrants into the sphere of randomized clinical studies. The nature of the clinical work of surgeons prevents them from being available outside of the operating room to devote time to clinical investigation. Compounding this problem is the traditional nature of surgical procedures which often requires nighttime work and irregular hours that can significantly interfere with the organization and administration of a surgical trial. The general absence of training and research methodology has only become an adequately addressed issue over the past decade with most subspecialty training requiring at least one or two years away from the operating room to devote full-time to research. With the preference of resident training focusing on acquiring clinical and operative skills, this

will always remain a challenge in surgical training.

Case series, case reports, pilot studies, and editorials comprise a large proportion of the traditional study design because they are less time consuming, cheaper, do not require a comprehensive knowledge of study design and do not interfere with the ethical dilemmas associated with blinding, withholding treatment, or exacerbation of the already high stress level of patients undergoing an operative procedure. Of interesting, surgical practice has been greatly influenced by such weak study designs and this may be due of several reasons. Firstly, outcomes analysis is a powerful motivator to change individual surgical practices and to introduce new ideas or techniques. Secondly, clinicians tend to be strongly influenced by studies performed by their colleagues and this is particularly important in surgical research, as much of this has traditionally been conducted by surgeons themselves with generally less influence by commercial interests.[33] Third, there are multiple differences between centres that are uncontrolled and these may relate to anesthetic technique, post-operative care, surgical approaches, and concomitant medical treatment that can produce variations in both short and long term outcomes between centers. These may serve as a driving force for surgeons to perform similar study designs that compare outcomes to identify what factors may be important in determining survival, left ventricular mass regression, or complications.

Publication bias should be considered an important issue in the cardiac surgical literature due to the paucity of studies reporting on the negative performance of one valve in comparison with another. In general, the studies tend to show a positive benefit of medical devices that are newly introduced into the clinical field. Studies with negative findings or studies with adverse effects from medical devices tend to not be reported in the literature.[78]

Selection bias can occur due to a knowledge of allocation of the groups by lack of concealment. Such knowledge is difficult but not impossible to hide to the large team that is necessarily works intimately with the surgeon and patient. This bias may occur in a RCT due to inadequate randomization. In cohort studies, this bias may be due to breach

of the rule of enrolling consecutive patients that satisfy eligibility criteria.

5.8 EVOLVING TECHNIQUES AND STANDARDS OF CARE

The **third objective** of the thesis was to create a framework for the design and implementation of a surgical trial. As indicated in Chapter 4, the choice of study design recommended for surgical trials is the RCT given the equipoise between new devices and current prosthetic valves being used. The RCT can only be possible given patient availability, adequate funding and expertise in designing and implementing such trials. The comparison of two bioprosthetic heart valve substitutes appeared to be a reasonable starting point for several reasons. Firstly, this area of surgery is familiar to the author. Secondly, comparison of two prosthetics is quite problematic as noted in this chapter. Thirdly, there is a strong aspiration on the part of the surgeons to acquire clear and reliable information regarding the durability, performance, complications and ease of implantation of such medical devices. Fourthly, a reproducible method for evaluating these devices is needed to obtain consistent data on presently available devices as well as future developments.

Over the past 20 years, major strides have been made in all facets of medicine, pharmacologic agents, critical care, and surgical techniques. Better surgical techniques and improved medical therapy of patients in the post-operative period have produced major reductions in morbidity and mortality in patients undergoing major types of surgery especially pertaining to cardiovascular diseases. This has also led to more complex and sicker patients being treated and in particular, over the past five years, patients of advanced age. Therefore the mean age, range of severity of illness, and standard of care has all changed and this has resulted in a difference in the morbidity and mortality of operations depending on the era when they were operated. This has also, in the opinion of the author, led surgeons to become somewhat conservative in trying new prosthetic heart valves if a current one in use has a proven and long track record. Long follow-up periods are necessary to enable surgical practice to adapt and change if

surgeons are unwilling to try a new product when the current one in use has been demonstrated to have satisfactory results. As for their patients, surgeons are reluctant to take unnecessary risks if the current standard of care or technology is acceptable.

Medical technology, particularly relating to heart surgery, only began to make substantial advances in the mid-1970's and appropriately the Medical Devices Amendment was passed in 1976 in the United States. These regulations required comprehensive testing of devices and their component materials with the intent to improve the standards of introducing new devices into the market and as well to improve safety. These regulations, however, were late in comparison to those that had been prepared years previously for medications.

5.9 POPULATION AND SAMPLE HETEROGENEITY

Heterogeneity of the patient population is the single most prominent factor that characterizes the patients that are entered into cardiac surgical studies. It obscures the presence of any true differences between control and experimental groups as well as between studies. It precludes any form of meta-analysis and has reduced analysis of the literature to only descriptive formats. Surgeons that are tempted to increase their homogeneity of the patient populations entered into their trials by stringent eligibility criteria have failed to either enroll adequate numbers of patients or to complete the study in a reasonable length of time. Even using multi-centre approaches for recruitment has introduced systematic differences that are present between centers as well as selection bias of patients that each centre uses. For example, large centres may be surrounded by more referring specialists such as cardiologists, and have more diagnostic facilities to perform accurate echocardiography such that cases may be referred for surgery at an earlier date. A small non-academic centre may elect to surgically treat simpler cases in patients with fewer co-morbidities.

There are three major sources of heterogeneity: patient sources, hospital sources, and

duration of study. Examples of patient sources of variability and heterogeneity are the incidence of co-morbidities such as diabetes, hypertension, renal failure, chronic obstructive pulmonary disease, previous cardiac surgical procedures, coexistent infection, peripheral vascular disease, cerebrovascular disease, age, and concomitant medications such as anti-hypertensive agents or anticoagulants.

Examples of hospital sources that introduce heterogeneity include the kind of anesthetic technique delivered, variations in ICU protocol, availability of hospital beds and specialized personnel to provide a shorter waiting period, and whether a single surgeon or a group of surgeons are involved in the implantation of the prosthetic valve.

The time when a study is conducted also has an important bearing on the outcome. Changes in technology over the past 25 years including better ventilators, cardiopulmonary bypass circuits, advancements in surgical instrumentation, new techniques in anesthetic monitoring, and a variety of new drugs such as antibiotics, antifibrinolytic agents, or inotropic drugs have an impact on the kinds of patients that are selected for surgery, their outcomes and complications. There have also been advances over the past 20 years in the understanding of the pathophysiologic processes associated with the stress of surgery, utilization of physiologic solutions, and blood conservation strategies. There have been better antibiotics developed, and the general surgical approach to management of these patients has also been substantially streamlined.

Finally, there has also been a change in the course of management of aortic valve disease and the timing for surgery. Diagnosis of the illness is picked up early with the increased availability of echocardiography, and patients are followed more closely and accurately so that surgery is performed in a very timely fashion. Availability of diagnostic equipment, cardiologists, and general medical care varies from one city to the next and may have an impact in the prompt and timely treatment of aortic valve disease.

5.10 OBSTACLES IN OUTCOMES ASSESSMENT

Details of follow-up on outcomes are limited and sketchy for post-operative cardiac patients for several reasons:

1. Patients feel well enough not to return for invasive or non-invasive diagnostic studies. Examples of these are transesophageal and precordial echocardiography.
2. A lack of resources to perform comprehensive follow-ups. These may include available clinic time and space, diagnostic facilities and surgeons' time.
3. Long-term outcomes related to durability of bioprosthetic valves require many years to assess. Patients often move geographically, succumb to other illnesses, or refuse further evaluation if they feel well. Investigators may also relocate or simply lose interest in the study. The surgical investigator may also choose to stay with implantation of a particular prosthesis if satisfied with the technical ease of the procedure or a paucity of operative complications.
4. New standards of care arise with completely novel approaches to surgical diagnosis and treatment of valvular heart disease, including the timing of procedures. Examples of diagnostic advances are better echocardiographic techniques, standards, equipment and availability for earlier diagnosis. Examples of perioperative care include better anesthetic, perfusion, and critical care. This will become more likely in long-term outcomes assessment.
5. Blinding of the choice of valve substitute may become more difficult as the years of follow-up go by due to the inherent curiosity of the patient and surgeon about what device has been implanted. Patients that are circulated through the various diagnostic personnel or who encounter other heart surgical patients may eventually receive information about their own operation and this may bias their subjectivity or that of the surgeon. The longer the duration of the study, the more likely this bias will occur.

CHAPTER 6

CONCLUSIONS, SUMMARY AND RECOMMENDATIONS

6.1 CONCLUSIONS – CONTENT

The systematic review of the published health care literature showed that most publications in cardiac surgery are not comparative trials. The vast majority tend to be case reports, case series, outcomes research, editorials, and reviews. Randomized control trials are rare where it is a surgical technique or medical device that is being evaluated. Studies that are conducted by surgeons that are published in surgical journals may follow the double-blind randomization strategy if it is a medication that the surgical group is evaluating. There are multiple deficiencies that preclude successful completion of randomized control trials. These include:

- lack of awareness on the part of the surgeon with regard to study design and methodology;
- heterogeneity in patient populations as well as in methodologies for assessment of valve hemodynamics;
- inadequate funding for detailed follow-up on a long term basis;
- difficulty in acquiring adequate numbers of patients for both treatment arms to obtain a balanced proportion of patients with comparable co-morbidities;
- inability to randomize and blind due to the nature of the disease process and surgical management;
- inability to control and recognize sources of bias including patient selection, surgeon's preference, patient self selection, and referral bias;
- variability with regard to a protocol for long term follow-up including patient compliance with regard to follow-up clinical evaluation;
- inability to control associated medications including anti-hypertensive agents and

anticoagulants and their impact on long term results.

There are other factors reported in the body of the thesis that are also contributory.

6.2 CONCLUSIONS - PROCESS

Despite the comprehensive literature search, the relatively small group of papers that were obtained for subsequent evaluation could not be characterized adequately to perform a meta-analysis. With the variation in study designs, population heterogeneity, interventions, and a variety of outcome measures including the time to follow-up it was not possible to perform a meta-analysis on the twenty-three studies finally selected. With the variations in outcomes assessed and the times at which they were assessed as well as missing data, it was also not possible to perform a chi square test for homogeneity.

A major concern in the systematic review and identification of obstacles was the presence of bias. To increase the reproducibility of this review, a variety of factors were introduced into the selection and data extraction processes. These included explicit criteria for selection of the studies. Those that were brought into question were discussed with the thesis supervisor, while those that were of borderline importance prior to exclusion were detailed in the review. Due to extreme heterogeneity of the papers that were finally included in the systematic review, one can conclude that substantial variations can exist in clinical findings in studies comparing two bioprosthetic valves. The cases of this are multi-factorial as described in Chapter 5.

6.3 SUMMARY

The relative paucity of comparative studies evaluating bioprosthetic heart valves and in particular randomized control trials occurs because of the many challenges in the design and implementation of surgical research. The study methodology of clinical research that may be applied to non-surgical studies cannot be easily applied to surgeons.

Many of the problems that have been used to support this position are elucidated in the revised list of obstacles. The patient population available for enrolment into surgical trials is extremely small in comparison to those that can be enrolled for many medical trials. Recruitment is an issue and informed consent is difficult given the rather irreversible nature of surgical procedures. To obtain a balanced proportion of patients with comparable co-morbidities and risk factors while avoiding patient selection bias, surgeon's preference, patient's self selection, and differences in the surgeons' practices, it is more difficult when a technique or a device is being considered compared to the side effects of medications. Hence, it is easier to recruit several thousand patients as part of a trial to test a given medication versus a placebo compared to enrolment of several hundred patients to undergo a major surgical procedure that can be standardized by several surgeons with regard to their techniques including the perioperative care. The kinds of medications used by various anesthetists, the variety of techniques used by different surgeons enrolled in the surgical study including their preferences, competences, choices of post-operative care, and centre-specific resource availability create significant heterogeneity in surgical trials. Patient compliance is more problematic with surgical therapies as the operation is a single event therapy compared with medical treatment which is generally ongoing for a prolonged period of time during which patient follow-up can be conducted. Unless a substantial complication has occurred following an aortic valve replacement, patients generally do very well and the treatment effect is dramatic enough that they tend to see no reason for ongoing follow-up and investigations. Patients in medical trials come back for the trial drugs as they tend to relate wellbeing to follow-up visits.[33] Hence, there is a lack of consensus to a standard protocol for extended follow-up of such patients. There is also a lack of control of associated medications used in such patients having undergone aortic valve surgery including anticoagulants and their interaction with the treatment effect of heart valve replacement.

The education of clinical surgeons with regard to the design and methodology of clinical trials, availability of expertise in conducting trials such as statisticians, research assistants, and study nurses as well as sufficient funds play an important role in whether

such studies are completed successfully. These represent some of the major obstacles to conducting cardiac surgical clinical research and were identified from clinical experience, obstacles encountered by surgical investigators, and substantiated by a systematic journal review.

6.4 RECOMMENDATIONS

A clear consensus needs to be developed for identification of endpoints and the time frames for measuring these endpoints. This can be achieved by a representative panel of subspecialty experts as has been achieved by the CCS for defining and treating a variety of cardiovascular disorders or the Society of Thoracic Surgeons for defining the specific measures for complications. There are three categories of endpoints that would be useful in the evaluation of heart valves. The first category involves echocardiographic evidence of cardiac and valvular function. The trans-prosthetic valve gradient, valve area, left ventricular mass and extent of left ventricular mass regression would give a detailed assessment of heart valve function and its impact on regression of the left ventricular mass. Second, detailed recording of thromboembolic and hemorrhagic complications with clearly defined criteria for major or minor events as well as other complications including bioprosthetic infection, structural valve degeneration, paravalvular leakage, and hemolysis should be documented. The third category should include survival until re-operation, survival until death, symptom classification pre-operatively as well as post-operatively for heart failure and angina, and time to recurrence of symptoms requiring hospitalization.

In order for the endpoints to be accurately measured, there should also be standardization of the times of follow-up. For example, there should be an early follow-up post-operatively to serve as a baseline and this should be done at two to three months post-operatively, a mid-term follow-up or repeated follow-up every three years and a long term follow-up extending at ten and fifteen years. Medication treatment prescribed post-operatively for the long term should also be standardized to maintain certain blood

pressure ranges that have been arrived at by consensus as well as the choice of medications. Consensus would be done on a national level by such organizations as the CCS or the American College of Cardiologists. Compliance should be monitored on this aspect.

Education of surgeons and surgical assistants should become the foundation for developing new surgical research methodology. Training surgeons in the development of well-controlled randomized studies that minimize bias will require integration of research methodology into the surgical curriculum. Surgical residency programs should seek to enroll trainees that will complete a Masters or a Doctoral level in research methodology. A second facet of education relates to the training of surgeons in the proper technique necessary for conducting a randomized controlled trial. As related to this thesis, the surgeons would be responsible for learning and practicing implantation of an experimental valve to a level that would be comparable to the valve substitutes that are already being used. It would be necessary to identify surgeons who would be involved in the study based on their aptitude for implanting a new valve and occasionally it would be necessary to assign implantation of both the study and control valves to one surgeon or a group of surgeons who would be specially trained for the study. Assignment to such surgeons would be critical although problematic and require a good personal knowledge of their abilities and outcomes possibly through the published work from that center or personal communication with the director of each division.

Standardization of peri-operative care for the two valves being compared in a study is essential. Anesthetic technique involving identical medications, equipment, cardiopulmonary bypass support, and fluid or blood product administration would have to be carefully delineated as part of the surgical protocol. Similarly, control over ICU care, in-hospital care and the personnel involved would be necessary as the usual standard of care would be inadequate in creating a balance in the treatment received by patients in the two study arms. Post-operative care including rehabilitation would also have to be well accounted for as patients returned to a reasonably good functional status. The rate and extent of recovery would be altered depending on their motivation and their enrollment

into a cardiac rehabilitation program and well as their preoperative functional status.

Financial support of an independent nature is integral to conducting good randomized controlled trials. The number of patients that are treated with surgical procedures is small in comparison to those requiring medications and those patients that require implantable prosthetic devices are extremely small. Hence, the market is relatively smaller for generating prosthetic device research. Little grant money is available to support surgeons for conducting such trials but the potential exists for industry funding. This is particularly important if the source of funding is independent such as universities, charitable foundations, or government agencies. Hence, much of the research conducted by surgeons tends to be low cost, short duration studies that are often case reports or retrospective reviews. The funding also is not available for full support of research associates that can continue to perform the research as most surgeons are physically unavailable to supervise such research. Hence, the research assistants have to be highly qualified and capable of conducting independent research when surgeons are present in the operating room. Funding should also exist to allow long term follow-up to be conducted that may span in excess of ten to fifteen years.

Finally, future surgical trials should take on an RCT design given the equipoise between currently used and new valve substitutes. Such RCTs are possible given the availability of such patients, adequate funding and methodological expertise.

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APPENDICES

APPENDIX A: New York Heart Association Functional Classification of Heart Failure[75]

Class I

Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea, or anginal pain.

Class II

Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnoea, or anginal pain.

Class III

Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitations, dyspnoea or anginal pain.

Class IV

Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken discomfort is increased.

APPENDIX B: Canadian Cardiovascular Society Classification of Angina[76]

Class I

Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Strenuous or rapid or prolonged exertion at work or recreation causes angina.

Class II

Slight limitation of ordinary activity by angina. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in the cold or in wind, or during emotional stress, or only during a few hours after awakening produce angina. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions causes angina.

Class III

Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace causes angina.

Class IV

Inability to carry on any physical activity without angina; angina may be present at rest.

APPENDIX C: Computer Search Strategy for a Systematic Review of Bioprosthetic Valves

Database: MEDLINE <1966 to June Week 4 2001>
Search Strategy:

1 Heart Valve Diseases/ (11407)
2 Aortic Valve Insufficiency/ (8196)
3 exp Aortic Valve Stenosis/ (15861)
4 (aortic adj (stenosis or insufficiency or regurgitation or incompetence or disease)).tw. (12312)
5 or/1-4 (35324)
6 Heart Valve Prosthesis/ (20150)
7 Bioprosthesis/ (5043)
8 6 and 7 (3672)
9 (bioprosthesis adj2 valve).tw. (898)
10 bioprosthesis .tw. (2618)
11 or/8-10 (4404)
12 5 and 11 (1340)
13 clinical trial.pt. (312475)
14 randomized controlled trial.pt. (147820)
15 controlled clinical trials/ (1551)
16 controlled clinical trial$.tw. (5477)
17 (random$ or nonrandom$ or non-random$).tw. (219445)
18 case-control studies/ or exp cohort studies/ (432190)
19 control.tw. (1002655)
20 or/13-19 (1609524)
21 5 and 11 (1340)
22 20 and 21 (531)
23 limit 22 to (adult <19 to 44 years> or middle age <45 to 64 years> or "aged <65 and over>" or "aged <80 and over>") (435)
24 from 23 keep 1-435 (435)
25 from 24 keep 1-199 (199)

APPENDIX D: Systematic Review - Data Extraction Forms for Cohort Studies

Article Title: Date of Publication: Authors: Language of Publication:	
Study Dates: Location of Study: Duration of Study:	
Type of Cohort: Prospective/Retrospective Number of Subjects:	
Mean Age of Subjects: # Men: # Women:	Range:
Valve Name: 1)	2)
New York Heart Association Class:	
Exclusion Criteria:	
Diagnostic Procedures Pre-Surgery: Diagnostic Procedures Post-Surgery:	
Mean Follow Up Time: Total Follow Up in Patient Years:	
Valve Failures:	Valve 1): Valve 2):
Concomitant Surgical Procedures:	
Pre-Op Diagnosis:	
Overall Operative Mortality:	Valve 1) : Valve 2):
Overall Hospital Mortality:	Valve 1): Valve 2):

Mean Systolic Gradient	Valve 1): Valve 2):
Drugs/Devices:	
Post Operative Complications:	
Outcome:	

APPENDIX E: Newcastle-Ottawa Scale (NOS) for Quality Assessment of Cohort Studies

NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1. **Representativeness of the exposed cohort**
    1. truly representative of the average _____(describe) in the community*
    2. somewhat representative of the average _____ In the community*
    3. selected group of users eg nurses, volunteers
    4. no description of the derivation of the cohort
2. **Selection of the non exposed cohort**
    1. drawn from the same community as the exposed cohort*
    2. drawn from a different source
    3. no description of the derivation of the non exposed cohort
3. **Ascertainment of exposure**
    1. secure record (eg surgical records)*
    2. structured interview*
    3. written self report
    4. no description
4. **Demonstration that outcome of interest was not present at start of study**
    1. yes*
    2. no

Comparability

i) **Comparability of cohorts on the basis of the design or analysis**
    i) study controls for _____ (Select the most important factor)*

    ii) study controls for any additional factor* (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

- ☐ **Assessment of outcome**
  - ☐ independent blind assessment*
  - ☐ record linkage*
  - ☐ self report
  - ☐ no description
- ☐ **Was follow-up long enough for outcomes to occur**
  - ☐ yes (select an adequate follow-up period for outcome of interest)*
  - ☐ no
- ☐ **Adequacy of follow-up of cohorts**
  - ☐ complete follow-up - all subjects accounted for*
  - ☐ subjects lost to follow-up unlikely to introduce bias - small number lost - > __% (select an adequate %) follow-up, or description provided of those lost)*
  - ☐ follow-up rate < ___% (select an adequate %) and no description of those lost
  - ☐ no statement

APPENDIX F: Jadad Scoring System for Randomized Controlled Trials[77]

Study Quality

RM # _____ **Reviewer:** _____

Randomization: Total Points: ☐ 0 ☐ 1 ☐ 2

A trial reporting that it is "randomized" is to *receive one point.* Trials describing an appropriate method of randomization (table of random numbers, computer generated) receive *an additional point.* However, if the report describes the trial as randomized and uses an inappropriate method of randomization (date of birth, hospital numbers) *a point is deducted.*

Double-blinding: Total Points: ☐ 0 ☐ 1 ☐ 2

A trial reporting that it is "double blind", it is to *receive one point.* Trials that describe an appropriate method of double blinding (identical placebo, active placebo) are to *receive an additional point.* However, if the report describes the trial as double blind and uses an inappropriate method (comparison of tablets versus injection with no double dummy), *a point is deducted.*

Withdrawals and dropouts: Total Points: ☐ 0 ☐ 1

A trial reporting the number and reasons for withdrawals is to *receive one point.* If there is no statement, *no point* is given.

TOTAL SCORE: ☐ Low (0-2 pts) ☐ Moderate (3-4 pts) ☐ High (5 pts)

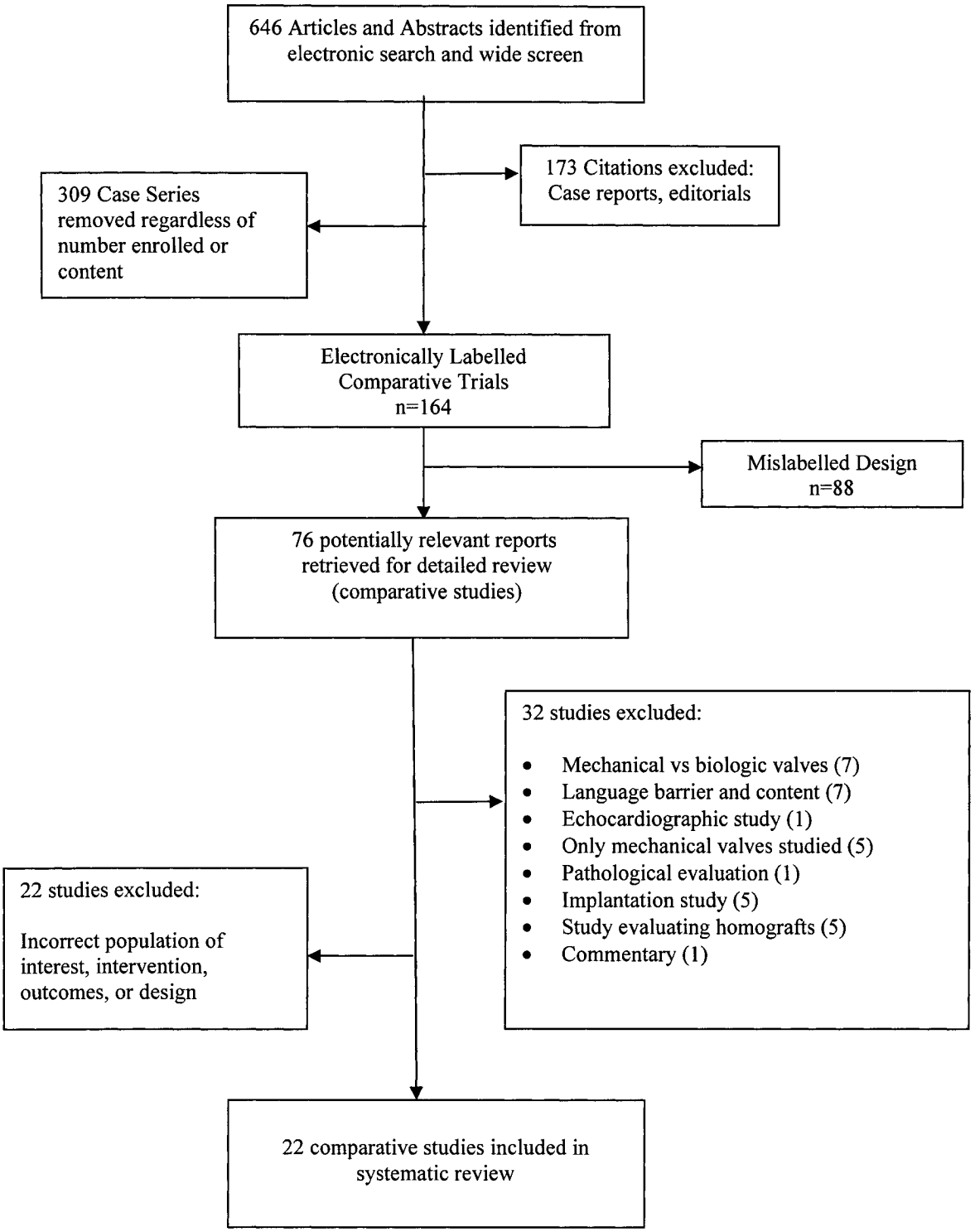
Allocation Concealment: ☐ Adequate ☐ Inadequate ☐ Unclear

Adequate: Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy; serially numbered, opaque, sealed envelopes, etc.

Inadequate: Alternation; reference to case record # or date of birth, etc.

Unclear: Allocation concealment approach is not reported or fits neither above category.

Appendix G: Article Selection Screening Tree



APPENDIX H: Table of Excluded Studies - Systematic Review 1986 – 2004

Journal Reference	Article Title	Reason for Exclusion
Journal of Thoracic & Cardiovascular Surgery 1999 May; 117(5): 890-7	Long-term outcome after biologic versus mechanical aortic valve replacement in 841 patients	Comparison made between biologic & mechanical valves.
Circulation 1999 Nov 9; 100(19 Suppl): II11-6	Mid-term comparative follow-up after aortic valve replacement with Carpentier-Edwards and Pericarbon pericardial prostheses	Comparisons made using mechanical valves.
Journal of Thoracic & Cardiovascular Surgery 1988 Mar: 95(3): 402-14	Aortic valve replacement combined with myocardial revascularization. Late results and determinants of risk for 471 in-hospital survivors	Comparison made between biologic & mechanical valves.
Journal of Cardiovascular Surgery 1990 Mar-Apr; 31(2): 213-9	Aortic insufficiency. A multivariate analysis of incremental risk factors for operative mortality and functional results.	Only mechanical valves used in study.
Journal of Heart Valve Disease 1998 Mar:7(2): 195-201	Use of bovine pericardial tissue for aortic valve and aortic root replacement: long-term results	Study uses grafts as well as replacement valves therefore deemed unsuitable for inclusion.
Annals of Thoracic Surgery 1999 Apr;67(4): 966-71	Left ventricular mass reduction after aortic valve replacement: homografts, stentless and stented valves	Homografts used in comparison.
Journal of Thoracic & Cardiovascular Surgery 1999 May; 117(5): 890-7	Long-term outcome after biologic versus mechanical aortic valve replacement in 841 patients	Comparison made with mechanical valves.
Journal of the American College of Cardiology 2000 Oct;36(4): 1152-8	Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial	Comparison made between biologic & mechanical valve replacements.
Journal of Thoracic & Cardiovascular Surgery 1984 Nov:88(5 Pt 1): 695-705	Early and late risk of aortic valve replacement. A 12 year concomitant comparison of the porcine bioprosthetic and tilting disc prosthetic aortic valves	Comparison made between biologic & mechanical valve replacements.
Medical Journal of Australia 1979 Jul 28;2(2): 53-6	Cardiac valve replacement (1963-1979)	Comparison made between biologic & mechanical valve replacements.
Archives des Maladies du Coeur et des Vaisseaux 1987 Jan;8091): 66-73	Results of valvular replacement in chronic or paucisymptomatic aortic insufficiency. Apropos of 79 patients	Language barrier – article in French. Comparison made between biologic & mechanical valve replacements.
Annals of Thoracic Surgery 1988 Sep;46(3):270-7	Aortic valve selection in the elderly patient	Comparison made between biologic & mechanical valve replacements
Scandinavian Journal of Thoracic & Cardiovascular Surgery 1989;23(1): 29-32	Heart valve replacement in septuagenarians	All valves used were mechanical
Annals of Thoracic Surgery 1988 Sep;46(3): 270-7	Aortic valve selection in the elderly patient	Comparison made between biologic & mechanical valve replacements
Zeitschrift fur Kardiologie 1991 Jan;80(1): 51-8	Flexible aortic valve prostheses: long-term functional results with porcine bioprostheses without mechanical commissure stent and aortic homografts	Language barrier – article in German. Comparison made between biologic and homografts
American Journal of Cardiology 1991 Mar 15;67(7):611-5	Doppler echocardiographic study of porcine bioprosthetic performance of bioprosthetic heart valves in the aortic valve position in patients without evidence of cardiac dysfunction	Echocardiographic study, not making comparisons between types of valve performance.

Journal Reference	Article Title	Reason for Exclusion
Annals of Thoracic Surgery 1991 Mar;51(3): 438-42	Management of aortic insufficiency in chronic aortic dissection	Comparison made between preservation of aortic valve versus replacement of valve
Annals of Thoracic Surgery 191 Jul;52(1): 84-91	Influence of type of prosthesis on late results after combined mitral-aortic valve replacement	Combined mitral-aortic valve replacement as well as mechanical valves used in comparison.
Journal of the American College of Cardiology 1992 Oct;20(4): 796-801	Long-term results of percutaneous aortic valvuloplasty compared with aortic valve replacement in patients more than 75 years old	Valvuloplasty compared with aortic valve replacement.
Japanese Journal of Thoracic Surgery 1995 Sept 48 910) 824-8	The long-term results of isolated aortic valve replacement with 19 mm prostheses	Article excluded because of language barrier (article in Japanese).
Zeitshrift fur Kardiologie 1986 Jun 75 (6): 321-8	Late complications following Bjork-Shiley and Carpentier-Edwards heart valve replacements	Article excluded because of language barrier (article in German).
Langenbecks Archiv fur Chirurgie 1987: 372: 613-8	Aortic valve replacement with a bioprosthesis-which type of prosthesis?	Article excluded because of language barrier (article in German).
Archives des Maladies du Coeur et des Vaisseaux 1991 Jun 84 (6) 785-91	Medium-term results of valve replacement with 2 types of pericardial heterograft. Apropos of 208 cases	Article excluded because of language barrier (article in French).
Ann Thorac Surg 1990; 49(5): 847-54	Crossovers in coronary artery bypass grafting trials	Article is a commentary, not a study therefore was excluded from analysis.
Journal of Heart Valve Disease 1999; 8(1): 4-15	Morphologic findings in explanted Hancock II porcine bioprostheses	Explanted Valves
Giornale Italiano di Cardiologia 1994 Dec;24(12):1551-66	Aortic valve replacement in old age. The results and follow-up echo-Doppler study of the prostheses	Paper is not directly comparing valves for their performance and language of article is Italian.
European Journal of Cardio-Thoracic Surgery 1995;9(10):562-6, discussion 566-7	Free-hand sewn allografts, stentless (Prima Edwards) and stented (CESA) porcine bioprostheses. A comparative hemodynamic study	Comparison is between allografts, stented and stentless aortic valves and is therefore not a suitable comparison.
Annals of Thoracic Surgery 1996 Sep;62(3):683-90	Effects of valve substitute on changes in left ventricular function and hypertrophy after aortic valve replacement	Allografts, mechanical, stented and stentless valves used in comparison. Paper therefore eliminated due to choice of valves used for comparison.
European Journal of Cardio-Thoracic Surgery	Mechanical versus biological isolated aortic valvular replacement after the age of 70: equivalent long-term results	Paper ruled out because comparison is made between biologic and mechanical valves.
Annals of Thoracic Surgery 1998 Dec;66(Suppl):S104-9	Reoperation on stentless aortic xenografts	Paper is not comparing valves. Addresses reoperation after implantation of stentless valves
Journal of Thoracic & Cardiovascular Surgery 2000 Jun; 119 (6):1185-93	Aortic valve replacement with the freestyle stentless bioprosthesis with respect to spatial orientation of patient coronary ostia	Paper is studying an implantation technique rather than a comparison of valve types based on performance.

APPENDIX I: Comprehensive Data Extraction Tables - Systematic Review 1986 - 2004

Table I-1: M. Achtelik, et al, 1995

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Stentless Aortic Valve Replacement with the Biocor Prosthesis: Indications & Outcome M. Achtelik, et al., 1995 Hanover, Germany English	• Retrospective cohort with externally derived ill-defined comparative group • Single centre group of surgeons • Biocor stentless prosthesis (GPI) enrolled 22 patients compared with Hancock porcine valve with root enlargement (GPII) having 10 patients • Enrolment of study group between February 1993 to June 1995 • No enrolment date given for control group • No clinical characteristics for control group • No randomization • Group determination by direct measurement for the study group but not defined for control group. The data has been obtained from published studies. • Ascertainment of outcome by direct measurement and medical records • Control group data obtained from published data • Clinical and echocardiographic follow-up data over a period of one to 25 months (mean 12.5) for GPI	• GPI patients were adults with mean age 63.9 +/- 15.4 years (range 17 to 85) • GPI patients obtained selectively from a population of 18 with aortic stenosis, and 4 with aortic insufficiency, one with combined disease • GPII obtained from published data • Inclusion and exclusion criteria not defined	• GPI patients underwent treatment with a Biocor stentless prosthesis • GPII patients had a Hancock porcine valve with an aortic root enlargement combined	• In follow-up data from one to 25 months there was no late mortality • Early post-operative deaths 3/22 and authors state that these deaths were associated with pre-existent morbidity unrelated to choice of prosthesis. Morbidity is not stated • Gradients for identical root diameters at size 21, GPI 7.5 mmHg, GPII 44.3 mmHg. • At size 23 GPI 7.8 mmHg, GPII 34.2 mmHg. GPII data is obtained from a published study that the authors quote • Regression of left ventricular hypertrophy demonstrated an average decrease in wall thickness from 13.6 mm to 11.2 mm with no comparative data	• Poor

Table I-2: Bloomfield, et al, 1986					
I.D.	**Methodology**	**Subject Characteristics**	**Intervention**	**Outcomes**	**Quality**
A prospective evaluation of the Bjork-Shiley, Hancock, and Carpentier-Edwards heart valve prostheses P. Bloomfield, et al, 1986 Edinburgh, Scotland English	• Prospectively randomized study with enrolment of patients from December 1975 to August 1979 • From a single pool of 612 patients referred by six participating cardiologists valve replacement was performed by three participating surgeons in a single centre • 540 patients were randomly assigned to a treatment group and 72 patients were excluded • During this period a total of 811 patients underwent valve replacement at the centre that were not included in the trial but were referred directly for surgery from other centres or were operated on by surgeons not participating in the trial • 262 patients underwent mitral valve replacement, 210 aortic valve replacement and 60 combined mitral and aortic valve replacements • Randomization was performed in groups of 10 to ensure even distribution of patients among surgeons and treatment groups. Group determination and ascertainment of exposure was by direct measurement • Follow-up data consisted of a visit with functional class, clinical evaluation, chest xray and ECG, and self-reporting by patients of any thrombo-embolic events	• Subjects were divided into three groups treated with a Bjork-Shiley mechanical (GPI), Hancock (GPII), or Carpentier-Edwards (GPIII) valve • All patients with valvular heart disease treated in two main cardiology referral hospitals and seen by six cardiologists all participated in the study • Three out of five consultant surgeons participated • Patients already entered in the study who required valve re-replacement were not re-entered • Patients were included in the study who required heart valve replacement • Exclusion occurred if long term anticoagulation was contra-indicated such as in young women anticipating pregnancy or if they were reluctant to take anticoagulants over a long term • Concomitant procedures were allowed, particularly coronary bypass grafting if there was a 70% or greater lesion in one of the three major coronary arteries • A total of 210 patients underwent aortic valve replacement. For purposes of data extraction those patients undergoing mitral valve replacement and combined aortic and mitral valve replacement are not recorded. • From January 1977 because of a significant cost advantage patients randomized to treatment with a porcine heterograft received a Carpentier-Edwards (160 patients) instead of a Hancock prosthesis (107 patients). All patients assigned to GPI received the Bjork-Shiley mechanical valve (273 patients)	• To avoid bias associated with the time of the operation patients in GPI receiving the valve in the first period of the trial were compared with those receiving bioprosthetic valves for that time period and this analysis was separated from those receiving the mechanical valve in the second time period. • A set of 34 pre-operative variables were identified but no statistical difference was found between GPI, II and III within the groups undergoing aortic, mitral or combined valve replacement. • The three surgeons implanting the valves placed equal numbers of each type of valve. • Three groups of patients in the aortic valve replacement series were created with GPI being treated with a mechanical valve (Bjork-Shiley), GPII the Hancock valve and GPIII the Carpentier-Edwards valve	• In-hospital mortality for patients undergoing aortic and mitral valve replacement was not significantly different for patients with the three prostheses undergoing aortic valve replacement or mitral plus aortic valve replacement although the latter group was small. • In-hospital mortality: GPI 8/108, GPII 5/46, GPIII 3/56 • Mean duration of follow-up was 5.6 years (range: 2.8 to 8.3) • Actuarial survival for all aortic valve replacements was 69.6 +/- 9.6% at 7 years • Aortic valve replacements alive and free from embolism at 7 years: GPI 66.1 +/- 6.2%, GPII 56.3 +/- 8.3%, GPIII 52.3 +/- 14% • There were no significant differences between the patients with the three prostheses with regard to functional class, later post-operative deaths, re-operation for valve failure, bacterial endocarditis. • Analysis of actuarial survival for patients with aortic valve replacement showed no significant difference between those with the three different prostheses • Survival curves of patients alive and free from embolism compared with the curves of simple survival of patients undergoing aortic valve replacement with the three different prostheses showed no significant difference in the overall curves for the three groups.	• Poor

Table I-3: R. Casabona, et al, 1992

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Stentless Porcine and Pericardial Valve in Aortic Position R. Casabona, et al, 1992 Torino, Italy English	• Prospective cohort study composed of four cohorts • Single centre group of surgeons with patients obtained from the same pool • 57 consecutive patients underwent isolated aortic valve replacement with a stentless aortic valve • Group I - 27 patients received a stentless porcine valve • Group II - 30 patients received a stentless pericardial aortic valve • Two control groups with Group III consisting of 30 patients treated with a stented porcine valve and Group IV made up of 30 patients treated with a mechanical valve • Measurements made by direct observation • Ascertainment of outcomes were made through direct observation • Follow-up consisted of trans-thoracic echocardiography a few days after the operation, at 3, 6, and 12 months post-operatively • Because the mechanical valve had a longer follow-up only the echocardiographic evaluations done at 6 and 12 months after the operation were considered • No method of randomization was discussed	• Age: GPI - 50.2 +/- 15.5 years, GPII - 61.1 +/- 14.3 years, GPIII 53.1 +/- 7.5 years, GPIV - 49 +/- 14.6 years • No differences in sex distribution, pre-operative diagnosis or body surface area • Prosthetic valve size although not perfectly matched was evenly distributed amongst the four groups (NS) • Majority of patients (107/117; 91.4%) were in sinus rhythm, none had complete heart block.	• Mean echocardiographic follow-up GPI - 9 +/- 4 months, GPII - 14 +/- 5 months, GPIII - 17 +/- 7 months and GPIV - 29 +/- 12 months. • 3 patients (11.1%) in GPI died within 30 days of surgery (heart block and malfunctioning pacemaker, and two from pulmonary insufficiency due to severe lung disease). One patient died in each of the other groups at 6 months or further after follow-up. • 83.3% of stentless porcine and 69.3% of stentless pericardial valve replacements were in NYHA Class I. • 81.5% of stented and 74.1% of mechanical valves were in NYHA Class I. The remaining in all groups was in Class II functional status. • Patients with the stented bioprosthesis were anticoagulated for 3 months while mechanical valves received it lifelong.	• Maximum velocity across the valve measured as a correlator of gradient was significantly lower with stentless pericardial and stentless porcine valves compared with stented mechanical valves. This trend was confirmed for each valve size with the data being statistically significant for smaller valve sizes ($p < 0.05$ for #23 and #25). • Similarly, aortic valve areas were significantly larger with stentless valves when compared with stented valves ($p < 0.05$) • Cardiac outputs obtained by Doppler technique were similar among the four groups of patients • Echo assessment of central aortic insufficiency was noted to be trivial or mild in 18 (31.6%) of stentless valves and this was more common in the stentless pericardial (13 cases, 43.3%) than the stentless porcine (5 cases, 18.5%) and was statistically significant ($p=0.04$). This was most significant at the #23 valve size ($p=0.01$).	• Poor

Table I-4: T. David, et al, 1998

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Aortic Valve Replacement with Stentless Porcine Aortic Valves: A Ten-Year Experience T. David et al, 1997 Toronto, Ontario English	Prospective, non-randomized Between 1987 and 1989 29 patients received a custom made stentless aortic valve (GP1) Between 1991 and 1997 213 patients received a Toronto SPV (GP2) All patients had echocardiography prior to discharge, three to six months later and annually thereafter Concomitant procedures were permitted There were no specific criteria regarding selection of patients for aortic valve replacement with the custom-made valves except for informed consent Guidelines were used for those patients receiving the Toronto SPV These criteria consisted of patients who were greater than 34 years with an expected life span of at least two years, were receiving AVR as a single valve replacement and those without chronic renal failure requiring dialysis.	Mean age GP1: 58 years, GP2: 63 years In both groups there were 165 males and 77 females The majority of patients were NYHA class II or III 182 patients have aortic valve stenosis, 30 aortic insufficiency and 30 both stenosis and insufficiency	GP 1 received a custom made stentless aortic valve GP2 received a Toronto SPV One third of the patients also had coronary artery bypass	There were two operative deaths One patient had isolated aortic valve replacement and had a cardiac arrest The second patient had aortic valve replacement and had an ascending aorta aneurysm and died soon after surgery There were 11 late deaths, four of cardiac causes and seven non-cardiac The actuarial survival of all patients with stentless porcine aortic valve was 89 +/- 4% at nine years Seven patients required repeat aortic valve replacement, five for aortic insufficiency and two for prosthetic aortic valve endocarditis. The freedom from thromboembolic complications was 92 +/4% at nine years The freedom from endocarditis was 98 +/-1% at nine years The follow up for this study was closed on October 31, 1997 224 patients were alive and had their original stentless aortic valve in place 180 were in NYHA class I and 39 were in class II and 5 were in class III	• Poor

Table I-5: D. Del Rizzo, et al, 1998

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Clinical and Hemodynamic Comparison of the Medtronic Freestyle and Toronto SPV Stentless Valves D.F. Del Rizzo, et al, 1998 Winnipeg, Canada English	• A non-concurrent cohort study design with prospectively collected data. • Prospective non-randomized cohort study where 995 patients received a Medtronic freestyle stentless valve (Group I) or a Toronto SPV valve (Group II) • All patients were part of two concurrent international (Canada, Europe and United States) phase II multi centre trials to assess the safety and efficacy of these two devices. • Date of enrolment from 1991 to 1997 • GPI - 849 patients were treated with the freestyle valve • GPII - 263 patients were treated with the SPV • Ascertainment of outcome was through direct measurement and clinical evaluation • Follow-up echocardiography was performed with the first examination in the immediate post-operative period prior to discharge, with subsequent follow-up examinations done at 3 to 6 months, one year and annually thereafter. • Assessment for valve function, mean systolic gradient, effective orifice area, left ventricular mass were conducted. • No blinding issues discussed • Randomization not performed	• Age: GPI - 70.7 +/- 8.6, GPII - 61.8 +/- 11.1 ($p < 0.001$) • Gender: no significant difference • NYHA Class - no significant difference between GPI and GPII for Classes I, II and III, but for Class IV: GPI - 12.5%, GPII - 7.4% ($p < 0.0001$) • Previous myocardial infarction: GPI - 14.1%, GPII - 3.7% ($p < 0.001$) • Coronary disease: GPI - 44.7%, GPII - 37.2% ($p = 0.07$) • Carotid disease: GPI - 7.8%, GPII - 0% ($p < 0.001$) • COPD: No significant difference • Inclusion criteria consisted of all patients requiring aortic valve replacement with or without coronary bypass surgery in the absence of other valvular disease and over the age of 35 years. These patients also were those in whom a bioprosthesis was an appropriate replacement device. This was done to minimize the potential for bias in patient selection. • Exclusion criteria included those patients where a 29 mm. valve which was not available in the freestyle configuration and a 19 mm. valve which was not available in the SPV configuration were excluded. • For purposes of the study only patients in whom the sub-coronary implant technique was used were included.	• GPI patients were treated with sub-coronary implantation of a Medtronic freestyle stentless porcine valve. • GPII patients were treated with the sub-coronary implantation of a Toronto SPV stentless bioprosthesis.	• No significant differences identified between the two groups with regard to cross-clamp time, duration for isolated valve replacement, valve plus coronary artery bypass grafting, and percentage of cases requiring concomitant bypass surgery (GPI - 35.7%, GPII - 34.0%). • There were no meaningful differences in early or late mortality or morbidity in the two groups with regard to early deaths, early valve related deaths, late deaths, late valve related deaths, total deaths, total valve related deaths, post-operative strokes, post-operative TIAs, total strokes, total TIAs, peri-operative myocardial infarction, late myocardial infarction, post-operative infection, post-operative endocarditis, and late endocarditis. • Incidence of aortic insufficiency by valve type for each follow-up time interval showed in the 3 to 6 month follow-up a higher incidence of trivial regurgitation in GPI (36.1%) compared to GPII (4.3%). ($p<0.0001$) • Incidence of clinically important regurgitation (moderately severe or worse) was negligible in both groups and did not increase during the follow-up period. • No differences in mean gradient between the two valves for each valve size with consistent decreases in the mean gradient as a function of time up to one year follow-up. • LV mass regression: There was a significant difference in the baseline LV mass (grams) and LV mass index ($grams/m^2$) for the two groups and this difference was maintained throughout the study period that is, there were no differences in the rate of the mass index regression between the two valves.	• Poor

Table I-6: R. De Paulis, et al, 1998

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Regression of Left Ventricular Hypertrophy After Aortic Valve Replacement for Aortic Stenosis with Different Valve Substitutes R. De Paulis, et al, 1998 Rome, Italy English	• Prospective cohort study with internal cohorts placed in three study groups with one control group of healthy subjects • Single centre group of surgeons • 30 consecutive patients were selected based on specific inclusion criteria from a total of 150 patients that underwent isolated aortic valve replacement from January 1994 to January 1996. GPI (stentless valve), GPII (stented valve) and GPIII (mechanical valve) each had 10 patients as did the control group • Control group consisted of healthy subjects without heart disease on routine diagnostic echocardiography and without a history of systemic hypertension • Follow-up consisted of evaluation before the operation, and after a mean time of 13 +/- 6 months for GPI, 15 +/- 4 months for GPII, and 12 +/- 7 months for GPIII • For patients of GPI and GPIII an echo study was also available after a mean of two years follow-up • Time frame of the study was 15 months • Ascertainment of outcome was through direct measurement • No randomization was done	• Age (Y): GPI 70.7 +/- 3.3, GPII 73.6 +/- 4.1, GPIII 64.8 +/- 8, Control 61.3 +/- 8.2 ($p < 0.01$) • No significant difference noted for gender ratio, body surface area, associated aortic insufficiency, ratio of annulus diameter/body surface area, diastolic blood pressure, maximum gradient pre-op • Diameter of the implanted prosthesis was significantly larger for patients receiving stentless valves than for other patient groups (mm): GPI 24.1 +/- 3.2, GPII 21.4 +/- 0.9, GPIII 21.4 +/- 0.9, ($p = 0.02$) • Patients receiving bioprostheses were slightly older than both the patients receiving mechanical valves and control subjects due to selection by policy to implant biologic valves after the age of 70 years • All patients had aortic stenosis • Two patients in each group had minimal aortic insufficiency • 3/10 patients in each group were receiving a daily dose of ACE inhibitor (10-20 mg) • Selection of the 30 consecutive patients required fulfilment of such inclusion criteria as (1) pre-op echo at the study centre (2) absence of associated other valvular disease (3) no previous hypertension or mild hypertension well controlled (4) normal left ventricular function (5) no or trivial aortic regurgitation at follow-up (6) a diameter between 21 and 23 mm for a stented valve	• 10 patients (GPI) received a stentless aortic valve of various sizes (Toronto SPV and Sorin stentless valve) • 10 patients (GPII) received a Hancock stented valve size 21 or 23 mm • 10 patients (GPIII) received a Carbomedics bileaflet mechanical valve size 21 or 23 mm • 10 healthy subjects comprised the control group without heart disease on routine echo and without a history of systemic hypertension • Analysis of the regression of hypertrophy in three groups of patients was evaluated with a baseline echo before the operation and at follow-ups previously described	• Stentless bioprostheses assured a significantly lower maximum and mean trans-prosthetic gradient independent of the size of prosthesis implanted ($p = 0.001$) • One 1-year follow-up echo after surgery showed left ventricular mass index to be significantly reduced ($p < 0.01$) for all patient groups but it was still significantly different from the control values ($p = 0.05$). There were no significant differences in the rate of regression in left ventricular mass among the three groups of patients. • Slight difference among the patient groups with respect to rate of regression although at follow-up no significant differences in ventricular wall thickness. • Similar values in ventricular mass thickness were reached in the three groups and they were still significantly higher than control values ($p < 0.003$) • ventricular mass index at two years in GPI and GPIII did not change significantly (137 +/- 33 g/m^2 and 136 +/- 35 g/m^2) with no significant difference compared with values at one year of follow-up respectively • Authors noted that all patients operated on for aortic stenosis had a significant reduction in ventricular mass irrespective of the type of valve substitute.	• Poor

Table I-7: J.G. Dumesnil, et al, 1998

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Hemodynamic Features of the Freestyle Aortic Bioprosthesis Compared with Stented Bioprosthesis J.G. Dumesnil, et al, 1997 Ste-Foy, Quebec, Canada English	• Retrospective cohort study with an external control group data obtained from previously published studies • Single centre group of surgeons • Study population consisted of 157 of the first 160 patients undergoing aortic valve replacement with a freestyle aortic stentless bioprosthesis • Enrolment was from January 1993 to May 1995 • Comparison was with previously published results from this laboratory in 28 patients with an Intact stented bioprosthesis studied an average of 20 months after operation and results obtained at 12 months after operation in 78 patients enrolled in a multi-centre study of the Mosaic stented bioprosthesis and subjected to a follow-up protocol similar to the one used in the present study. Data for the Mosaic prosthesis was provided by the manufacturer (Medtronic Inc) • Study group (GPI) was followed at 3 to 6 months, for 129 patients, 79 were followed at up to one year and 21 were followed up to 2 years • Follow-up consisted of direct measurement with echocardiography performed at one week, 3 to 6 months, one year and two years after operation • Ascertainment of outcome was through direct measurement including echocardiography identifying prosthetic trans-valvular mean gradient, stroke volume and cardiac output and detection of severity of aortic insufficiency • No randomization	• GPI (study group) consisted of 69/157 men and 88/157 women (mean 69 +/- 7 years) and range 48 to 85 years • Pre-operative diagnosis: aortic stenosis 58/157, aortic insufficiency 11/157, mixed aortic disease 88/157 • Prosthetic sizes were 19 mm (4 patients), 21 mm (22), 23 mm (42), 25 mm (52), and 27 mm (37) • Inclusion and exclusion criteria not defined • Single source of exposed patients	• Study patients received aortic valve replacement with the freestyle aortic bioprosthesis • Comparative groups were previously studied with a multi-centre trial using the Mosaic stented bioprosthesis and the Intact stented bioprosthesis published previously	• EOAs (effective orifice areas) measured in vivo for each size of freestyle prosthesis were markedly lower then the range of values for EOA calculated in vitro for the same prosthesis • EOAs for Intact and Mosaic stented prostheses reflected good agreement between in vivo and in vitro EOAs • A significant decrease in gradient (-3.3 +/- 4.1mmHg; $p < 0.001$) and a significant increase in EOA (+0.25 +/- 0.26 cm^2; $p < 0.05$) were observed during the first 3 to 6 months after operation in patients with the freestyle prosthesis, no such change seen with the Mosaic valve under a similar follow-up protocol • Comparison of mean gradients and EOAs for each type and size of prosthesis showed size-for-size gradients were markedly lower for the freestyle (GPI) prosthesis in comparison to the stented (GPII) prostheses. Confidence limits not shown however. • Indexed EOA: where index was for body surface area identified an indexed EOA greater than 0.85 cm^2 per m^2 to have lower gradients (< 10 mmHg) whereas gradients greater than 10 mmHg were found only in patients with an indexed EOA less than 0.85 cm^2 per m^2	• Poor

Table I-8: W. Eichinger, et al, 1998

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
The Mosaic bioprosthesis in the Aortic Position: Hemodynamic Performance After 2 Years W. Eichinger, et al, 1998 Munich, Germany English	•Retrospective cohort with internal cohorts •Although randomization into each cohort is mentioned the mechanism of randomization is not discussed and the study appears retrospective •Single centre group of surgeons •Mosaic (GPI) had 55 patients and Hancock II (GPII) had 52 patients •Date of entry into the study began since February 1994 but no determination of closure is given. The paper does not define the time period of enrolment suggesting differences in time for the two cohorts and confirming absence of randomization •Ascertainment of outcome was by direct measurement including trans-thoracic echocardiography performed at six and twenty-four months post-operatively	•Adults undergoing aortic valve replacement •Mean age GPI 72 +/- 5.9 years, GPII 76.8 +/- 4.7 years •Gender: GPI 24/55 were male, GPII 20/52 were male •It is unclear whether a single source for the two cohorts was present as differences in enrolment time frame may be possible •No exclusion criteria were defined	•GPI received the Mosaic porcine bioprosthesis and GPII received the Hancock Modified Orifice II porcine bioprosthesis •Part of the inclusion criteria involved patients undergoing isolated aortic valve replacement •Exclusion criteria included all three remaining valves had to be of the native tissue •Inclusion criteria allowed for concomitant procedures such as coronary artery bypass grafting	•Early mortality in GPI was 3.6%, in GPII 3.8% •Overall mortality was 12.7% and 13.5%, respectively •No statistical difference between pressure gradients and effective orifice areas for GPI and GPII for size 21, 23 and 25 valves at the two year follow-up. Although the Mosaic valve had a tendency towards lower pressure gradients for all sewing ring diameters, these did not achieve statistical significance in any category at two years although the study concluded that it may be a better valve •Early mortality was defined as within thirty days	• Poor

Table I-9: B. Goldman, et al, 1988

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Clinical results of pericardial xenograft valves: The Ionescu-Shiley and Hancock Valves B. Goldman, et al., 1988 Toronto, Canada English	• Retrospective cohort study with internal cohort comparing two different valves • Prospective follow-up: patients included in the study from April 1979 to December 1985 with follow-up being completed over a three month interval from June to August 1987. • Single centre group of surgeons • Patients studied were 552 Ionescu-Shiley (IS) valves in 551 patients between 1979 and 1985 compared with 129 Hancock (H) valves in 122 patients treated between 1982 and 1983. Patients received treatment for aortic or mitral valve disease. • Aortic valve replacement: 320 (60%) IS and 81 (60%) Hancock • Limited stratification of data based on aortic or mitral valve replacement • Date of study enrolment for IS patients was 1979 to 1985 and for Hancock patients between 1982 and 1983. The type of follow-up entailed registering all surviving patients into a valve clinic for examination or contact at annual intervals. Follow-up was completed over a three month interval from June to August 1987 and was obtained on 472 patients (99% complete). No method of randomization was identified. • Ascertainment of outcome was through medical records of the clinic and direct measurement. No other details were provided.	• For aortic valve replacement a total of 322 patients for the IS group and 81 patients for the Hancock group. The IS group had 41 patients with combined valve replacement and the Hancock group had 7. • Mean age IS group 58.6 +/- 14 years, Hancock 56 +/- 15 years • Male to female ratio: IS group 53:47, Hancock group 65:35 • Prior operation IS group 12%, Hancock group 20% • Concomitant CABG, IS group 25%, Hancock group 31% • Replacement ascending aorta, IS group 3, Hancock none • Hospital survivors, 93% vs 94% • Late deaths 15% vs 17% • Follow-up mean interval 38 vs 37.2 months • Cumulative (patient years) 1497 vs 375.4 • Exclusion criteria not recorded • Inclusion criteria based on the time frame for patients referred for valve replacement	• Two types of bioprosthetic valve substitutes were compared in this study: The Ionescu-Shiley low profile bovine pericardial prosthesis and the Hancock porcine bioprosthesis . Valves were inserted into both the aortic and the mitral position and follow-up data for patient survival and complications were recorded as aggregate for the two positions. • Only valve pathology at re-operation was separated according to the aortic or mitral position	• A mean follow-up of 38 months was obtained for each valve population (1497 patient years for IS and 375.4 for Hancock valve) • For Group I vs Group II, • Primary tissue valve failure: 1.1% vs 5.9% (significant) • Anticoagulant bleed: 1.0% vs 0.5% • Thromboembolism: 1.0% vs 1.6% • Perivalvular leak: 0.3% vs 0.3% • Prosthetic valve endocarditis: 0.8% vs 1.3% • Although a significant difference is noted in primary tissue valve failure between the IS group vs the Hancock group, there were inadequate details provided as to the causes of primary tissue failure in the Hancock group.	• Poor

Table I-10: R. Houel, et al, 1999

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Lack of Durability of the Mitroflow Valve does not Affect Survival R. Houel, et al., 1999 Creteil, France English	• Retrospective cohort, internal cohort • Group I - 94 patients, Group II - 118 patients • Single centre group of surgeons • Patients subjected to isolated aortic valve replacement between 1980 and 1987 • No method of randomization • Follow-up through medical records for both group determination and ascertainment of outcome • Patients lost to follow-up not identified	• All adult patients undergoing isolated aortic valve replacement. No details of inclusion or exclusion criteria documented • Same clinical source and time frame for both groups of patients • Mean age for Group I not given, mean age for Group II 66.5 years • No significant difference between the groups for gender ratio, origin of valvular disease whether it was aortic insufficiency, stenosis or mixed disease, and no difference in NYHA functional class between the two groups in terms of severity of disease. A significant difference was identified in the choice size between Group I and II with Group II receiving the smaller valve sizes with a higher frequency (19 and 21 mm) • 18% of CE received valves of this size compared with 54% of M patients received these sizes.	Group I received the Carpentier Edwards Perimount bioprosthesis, Group II received the Mitroflow pericardial bioprosthesis. Although both are pericardial valves the CE valve is made from three pieces of pericardium in a composite design and is selected for tissue thickness, and collagen orientation. The Mitroflow consists of a single piece.	• Follow-up: 1693 patient years, mean duration being 9.85 +/- 4.8 years for CE and 8.15 +/- 3.4 years for M group. • In-hospital mortality rate for both groups was 6.1%. No valve related deaths in either group. • Late mortality: 41.5% in CE group and 28% in M group. • Actuarial Survival at 5, 10 & 15 years, including in-hospital mortality: 86.9 +/- 3.7%, 66.3 +/- 5.3% and 45.1 +/- 6.4% in the CE group. In the M group 81.0 +/- 3.6%, 59.8 +/- 5.2% and 39.9 +/- 10.5%. •Non-structural valve dysfunction: 3 in CE group, 5 in M group. • Endocarditis: 4 in CE, 7 in M. • Thromboembolism: 7 in CE, 7 in M. • Structural valve deterioration: 17 in CE, 33 in M. • Re-operation: 14 in CE, 36 in M. • Valve-related mortality: 9 in CE, 6 in M died from valve-related complications, re-operation or sudden death.	• Poor

Table I-11: W. R. Jamieson, et al, 1998

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Carpentier-Edwards Standard and Supra-annular Porcine Bioprostheses: Comparison of Technology W.R. Jamieson, et al, 1998 Vancouver, B.C. English	• Retrospective internal cohort study • University of British Columbia teaching hospitals group of surgeons • The CES porcine bioprosthesis was implanted in 567 aortic valve replacements and 486 mitral valve replacements from 1976 to 1988. The CE-SAV porcine bioprosthesis was implanted in 1670 AVR and 1096 MVR cases from 1981 to 1997 • No documentation of loss to follow-up • Group determination was by direct measurement • Ascertainment of outcome was by direct measurement, medical records and self report • Blinding was not discussed • Randomization was not noted	• Patient population was classified into five age groups: 21-40 years, 41-50 years, 51-60 years, 61-70 years and 71 years or older • No other patient characteristics recorded • Source of cohort groups not defined although different time frames used for each cohort • Inclusion and exclusion criteria not defined	• GPI received the CE-S porcine bioprosthesis, GPII received the CE-SAV porcine bioprosthesis but in a different time frame • The Kaplan-Meier method was used to estimate the actuarial freedom from SVD, and the log rank test was used to compare the survival curves between the two bioprosthetic types for each specific age group • Wilcoxon rank-sum test was used to compare age distribution between the two bioprostheses by specific age groups	• Only significant difference between the two prostheses for AVR occurred in the 21-40 year age group • In this category freedom from SVD at 15 years was 68.2 +/- 9.7% for GPII and 31.4 +/- 8.1% for GPI ($p < 0.05$). For all other age groups no significant difference was noted. • For the 41-50 year age group, GPI 56.0 +/- 8.1, GPII 48.6 +/- 11.7 (no signif.) • For the 51-60 year age group, GPI 68.4 +/- 4.9, GPII 60.6 +/- 6.9 at 15 years (no signif.) • For the 61-70 year age group at 15 years, GPI 76.0 +/- 6.4, GPII 83.6 +/- 5.6 (no signif.) • For the 71 or older age group at 15 years, GPI 88.9 +/- 7.4, GPII 94.6 +/- 3.4 (No signif.)	• Poor

Table I-12: Y. Kobayashi, et al, 1998

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Serial Doppler Echocardiographic Evaluation of Carpentier-Edwards Pericardial Valve Dysfunction: Comparison with Ionescu-Shiley Valve Y. Kobayashi, et al., 1998 Osaka, Japan English	• Retrospective cohort study with internal comparison group • Single centre group of surgeons • 191 patients in total with 70 patients undergoing aortic valve replacement • Enrolment between July 1984 and April 1993 • Group I (GPI) Carpentier-Edwards pericardial valve, Group II (GPII) Ionescu-Shiley valve • Follow-up was performed with Doppler echocardiography within one month and at intervals of at least two years after surgery • No other clinical evaluation at follow-up • No documentation of patients lost to follow-up • No randomization • Group determination was by direct measurement • Ascertainment of outcome was through direct measurement using echocardiography	• Patient characteristics for age, gender, pathology, previous valve replacement, functional status and presence of atrial fibrillation were combined for aortic and mitral valve replacement • GP1 mean age 56 +/- 13.5 years • GPII 50.1 +/- 9.4 ($p < 0.01$) • Gender no differences • Rheumatic pathology GPI 60%, GPII 77% ($p < 0.05$) • Previous valve replacement GPI - 16%, GPII - 1% ($p < 0.01$) • NYHA Class III or IV status no difference • Atrial fibrillation no difference • Both cohorts obtained from a single source • Patients that did not undergo serial Doppler echocardiographic examinations were excluded, therefore GPI had 30 patients and GPII had 40 patients	• GPI was treated with a Carpentier-Edwards Perimount bioprosthesis and GPII received the Ionescu-Shiley pericardial prosthesis • Inclusion criteria based on presence of full serial echocardiographic examinations being documented. Patients without this were excluded • All patients had undergone aortic and/or mitral valve replacement with these bioprosthetic substitutes and were of adult age although age range was not given • Concomitant procedures included tricuspid annuloplasty, mitral valvuloplasty, and coronary artery bypass grafting • No significant difference between the two groups for concomitant procedures • For aortic valve sizes no difference (21% versus 15%) between the two groups for patients undergoing replacement with size 19 valves and no difference between the two groups (81% versus 85%) for patients undergoing size 21 or greater valves.	• Late deaths: GPI 4/30, GPII 5/40 • No valve related death in GPI • One valve related death (prosthetic endocarditis) in GPII • Prosthetic valve endocarditis: GPI - 1, GPII - 2 • Bioprosthetic valve stenosis: GPI - 1, GPII - 6 • Actuarial freedom from bioprosthetic valve stenosis at 10 years: no significant difference (90% versus 88%) • Transvalvular bioprosthetic regurgitation at follow-up defined as greater than Grade III: GP1 - 1, GPII - 21 • Perivalvular bioprosthetic regurgitation: GPI - 1, GPII - 2 • One patient of GPI underwent re-operation, 24/25 patients with GPII dysfunction underwent re-operation • Actuarial rate of freedom from re-operation for aortic valve replacement significantly higher for GPI at 10 years than GPII (86% versus 54% +/- 9%, $p < 0.01$) • Typical mode of failure for GPII was leaflet tear, for GPI structural deterioration caused by valve calcification	• Poor

Table I-13: J.F. Legare, et al, 1998

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
St. Jude SPV Versus Medtronic Freestyle: A Single Institution Comparison of Two Stentless Aortic Valves J.F. Legare, et al, 1998 Halifax, Canada English	• Prospective cohort with two groups of patients obtained from the same internal pool • Single centre group of surgeons • 112 patients treated with aortic valve replacement using a stentless valve • Enrolment from 1993 to 1997 • GPI: 69 patients were treated with the St. Jude SPV • GPII: 43 patients treated with a Medtronic Freestyle • Patients followed prospectively with mean echocardiographic follow-up of 28.9 +/- 15.8 months for GPII and 15.9 +/- 13.04 months for GPI patients • Ascertainment of outcome was through direct measurement with echocardiographic follow-up • Trans-thoracic echocardiographic assessment was obtained at discharge, 3 to 6 months follow-up and annually thereafter •Highest trans-valvular velocities from pulsed Doppler recordings of outflow tract were measured including mean trans-valvular gradient and effective orifice area. Severity of regurgitation was graded. • No blinding issues discussed.	• Age: GPI - 70.8 (39 to 87), GPII - 67 (40 to 82 years)(NS) • Gender (M/F: GPI 63/37%, GPII 65/35% [NS]) • Ejection fraction: GPI - 64.6% (29 to 85), GPII - 67.6% (31 to 84) (NS) • Technique: GPI sub-coronary for all patients, GPII sub-coronary (21 miniroot) 22. • Other procedure: GPI CABG 30, GPII CABG 8 • No significant differences between the two valve groups in terms of pre-operative age, gender, NYHA Class and ejection fraction • Inclusion criteria consisted of adult patients with aortic valvular disease that were symptomatic with NYHA Classes III and IV.	• GPI patients were treated with a Toronto stentless porcine aortic valve (SPV) and GPII patients were treated with the Medtronic Freestyle stentless porcine valve • GPI patients were treated with the sub-coronary technique for all 69 patients and GPII with a sub-coronary (21) and miniroot (22) approaches. • If the sino-tubular junction was larger by > than 10%, the SPV valve was not used.	• There were no deaths within 30 days in either group. There were 6 late deaths in GPI (8.7%) and 6 late deaths in GPII (14%) • Cardiovascular related deaths: GPI - 4 (5.8%), GPII - 3 (7%) • 8 pacemakers were required for GPI and 2 for GPII • 2 strokes occurred in GPI and 2 in GPII • Mean gradients and effective orifice areas for the two valves are charted but no statistical comparison is made • Prosthetic valve insufficiency is compared and at one year is significant (p=0.03) with GPI showing 26.2% compared with GPII 5.9% with 1+ or greater aortic insufficiency • The severity of aortic insufficiency observed was 1+ for all patients except one GPI patient which had 2+ aortic insufficiency.	• Poor

Table I-14: C.J. Mullany, et al, 1994

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Early Clinical and Hemodynamic Evaluation of the Aortic Intact Porcine Bioprosthesis C.J. Mullany, et al., 1994 Rochester, Minnesota English	•External cohort study where 89 patients were enrolled between October 1990 and June 1992 in a non-randomized fashion for the study •Comparison cohort was obtained from a retrospective review of patients where the ascertainment of outcome was from medical records of Carpentier Edwards implanted valves. The comparison cohort consisted of 130 patients reviewed retrospectively at the Mayo Clinic within the same time frame •The study valve underwent hemodynamic assessment with 2-D echo with Doppler at seven days, six weeks and twelve months and this was collated with retrospectively derived data from medical records on the patients (GPII) that were treated with the Carpentier Edwards porcine bioprostheses. •For purposes of reporting and analysis the results for the GPII patients were measured at various intervals after surgery but for the purpose of the study were reported under the six week column •The authors justified this action as they felt there were no differences between the Intact measurements at six days, six weeks or six months •No method or randomisation	•GPI 89 patients, 63% male, mean age 74.6 +/- 7.8 years, range 48 to 92 years •86% were NYHA Class III to IV pre-op with 78% having aortic stenosis and 10% had aortic regurgitation. Pre-operative ejection fraction measured less than 0.50 in 32% of patients •Source of exposed patients not defined •Inclusion and exclusion criteria not defined •GPII characteristics not described in the study	•GPI patients underwent consecutive entry into the study and treatment with the Medtronic Intact Porcine bioprosthesis •GPII consisted of a retrospectively reviewed cohort of 130 patients treated with the Carpentier Edwards porcine bioprosthesis •GPI underwent echo assessment at one week, six weeks and twelve months determined a priori •GPII outcomes were from records of patients treated with the CE porcine valve	•Comparison of GPI and GPII mean gradients is only possible at six weeks as comparative data for hemodynamics is not available at one week or at twelve months for the GPII patients from the chart review •Statistical significant differences are noted in gradients between GPI and GPII in the size 23 and 25 valves but not in any other sizes chosen for the study such as 21, 27 or 29 •No differences are found in effective orifice area or index effective orifice area of the two valves at all sizes measured •Mortality in-hospital for GPI is reported at 4.5%. Limited data obtained from historical review of GPII valves	• Poor

Table I-15: F. Nistal, et al, 1986

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Comparative Study of Primary Tissue Valve Failure Between Ionescu-Shiley Pericardial and Hancock Porcine Valves in the Aortic Position F. Nistal, et al, 1986 Santander, Spain English	• Retrospective cohort, internal cohorts • Single centre group of surgeons • 221 patients received a Hancock porcine valve and 133 an Ionescu-Shiley bovine pericardial valve • Study enrolment from August 1977 to June 1981 • Author states no special selection or randomization was used but surgeons preference • All surviving patients were followed routinely and those that failed to report to the hospital were contacted by letter • Follow-up was conducted until June 1984 • Two patients were lost to follow-up in the Hancock group • Primary tissue valve failure was established either at hemodynamic study, re-operation or autopsy by detection of bioprosthetic regurgitation or stenosis owing to cuspal tears, perforations, calcific deposits or stiffening of the leaflets in the absence of an infective process • Endpoint for the definition of primary tissue failure was re-operation, or death with either autopsy or hemodynamic confirmation of valve failure • Patients alive with hemodynamic or clinical diagnosis of valve dysfunction were not included because they were awaiting confirmation of the process. • Ex-planted valves were examined, described and photographed macroscopically and microscopically	• GPI (Hancock) and GPII (IS) • Age: GPI 48 +/- 13, GPII 50 +/- 13 • No significant difference between the two groups with regard to patients less than 40 years or patients over the age of 40 years • Gender: Males GPI 68% vs GPII 43% (significant difference) • Significant difference between GPI and GPII with regard to functional class (NYHA) • Type of lesion: no significant difference between the two groups for aortic stenosis (12% vs 16%) but significant for regurgitation 37% vs 27% at 0.05 level of significance • No significant difference between the two groups with regard to other aetiologies such as rheumatic, aortic dissection, endocarditis, or congenital or others • A single source of patients was used for both cohorts • No specific inclusion or exclusion criteria documented	• Two types of bioprosthetic valves were selected for the study. GPI patients received the Hancock porcine valve and GPII received the IS bovine pericardial substitute	• Follow-up for the entire series was 978 patient years for GPI and 474 for GPII • Late deaths: GPI 10% and GPII 14% • Linearized incidence of valve failure was GPI 0.61 failing valves per 100 patient years and GPII 1.70 per 100 patient years • Mean age of patients at the time of valve implantation was GPI 38 years, GPII 39 years • Mean implantation valve size was significantly smaller for GPII than for GPI with size 21 or smaller being implanted significantly more often in GPII and size 27 or larger more frequently in GPI ($p < 0.0001$) • Failing valves were not concentrated among either the large or the small valves but scattered over the whole size range for both GPI and GPII • Primary tissue failure was more prevalent in GPI patients less than age 40 years (5 of 55 vs 1 of 144, $p < 0.002$) and in the GPII patients younger than 30 years (4 of 12 vs 4 of 106, $p < 0.001$) • Endpoint for the definition of primary tissue failure was not only re-operation but also deaths with either autopsy or hemodynamic confirmation of valve failure • Late deaths: GPI 10%, GPII 12% • Actuarial rate of freedom from primary tissue valve failure was 93 +/- 3.6% for GPI and 80 +/- 8% for GPII at 83 months of follow-up	• Poor

Table I-16: J. Oury, et al, 1998					
I.D.	**Methodology**	**Subject Characteristics**	**Intervention**	**Outcomes**	**Quality**
Comparison of Hancock I and Hancock II Bioprostheses J. Oury, et al., 1988 LaJolla, California English	• External cohort where the two groups come from different time frames • Single centre and group of surgeons • Group I - 119 patients in the Hancock I series treated between 1975 to 1983. 15 patients lost to follow-up during the post-operative course • Group II - 104 patients treated with Hancock II valves treated from 1983 to 1987. • Group I measurements obtained through medical records •Group II measurements obtained by direct observation. No blinding discussed or performed. • Ascertainment of outcome in Group I consisted of review of medical records for peri-operative and late mortality. Group II measurements were done directly and a small series underwent intra-operative and post-operative echocardiography. Secondary outcomes measured included complications such as thromboembolism, bacterial endocarditis, primary tissue failure, thrombosis, and haemorrhage. • No blinding issues discussed	• Group I vs II • Mean age 58 vs 67 years, similar gender ratios, peri-operative mortality 2 vs 5%, late mortality 31 vs 8%, patient follow-up 5 to 13 years vs 2 to 5 years, similar distribution in both groups for single and double valve replacements, single valve and valve reconstruction, single valve and CABG, double valve and CABG and other. •Detailed description of the source of exposed and unexposed cohorts were not described. Inclusion and exclusion criteria not defined although patients who were adult humans undergoing valve replacement with no details of the position of the valve.	• Not clearly defined although the methodology suggests that the valve substitutes were Hancock I and Hancock II porcine bioprostheses that were placed for any valve disease of the heart. It is assumed that the valves were placed for aortic or mitral valve disease. A small series of patients underwent intra-operative measurement of gradients by cardiac catheterization and post-operative echocardiography. Two different methods of measuring the gradient were compared. The number of patients undergoing this hemodynamic monitoring were not reported and no comment was made on the different techniques used to measure gradients.	• Overall patient survival curves compared for the two groups with early comparison revealing no significant difference in survival rates when the average of the patients in the Hancock II series is considered. The overall survival rate in the Hancock I series is 50% at 12 years and cannot be compared at this point to the Hancock II series. • Complications (1% per patient year): Thromboembolism 1.49 vs 2.33; Bacterial endocarditis 0.93 vs 0.46; Primary tissue failure 2.34 vs 1.30; Thrombosis 0.13 vs – Haemorrhage 0.64 vs –	• Poor

Table I-17: L.C. Pelletier, et al, 1988

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Porcine Versus Pericardial Bioprostheses: A Comparison of Late Results in 1593 Patients L.C. Pelletier, et al, 1988 Montreal, Canada English	• Retrospective cohorts followed prospectively, internal cohorts • Single centre group of surgeons • Study enrolment consisted from 1976 to 1988, 1593 patients that underwent heart valve replacement with a bioprosthesis with 701 aortic, 678 mitral and 214 multi-valve replacements • Follow-up was obtained for 1559 patients (98%) • Separation of the aortic and mitral valve data yielded 438 patients in the porcine valve group (GPI) and 427 patients in the pericardial valve group (GPII) • No controls • Patients were followed on an annual basis at either an outpatient clinic or through their own physician • Overall 2.16% were lost to follow-up in GPI and 2.10% were lost to follow-up in GPII (combined aortic and mitral valve data). Global follow-up rate was 97.9% • Duration of follow-up for patients with porcine bioprosthesis averaged 74 months compared with 34 months for the pericardial valve group. • No randomization • Ascertainment of exposure was through medical records and direct measurement • Ascertainment of outcome was through clinical evaluation	• Characteristics were inseparable for aortic and mitral and combined patients but were stratified based on porcine versus pericardial bioprosthesis • Male to female ratio: GPI - 0.93, GPII - 1.16, ($p < 0.05$) • GPII had a greater proportion of patients older than 60 years with a mean age of 57 +/- 12 years higher than GPI (54 +/- 12 years) ($p < 0.01$) • No difference in functional Class III or IV between GPI and GPII • Aortic insufficiency ($p < 0.0001$) was more frequent in GPI patients as well as mitral stenosis and mitral regurgitation • Aortic stenosis was more frequent in GPII patients ($p < 0.0001$) • No difference in the presence of a previous cardiac operation in both groups • GPI patients were more likely to have had a previously failed valve prosthesis than GPII patients ($p < 0.0001$) • Associated coronary artery bypass grafting was present in 15.4% of GPI and 21.7% of GPII patients ($p < 0.01$) • Source of patients from the same clinical pool for this institution • No inclusion and exclusion criteria defined	• GPI patients received Carpentier-Edwards porcine bioprostheses with 1024 valves being used in 878 patients while GPII received 789 pericardial bioprostheses in 715 patients with three different models of valves for each group. There were 808 male and 785 female patients aged 13 to 80 years • All events were recorded at follow-up visits.	• Early mortality rates (30 days) were 6.6% for GPI and 3.8% for GPII and in multi-valve replacements 15.6% for GPI and 10.5% for GPII with no significant difference in the latter • Global actuarial survival of patients with GPI was 80 +/- 1% at 5 years and 62 +/- 3% at 10 years whereas for GPII they were 79 +/- 2% after 5 years. Overall survival curves for both groups were similar as were those for AVR, MVR and multi-valve replacement. • Most frequent cause of death was congestive heart failure 32% versus 30% (no significant difference). No significant difference in the non-cardiac cause of death. • Thromboembolism actuarial curves of freedom from thromboembolism were not significantly different. • Endocarditis freedom rate curves were not significantly different between GPI and GPII (92 +/- 4% freedom at 6 years for GPII and 95 +/- 2% at 10 years for GPI). • In the multi-valve group endocarditis was more frequent with pericardial than with porcine valves with respective freedom rates of 88 +/- 5% at 6 years and 96 +/- 3% at 10 years ($p < 0.05$) • Haemorrhage no significant difference • Haemolysis no significant difference • Re-operation valve dysfunction: After 6 years actuarial freedom rate was similar for both valves in the aortic position (98 +/- 1% and 94 +/- 4%; $p > 0.05$) • Freedom from all valve related complications after 6 years was significantly better with porcine than pericardial prostheses for AVR: 90 +/- 2% versus 79 +/- 5% ($p = 0.05$)	• Poor

Paper I-18; D.F. Pupello, et al, 2000					
I.D.	**Methodology**	**Subject Characteristics**	**Intervention**	**Outcomes**	**Quality**
Long-Term Results of the Bioprosthesis in Elderly Patients: Impact on Quality of Live D.F. Pupello, et al, 2000 Tampa, Florida English	• Retrospective cohort with internal cohorts • Single centre group of surgeons • Enrolment from October 1974 to May 1998 of 2075 patients 65 years or older • A total of 2210 porcine bioprostheses were implanted with 1402 implanted in the aortic position, 789 in the mitral position, 17 in the tricuspid position and 2 in the pulmonic position • Follow-up was obtained with peri-operative data by review of patients' charts, catheterization reports, angiograms and echocardiography • Follow-up data included activity level, current symptoms, diagnostic tests, late cardiac events and medications • A quality of life assessment was conducted • Follow-up ranged from 1 month to 23 years (mean 60.8 months)	• Of the total data 1126 men and 949 women with a mean age of 73.9 years. Range of ages from 65 to 104 years • Single source of patients • Inclusion criteria consisted of patients undergoing valve replacement of the age of 65 years or older • Exclusion criteria not defined • No comparative data between the different valve groups was identified but rather patient characteristics were grouped together for the four different valves.	• 4 types of porcine bioprostheses were implanted in the aortic, mitral, tricuspid and pulmonic positions: 1) 64 Medtronic Intact valves (2.9%) 2) 1428 Carpentier-Edwards valves (64.6%) 3) 448 Medtronic Hancock valves (20.3%) 4) 270 Medtronic Hancock modified orifice valves (12.2%) • Mean cardiopulmonary bypass time was 103.2 +/- 39.2 minutes (range 34 to 334 minutes), mean aortic cross-clamping time was 69.4 +/- 31.4 minutes (range 15 to 533 minutes)	• All data were pooled for aortic, mitral, pulmonic and tricuspid valves including the different manufacturer valves. • Overall hospital mortality was 10.2% (212/2075), women versus men: 12.3% versus 8.4% ($p < 0.0045$) • Follow-up ranged from one month to 23 years (mean 60.8 months). Cumulative follow-up 9442.1 patient years • Following surgery 96.3% of patients were in NYHA Class I or II • Actuarial freedom from valve failure at the aortic site at 9 years: 97.5 +/- 0.9%, at 18 years: 89.4 +/- 3.5% • SF36 was used to help assess quality of life in patients who underwent valve replacement • A total of 74 valves failed with an overall linearized failure rate of 0.78 +/- 0.09% per patient year. There were 33 valve failures in the aortic site with a linearized rate of 0.5 +/- 0.07%. No distinguishing features between the valves were given. • Male patients undergoing treatment with porcine bioprostheses scored significantly higher in physical health summary ($p = 0.001$) than male age adjusted normal groups • Similar findings were noted in female patients when compared ($p = 0.012$) • Findings indicated that in physical health porcine bioprosthesis patients in the study achieved an enhanced level of functioning compared with age adjusted norms. • The mental health summary scores also showed they were functioning at least at the level of age adjusted norms. • Compared with the age adjusted norms, both male and female cohorts treated with porcine bioprostheses scored significantly better with regards to bodily pain ($p= 0.001$), general health ($p=0.001$), role emotional ($p=0.001$), and mental health ($p=0.001$). With females with comparison with age adjusted norms, scoring was significantly better for social functioning as well ($p=0.003$).	• Poor

Table I-19: R.D. Riley, et al, 1999

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Stentless Aortic Valve Replacement With Freestyle or Toronto SPV: An Early Comparison R.D. Riley, et al, 1999 Winston-Salem, North Carolina English	• Prospective cohort • Non-randomized • Internal cohort • Single centre group of surgeons • A total of 58 consecutive patients were enrolled between May 1997 and May 1999 to undergo stentless aortic valve replacement with GPI being treated with the freestyle valve and GPII with the Toronto SPV • Choice of valve implanted was based on surgeon preference and not valvular or aortic pathology except for when the sino-tubular junction was dilated which precluded the Toronto SPV insertion. Group determination was by surgeon preference. • Ascertainment of outcome was through direct measurement, clinical and echocardiographic follow-up. • Echocardiographic follow-up was performed routinely pre-operatively, intra-operatively, before hospital discharge, and again at 3 to 9 months in follow-up. • Surgical technique for freestyle valve implantation as a freestanding total root replacement was as described in previous literature. • Toronto SPV sub-coronary implantation was also described previously. • Concomitant procedures were performed simultaneously.	• Mean age and range: GPI 72 (57 to 85), GPII 74 (64 to 82) (NS) • Male gender: GPI 48%, GPII 79% ($p = 0.04$) • No significant difference in body surface area, incidence of hypertension, diabetes, valvular pathology, and pre-operative NYHA functional class I, II and III. • Functional Class IV: GPI 4.5%, GPII 21.4% ($p=0.05$) • LVEF less than 40%: GPI 4.5%, GPII 28.6% ($p=0.01$) • Source of both groups from the same pool of patients referred for aortic valve replacement • Inclusion and exclusion criteria not explicitly stated	• All available sizes of freestyle valve were used for GPI from 19 to 27 mm. • Only the larger sizes of the SPV valve from 25 to 29 mm were used for GPII related to the concept of oversizing of this type of valve • Most patients (64% for each group) had any concomitant procedure although there were significantly more associated mitral procedures (14% versus 2%) for GPII versus GPI ($p = 0.08$) • Associated aortic procedures were done in 9% of GPI versus none of GPII patients although this did not reach statistical significance ($p = 0.25$) • Ischemic times were not significantly different for both groups whether or not their valve replacement was done isolated or with a concomitant procedure	• Post-operative functional classification at 3 to 9 months showed all GPI patients to be in NYHA Class I versus 64% in Class I ($p<0.001$) and 36% in Class II ($p<0.001$) for the second group • For post-operative aortic insufficiency all patients in GPI had none to trace compared with 79% for GPII ($p = 0.001$) and 14% having mild insufficiency ($p=0.007$) • There were no operative deaths in either group and peri-operative mortality was defined as in-hospital or within 30 days was 3.4% overall • Thromboembolic complications manifested as neurological events occurred in one patient for each group as well as endocarditis developing in one patient in each group. Late mortality was not significantly different between groups (GPI versus GPII 2.3% versus 8.3%) • Thirty day mortality: GPI - 0%, GPII - 14.3%. • Late mortality: GPI - 2.3%, GPII 8.3%	• Poor

Table I-20: F. Santini, et al, 1997

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Hancock Versus Stentless Bioprostheses for Aortic Valve Replacement in Patients Older Than 75 Years F. Santini, et al, 1997 Verona, Italy English	• Prospective randomized study comparing a stented and a stentless bioprosthesis • Single centre group of surgeons • 77 patients were enrolled between January 1993 and December 1996 to undergo aortic valve replacement • Group determination was by direct measurement • Ascertainment of outcome was through direct measurement • Follow-up was 97% complete • Method of randomization was not stated	• 77 patients, 36% men and 64% women with an age range from 75 to 83 years (mean 77 +/- 2.6 years) • GPI (Hancock II) porcine bioprosthesis was compared with GPII (stentless porcine valve 2 types: Toronto SPV and Biocor) • Source of patients for both groups was from a single institution • Gender: GPI 40% male, GPII 32% (NS) • Age range GPI - 75-83 years, GPII - 75-82 years (NS) • Predominant lesion: aortic stenosis GPI - 42.5%, GPII 78%. Aortic insufficiency GPI - 10%, GPII - 3%, combined lesion GPI - 47.5%, GPII - 19%. • Clinical symptoms: no significant difference in the distribution between NYHA Classes I to IV • Echocardiographic data mean ejection fraction: GPI 57 +/- 15%, GPII 57 +/- 12% (NS) • Left ventricular mass: GPI 301 +/- 74 grams, GPII 330 +/- 97 grams (NS) • Inclusion criteria and exclusion criteria not clearly defined although adult patients over the age of 75 with aortic valve disease were entered into the study. • Concomitant myocardial revascularization: GPI-27.5%, GPII-13.5% • For intra-operative data no significant difference in bypass time, combined procedures, cross clamp time, associated coronary bypass grafting, or method of cardioplegia	• GPI treated with a Hancock II bioprosthesis with or without concomitant coronary artery bypass grafting. GPII patients were treated with either of the Toronto SPV stentless or the Biocor stentless porcine valve • 11 patients in GPI (17.5%) and 5 patients in GPII (13.5%) had enlargement of the aortic annulus	• Early mortality: GPI-5%, GPII - 8% • No significant difference between the two groups with regard to duration of ventilatory support, ICU stay, and hospital stay • Mean follow-up time for GPI and GPII was 14.5 +/- 10 months (range 5 to 51 months) and 18.5 +/- 12 months (range 6 to 51 months) respectively • Post-operative evaluation of ejection fraction, LV mass, aortic valve gradient, and degree of valve regurgitation were performed at regular intervals • EF for the two groups did not change significantly during the follow-up period • Peak gradient at one week: GPI 25 +/- 6 mmHg., GPII 21 +/- 12 mmHg. (NS). Trend towards the reduction of the trans-aortic gradient in the stentless group did not approach statistical significance at one year. • Percentage change in LV mass at one year: GPI-10.5 +/- 18%, GPII-19 +/- 23% (NS) • Although analysis of total cross clamp time and CPB time did not show any difference between the two groups, patients undergoing isolated AVR when analysed independently, a significantly longer operating time was found in stentless group ($p < 0.05$)	• Poor

Table I-21: G. Van Nooten, et al, 1999					
I.D.	**Methodology**	**Subject Characteristics**	**Intervention**	**Outcomes**	**Quality**
Stentless or Stented Aortic Valve Implants in Elderly Patients Van Nooten et al., 1999 Brussels, Belgium English	Between July 1992 to December 1997, 103 Toronto SPV valves were implanted 51 patients received a stented porcine Carpentier-Edwards valve Procedure standardized in all cases Follow up done by direct measurement Follow up was 97 and 100% complete and ranged from 6 – 66 months (302 and 139 patent-years) Retrospective, non-randomized Concomitant procedures permitted All valve replacements were evaluated by postoperative transesophageal or trans-thoracic echocardiography	Mean age was 75 years Group 1 of 103 patients received a stentless valve The average age of G1 was 75.2 years with a NYHA class of 3.3 preoperatively Group 2 consisted of 51 patients with an average age of 74.4 years and an average NYHA preoperative class of 3.2 Gender: GP1: 60% female, GP2: 21% female GP1 NYHA class preoperatively: 3.3 GP2 NYHA class preoperatively: 3.2	GP1 received a Toronto SPV_TM aortic valve GP2 received a stented porcine Carpentier-Edwards valve Approximately 10% of patients in each group had additional concomitant vascular pathology Standard cardiopulmonary bypass was used in all cases	Patients followed up at 7 weeks, 6 months and every year following discharge 30 day mortality: GP1:5, GP2: 2 All patients except 3 received Coumadin for 3 months post operatively Late deaths: GP1: 6, GP2: 12 All surviving GP 1 patients were in NYHA class I or II One patient in GP2 remained in NYHA class III, the rest were in I or II. Survival showed a statistically significant difference in favour of the stentless procedures The freedom from thrombo-embolism at five years was 83 and 94% for groups one and two Two patients had episodes of bleeding (one from each group) at 23 and 40 months Leaflet calcification and/or loss of mobility rarely occurred in the stentless group but over half of the controlled stented bioprostheses showed marked calcifications after four years	• Poor

Table I-22: T. Walther, et al, 1999

I.D.	Methodology	Subject Characteristics	Intervention	Outcomes	Quality
Prospectively Randomized Evaluation of Stentless Versus Conventional Biological Aortic Valves: Impact on Early Regression of Left Ventricular Hypertrophy T. Walther, et al., 1999 Leipzig, Germany English	•Prospective randomized control surgical study •Single centre group of surgeons •180 patients •Enrolment from March 1996 through April 1998 •Follow-up was performed at an outpatient clinic after six months and compared with intraoperative transesophageal echocardiography as baseline •At all visits patients were assessed for functional state and quality of life through the specific activity questionnaire and had routine trans-thoracic echocardiography •Because of longer distances to the hospital 15% of patients were followed by their family physicians •No patient was lost to follow-up •Randomization occurred after pre-operative echocardiographic examination •Randomization method not discussed •Ascertainment of outcome was achieved by direct measurement •Group determination was achieved by direct measurement based on pre-operative echocardiographic examination •Blinding was not defined from the information provided	•Stentless aortic valves (GPI) were 106 patients, conventional stented bioprostheses (GPII) were 74 patients •Mean age GPI 72.3 +/- 7 years, GPII 74.8 +/- 4 years •GPI 50% female, GPII 54% •Single source of patients exposed to both treatment groups •Inclusion criteria defined as patients who were adults undergoing aortic valve replacement, GPI 95% and GPII 96% had aortic stenosis •Exclusion criteria explicitly defined as (a) severe calcification of the aortic sinuses diagnosed intra-operatively, (b) very low coronary ostia in relation to the annulus, (c) atypical insertion of the coronary ostia making it impossible to implant a stentless valve. •Subject characteristics without any significant difference between the two groups included left ventricular ejection fraction and maximum pre-operative trans-aortic pressure gradients •Pre-operative body surface area was 1.82 +/- 0.2 m^2 for GPI and 1.74 +/- 0.2 m^2 for GPII ($p < 0.05$)	•GPI consisted of stentless aortic valves either freestyle or the Toronto valve (49 and 57) •Stented valves consisted of a Carpentier Edwards porcine valve	•Aortic annulus diameter index GPI 13.46 mm, GPII 13.55 mm (p = NS) •In-hospital mortality GP I 3, GPII 1 (not valve related) •Functional status at follow-up: All patients were in NYHA Class I or II •Baseline end-diastolic left ventricular posterior wall thickness: In-hospital GPI 15.6, GPII 14.8 •At six months GPI 11.8, GPII 13.2 ($p < 0.05$) •LV mass index: GPI 213, GPII 202 g/m^2 at baseline (p = NS) •At six months GPI 141, GPII 170 g/m^2 ($p < 0.05$) •Specific activity questionnaire had improved in all patients: GPI 1.1 +/- 0.4 up to 5.5 +/- 1 •GPII 1.1 +/- 0.3 up to 5 +/- 1 (p = NS)	• Poor

Table I-23: R. Williams, et al, 1999					
I.D.	**Methodology**	**Subject Characteristics**	**Intervention**	**Outcomes**	**Quality**
Randomized Controlled Trial of Stented and Stentless Aortic Bioprostheses: Hemodynamic Performance at 3 Years R. Williams et al, 1999 English	Forty patients were randomized to receive a Toronto SPV stentless valve (GP1) or a Carpentier-Edwards SAV stented bioprosthesis (GP2) Criteria used for bioprosthesis use were age greater than 65 years or a specific contraindication to long-term anticoagulation Those patients who had severe calcification of the aortic root or a sinotubular junction diameter 2 mm or greater than the aortic annulus were excluded from a Toronto SPV insertion and therefore not randomized Randomization was done after annular sizing for both types of prostheses	GP1 consisted of 19 patients, 9 males and 10 females GP2 was 20 patients, 7 males and 13 females The mean age was 72 for GP1 and 73.2 for GP2 Length of stay in intensive care for GP1 was 4.6 +/-8.3 days and 1.1+/-0.2 days for GP2 Hospital stay was 14.2 +/-21.8 days for GP1 and 9.7+/-6.1 for GP2 Patients in GP2 were significantly heavier than those in GP1	A standard technique of cardiopulmonary bypass was used Left ventricular mass was assessed using magnetic resonance imaging (MRI) at one week, six months, and thirty two months	The mean cross-clamp time and the cardiopulmonary bypass time was longer in GP1 than in GP2 but the overall operating times were shorter There were no significant differences in cardiac index, left ventricular stroke volume, or work index at any time during the first 24 hours between the 2 groups. One patient in the stented valve group developed low cardiac output that required an intra-aortic balloon pump; this patient was withdrawn from the study There were no thromboembolic complications Echocardiographic follow up at 32 months showed a continuing reduction in the peak and mean gradients across both types of valves although it reached significance only in the stented group Mild aortic regurgitation was seen in GP1 No regurgitation was seen in GP2 MRI studies at 6 months shoed improvements in left ventricular volume and end-diastolic and-systolic muscle mass indices in both groups, but these trends did not reach statistical significance	• Poor

APPENDIX J: Comprehensive Data Extraction Tables - One Year Review of Journals 2001 - 2002

The Journal of Thoracic and Cardiovascular Surgery				
Study	**Participants**	**Methodology**	**Outcomes**	**Obstacles**
E. Butchart, et al., June 2001 J Thorac Cardiovasc Surg 2001; 121: 1090-1100 Portland, Oregon, USA	1766 valve replacements with the Medtronic Hall mechanical valve (736 aortic, 796 mitral, and 234 double). Mean age of patients receiving aortic valves was 60 +/- 11 yrs. Operative diagnosis aortic valve replacements: 59 % stenosis, 21 % regurgitation, 20 % mixed lesion. 69 % of aortic valve recipients were male.	Patients were followed up prospectively at 6 to 12 month intervals for a total of 12688 follow up years. All patients received warfarin, starting on the first postoperative day. Most patients attended follow-up clinics; those who didn't were contacted by telephone for updates. No randomization discussed.	Early mortality: 4.2 % AVR, 7.7 % MVR, 12 % DVR. Analysis of functional status changes showed an improvement in 69 % of AVR patients, 73 % of MVR patients and 74 % of DVR patients at 5 years. Improvement was maintained in 66 %, 64 %, and 73 % respectively at 10 years.	This paper did not comment on any limitations of their study. However, study was not randomized. Study examined only one type of valve and compared results with literature from previous studies - no controls or matching of patient populations.
Khan et al., August 2001 J Thorac Cardiovasc Surg; 122: 257-269 Los Angeles & Santa Monica, CA, USA	2533 patients 18 years or older undergoing initial aortic, mitral, or combined aortic and mitral valve replacement with a tissue valve or a St. Jude Medical mechanical valve.	Patients were prospectively entered into a patient database since 1969. Patients were mailed annual questionnaires. Patients who reported issues were contacted by a research nurse. Operative mortality was defined to include all deaths occurring during the hospitalization or within 30 days of the operation. Patients were excluded if they received homografts, a combination of mechanical & tissue valves or prior valve replacement. No randomization discussed.	Mechanical valve recipients were younger than tissue valve recipients and more often female. Degenerative aortic valve disease was the most common cause for valve replacement for both groups. Minimal differences in operative mortality between valve types (9.8 % tissue valves vs. 7.8 % mechanical) Mortality did differ significantly by valve placement (6.1 % aortic vs. 11.8 % mitral) At 15 years between 71 % & 75 % of all patients were free of embolic events after tissue and mechanical valve replacement regardless of valve position.	Study not randomized comparison - creates a potential for bias in valve selection. Use of standard porcine & pericardial valves - other tissue valves may show different outcomes. Two most common & most clinically significant long-term complications of valve replacement are embolic events and hemorrhage.
K. Lim, et al., January 2002 J Thorac Cardiovasc Surg; 123: 21-32 Bristol & Cardiff, UK	485 patients received either a CarboMedics (CM) or St Jude Medical (SJM) prosthesis for aortic, mitral or double valve replacements between July 1992 and June 1996. 485 patients were included in the study. 234 patients received a CM and 251 patients received a SJM. There were 288 AVR, 160 MVR, and 37 DVR. The mean ages were 60 in the CM group and 61 in the SJM group. There were 45 % female patients in each group. Preoperatively, 39 % of patients were in NYHA class II and 34 % in class III. The main cause of valve dysfunction among patients undergoing AVR was calcific stenosis, with rheumatic origin the most common cause for those undergoing MVR and DVR. 44 patients were undergoing reoperation to replace dysfunctional previously implanted prosthetic valves.	Patients were randomly assigned to one of the two surgical arms at the time of surgery. Exclusion criteria were used in the selection of subjects. Patients were followed annually post surgery primarily by patient questionnaire. This is a midterm report of a study through a projected 10 year period. Surgery was performed by five consultant surgeons.	The early mortality was 5.1 % (n=25, CM n=14, SJM n=11). There were no early valve related deaths. There were 64 deaths during late follow up (CM n=28, SJM n=36).	There was a baseline imbalance in the two groups of randomized patients. More patients in the CM group had infective endocarditis & congenital valve pathologic conditions Such baseline imbalances could have been avoided through the use of a more sophisticated method of randomization that included strategic stratification, block randomization, or minimization. Recognize that this is an interim report and more time (10 year) will provide a more accurate comparison between the two valve types.

The Journal of Thoracic and Cardiovascular Surgery				
Study	**Participants**	**Methodology**	**Outcomes**	**Obstacles**
N. Vitale, et al., October 2001 J Thorac Cardiovasc Surg; 122: 691-698 Bari, Italy	140 patients with 21 mm and 23 mm annulus diameters were to receive either a Hemodynamic Plus or a standard cuff valve. Patients were admitted to the study with isolated aortic valve disease. Patients with other associated cardiac disease, such as coronary artery disease, were not eliminated.	This was a controlled study undertaken by 8 academic units of cardiac surgery. Study enrollment was limited to 140 patients. The St Jude Medical (HP) valve was compared with the St Jude Medical standard cuff valve (SC). Exclusion criteria eliminated patients requiring aortic valve replacement on an emergency basis. Enrollment period lasted 1 year and each patient had a requisite 6 month follow up. Patients were randomized in the operating theatre once the annulus was sized. Randomization was carried out in a blind manner for both the patient and surgeon. Echocardiograms were always carried out by the same echocardiographer who was unaware of the type of valve implanted.	3.5 % 30 day mortality. One patient died at reoperation for aortic dissection. Of the remaining 133 patients, 125 completed the 6 month follow up, but 8 patients were censored because they refused to undergo evaluation at 6 months. Mean gradient: 21 mm SC and HP valves had equal mean gradients; the 23 mm HP valve had a slightly lower gradient than 23 mm SC valve. All gradients decreased over time and all differences were statistically significant except for those of the 23 mm SC valves. No statistically significant difference in effective orifice areas between the groups. After the end of the 6 month follow up, no valve thrombosis, thromboembolic events, or anticoagulation-related hemorrhages were observed.	Authors stated that there may be bias in the study. Differences in cardiac output were observed that may have caused the difference in transvalvular gradients. Also, cross-sectional areas of the valves were measure with an edge-to-edge method, and in patients with a hypertrophic ventricular septum this may reduce effective orifice areas. Longer follow up time is necessary to confirm the this study.

Annals of Thoracic Surgery				
Study	**Participants**	**Methodology**	**Outcomes**	**Obstacles**
M. Banbury et al., May 2002. Ann Thorac Surg 2002; 73: 1460-5 Cleveland, OH, USA	267 patients received a bovine pericardial aortic valve prosthesis between September 24, 1981 and December 28, 1983. Mean age: 65 +/- 12 years, 64 % male. Coronary artery disease (n=133), congestive heart failure (n=58) and previous myocardial infarction (n=45) were the most common preexisting conditions.	Of the 267 patients receiving aortic valve replacements at four institutions, 85 had a total of 168 echocardiographic studies during a 17 year period of yearly follow-up examinations. The studies were reviewed and quantified in a core echocardiographic facility. Concomitant procedures were performed in 123 patients. Mean follow-up among survivors was 12 +/- 4.5 years. Patients were assessed yearly, usually during an office or hospital visit or by means of detailed questionnaire by mail or phone.	36 prostheses were explanted, 30 for valve-related complications and 27 for structural valve dysfunction. The 85 patients with echocardiographic studies were similar to the 182 without studies with respect to demographics, valve lesion, prosthesis size and concomitant procedures. Mean transvalvular gradient ranged from 0 to 93mmHg. In vivo effective orifice area ranged from 0.5 to 3.6 cm^2, median 1.03 cm^2. Ejection fraction ranged from 25 % to 80 %. Hemodynamic assessment of the CE stented aortic pericardial prosthesis showed reliable function as late as 17 years after implantation.	Main limitation was the non-random selection of the echocardiographic cohort from the original cohort of 267 patients. Only patients with clinical indications had echocardiograms, therefore the groups were not homogeneous.

Annals of Thoracic Surgery				
Study	**Participants**	**Methodology**	**Outcomes**	**Obstacles**
M. Banbury et al., Sept. 2001 Ann Thorac Surg 2001; 72: 753-7 Cleveland, OH, USA	Between September 1981 and January 1984 267 patients received an aortic Carpentier-Edwards stented bovine pericardial prosthesis	Patients were selected from four investigational centers as part of a pre-marketing clinical investigation for the US Food and Drug Administration. Surgery performed with standardized techniques and concomitant procedures were permitted. Patient follow up was conducted by hospital or office visit or a detailed patient questionnaire. The primary end point was explant for structural valve dysfunction.	36 pericardial valve explants were performed and 30 were classified as valve related. The cause of explant was structural valve deterioration in 27 patients. Other causes of explant were prosthetic valve endocarditis in 2 patients and periprosthetic leakage in 1 patient.	Study had relatively small sample size. The competing risks estimates presumed that death and structural valve deterioration were unrelated Reliable post-mortem information was not available for this study population.
G. Cohen et al., March 2002. Ann Thorac Surg 2002; 73: 767-78 Toronto, Canada	Between September 1996 and December 1999 53 patients were randomized to receive the stented CE pericardial valve (CE) and 46 patients the Toronto Stentless Porcine valve (SPV). Annuli were sized for the optimal insertion of both valve types so that the surgeons were required to commit to specific valve sizes before randomization	Randomization was done in the operating theatre with sealed envelopes. Eligible patients were those who had aortic stenosis and who required a bioprosthetic valve. Candidates would have to meet the surgical and technical requirements for implantation of both stented and stentless valve types before randomization. Exclusion criteria included possible concomitant cardiac procedures, reoperation as well as patient unwillingness or inability to return for echocardiography at follow-up.	The primary outcome of the study was regression of left ventricular mass indexed on body surface area (LVMI). The mean decrease in left ventricular outflow tract diameter (LVOT) after prosthetic valve implantation was similar in both groups. (CE, -3.7 +/- 1.3 mm; SPV, -3.4 +/- 1.1 mm). Effective orifice areas improved significantly in both groups over time, but were most significant within the first 3 months after operation.	Long-term follow-up is necessary to assess late patient outcome and valve durability. Stratification for gender and hypertension may affect LVMR and was not done in this study. Oversizing of valves may have caused another possible source of bias.
Goldsmith, et al., May 2001 Ann Thorac Surg 2001; 71: 1471-6 Cleveland, UK	493 patients received aortic, mitral and both aortic and mitral valve replacements between January 1991 and January 1999. 417 patients had an aortic valve replacement. There were 287 men and 206 women. Preoperatively, 68 % of patients were in NYHA class III or IV. Preoperative diagnosis was aortic stenosis in 269 patients, aortic regurgitation in 49 patients and regurgitation in 83 patients.	7 cardiac surgeons participated in the study. Patient follow-up was conducted by clinical review, mail questionnaire or direct telephone contact. Valve-related complications were defined as thromboembolism, hemorrhage, structural valve deterioration, nonstructural dysfunction, and prosthetic valve endocarditis.	Mean follow up was 46.1 months (range 1-95.6 months). The 30 day mortality for AVR patients was 8.6 %, for MVR patients 20.6 % and DVR was 15.4 %. After AVR there was no significant difference in the size of implant and patient's survival at 8 years. Overall patient survival at 8 years was 45.6 % +/- 6.8 %. At follow up 98 % of survivors were in NYHA class I or II. Survival was significantly higher for those with pure aortic stenosis as compared with those with pure aortic regurgitation and mixed aortic valve disease. There were no episodes of structural valve deterioration at 8 years.	An increased evaluation time course is necessary to determine the long-term durability of the Tissuemed porcine bioprosthesis. 8 year follow-up showed 100 % freedom from structural valve deterioration in patients over 70 years; however studies have shown that biologic valves on average begin to fail at about 8 years.

Annals of Thoracic Surgery				
Study	**Participants**	**Methodology**	**Outcomes**	**Obstacles**
E. Jamieson, et al., May 2001. Ann Thorac Surg 2001: 71: S282-4 Vancouver, Canada	53 patients received a Carpentier-Edwards supra-annular porcine valve (CE-SAV), 48 a pericardial valve (CE-P), and 98 a Medtronic Mosaic porcine bioprosthesis (MM).	The echocardiograms were not performed concurrently and were not randomized. They were performed between 1 & 2 years after valve replacement. The CE-SAV study was a prospective evaluation between 1991 & 1992. The MM evaluations were conducted between 1994 & 1998 as part of an international trial. The CE-P echocardiographic data was collected between 1995 & 1999 as routine practice and the results were collected retrospectively. The echocardiographic comparisons were made for mean gradient and in vivo effective orifice area indexed (EOAI) to body surface area.	There were no significant differences in the mean gradients between prostheses. The comparisons made between effective orifice areas were all non-significant except for size 19, for which the (EOAI) was larger for CE-P than for CE-SAV.	There is a need to study prosthesis performance with intraoperative annular sizing as a more realistic indicator of left ventricular outflow tract performance. There is also a need to compare stentless and stented prostheses for all prostheses sizes to determine indicators for implantation, so as to avoid prosthesis-patient mismatch, to optimize ventricular mass regression and to optimize intermediate and long-term survival.
A. Milano, et al., July 2001. Ann Thorac Surg 2001: 72; 33-8 Pisa, Italy	84 patients with small aortic roots were selected from all patients who underwent isolated aortic valve replacement (AVR) and received a bioprosthesis, the main indication being patient age (> 70 years) between January 1995 and December 1998. Group 1: 37 patients with a 21 mm aortic annulus received either an Edwards Perimount or a St. Jude Toronto bioprosthesis. Group 2: 47 patients with a 23 mm aortic annulus received a Medtronic Mosaic or an Edwards Prima bioprosthesis.	Stented valves were compared with stentless prostheses one size larger. All patients were evaluated at 1, 6 and 12 months and then yearly thereafter at an outpatient clinic. Mean follow-up was 23 +/- 6 months. At each postoperative visit echocardiography was performed.	Overall patient survival with a 19 mm or 21 mm SJP was similar at 5, 10, and 15 years. Older age and CABG associated with AVR were independent predictors of overall death. This study found that body surface area is an independent risk factor for hospital mortality but not for overall death and sudden death as has been observed in other studies. A significant difference between patients with a 19mm and those with a 21mm SJP was found in terms of 15year freedom from cardiac events (56% +/- 13% vs. 86% +/- 4%). A complete regression of left ventricular hypertrophy was not observed in either group of patients.	Study has limitations of a retrospective study where follow-up is carried out at only one point and analyzes a relatively small population.

Annals of Thoracic Surgery				
Study	**Participants**	**Methodology**	**Outcomes**	**Obstacles**
A. Milano et al., January 2002. Ann Thorac Surg 2002; 73: 37-43 Pisa, Italy	Between 1981 and 1995, 229 consecutive patients underwent aortic valve replacement with 19 mm (group 1, 53 patients) or 21 mm St. Jude Medical standard prostheses (group 2, 176 patients	Patients with more than mild aortic regurgitation and patients undergoing concomitant mitral or tricuspid valve operations were excluded. Preoperative and operative data were obtained by retrospective review of clinical and operative records and pathology reports. Follow-up information on hospital survivors was collected during a 6-month intervals	Overall patient survival with a 19 mm or 21 mm SJP was similar at 5, 10, and 15 years. Older age and CABG associated with AVR were independent predictors of overall death. This study found that body surface area is an independent risk factor for hospital mortality but not for overall death and sudden death as has been observed in other studies. A significant difference between patients with a 19mm and those with a 21mm SJP was found in terms of 15year freedom from cardiac events (56% +/- 13% vs. 86% +/- 4%). A complete regression of left ventricular hypertrophy was not observed in either group of patients.	Study has limitations of a retrospective study where follow-up is carried out at only one point and analyzes a relatively small population.
3S. Silberman et al., October 2001 Ann Thorac Surg 2001; 72: 1217-21 Jerusalem, Israel	Toronto stentless porcine valve (TSPV), n=13 Medtronic Freestyle (FR), n=11 Sorin Bicarbon (SOR), n=11 St. Jude Medical (SJM), n=10 Normal native aortic valves (NOR), n=10 (Control group)	Dobutamine echocardiography was used to assess aortic valve function in 55 patients. Study compared the hemodynamic performance of nonstented bioprostheses and mechanical valves with normal native aortic valves at rest and exercise. Patients were examined at least 6 months following aortic valve replacement surgery. The study was retrospective. Echocardiographic measurements were performed at rest and at maximal cardiac output.	All groups demonstrated a major increase in cardiac output with dobutamine infusion. In both mechanical groups, mean gradients at exercise rose significantly in comparison with that of normal subjects. In the nonstented groups there was no significant change in gradient at exercise, similar to normal valves.	Study was retrospective. It might have been advantageous to prospectively size each annulus for each valve type. Study group was not homogeneous in terms of preoperative aortic valve pathology. The adequacy of dobutamine echocardiography to assess valve function at exercise has been questioned.

APPENDIX K: Sources of Financial Support for Comparative Studies of Bioprosthetic Valve – Review of Journals 2001 - 2002

The Journal of Thoracic & Cardiovascular Surgery: 2001-2002					
Study	**Support Not Indicated**	**Unclear Type of Support**	**Financial Funding Indicated: Yes/No/Unclear**	**Sources of Support**	**Study Specific Yes/No/Unclear**
E. Butchart, et al., June 2001 J Thorac Cardiovasc Surg 2001; 121: 1090-1100 Portland, Oregon, USA	No	No	Yes	Medtronic, Inc, Minneapolis, Minnesota	Yes
Khan et al., August 2001 J Thorac Cardiovasc Surg; 122: 257-269 Los Angeles & Santa Monica, CA, USA	No	Yes	Unclear	Divisions of Cardiothoracic Surgery, Cardiology, and Biostatistics, Departments of Surgery and Medicine, The Cedars-Sinai Medical center Burns & Allen Research Institute, University of California at Los Angeles, CA, and the Division of Cardiothoracic Surgery, St John's Hospital, Santa Monica, CA	Unclear
K. Lim, et al., January 2002 J Thorac Cardiovasc Surg; 123: 21-32 Bristol & Cardiff, UK	No	No	Yes	St Jude Medical and Sulzer-CarboMedics	Yes
N. Vitale, et al., October 2001 J Thorac Cardiovasc Surg; 122: 691-698 Bari, Italy	No	Yes	Unclear	Italian Multicenter Study Group for the St Jude Medical Hemodynamic Plus Aortic Valve Prosthesis	Unclear

The Annals of Thoracic Surgery: 2001-2002					
Study	**Support Not Indicated**	**Unclear Type of Support**	**Financial Funding Indicated: Yes/No/Unclear**	**Sources of Support**	**Study Specific Yes/No/Unclear**
M. Banbury et al., May 2002. Ann Thorac Surg 2002; 73: 1460-5 Cleveland, OH, USA	No	No	Yes	Edwards Lifesciences LLC, Irvine, CA, supplied funding for the interpretation of echocardiograms at the Echocardiographic Core Facility of The Cleveland Clinic Foundation.	Yes
M. Banbury et al., September 2001 Ann Thorac Surg 2001; 72: 753-7 Cleveland, OH, USA	No	No	Yes	Research Grant from Edwards Lifesciences LLC, Irvine, CA	No
G. Cohen et al, March 2002 Ann Thorac Surg 2002, 73: 767-78 Toronto, Canada	Yes	No	No	No	No
I. Goldsmith, et al., May 2001 Ann Thorac Surg 2001; 71: 1471-6 Cleveland, UK	Yes	No	No	No	No
E. Jamieson, et al., May 2001. Ann Thorac Surg 2001: 71: S282-4 Vancouver, Canada	Yes	No	No	No	No
A. Milano et al., January 2002. Ann Thorac Surg 2002; 73: 37-43 Pisa, Italy	Yes	No	No	No	No
A. Milano, et al., July 2001. Ann Thorac Surg 2001: 72; 33-8 Pisa, Italy	Yes	No	No	No	No
S. Silberman et al., October 2001. Ann Thorac Surg 2001: 72; 1217-21 Jerusalem, Israel	Yes	No	No	No	No

APPENDIX L: Glossary of Terms

- **allograft** - a graft or transfer of tissues between individuals of the same species but of disparate genotype; also called allogeneic graft and homograft.
- **angina** - spasmodic, choking, or suffocative discomfort or pain manifested in the chest, neck, jaw, back, upper abdomen, shoulders or arms; now used almost exclusively to denote angina pectoris or discomfort related to inadequate coronary blood flow.
- **angiotensin converting enzyme (ACE)** - a protein dipeptidyl carboxypeptidase I found in the lung that converts angiotensin I secreted by the liver into angiotensin II the latter being a powerful vasopressor and stimulus of aldosterone production by the adrenal cortex, resulting in sodium retention and blood pressure elevation.
- **annulus** - a ring or a ring like or circular structure. Fibrous or fibromuscular ring support structure for cardiac valves.
- **anti-hypertensive agent** - an agent that lowers blood pressure.
- **aortic valve** - a passive valve mechanism which opens and closes with minimal pressure differences between the left ventricular chamber of the heart and the main outflow passage of the heart called the aorta which supplies blood to the rest of the body.
- **arterial** - pertaining to an artery or the arteries.
- **autograft** - a graft of tissue derived from another site in or on the body of the organism receiving it; called also autologous or autochthonous graft, and autoplast.
- **bacteremia** - the presence of bacteria in the blood.
- **bicuspid** - having two cusps, leaflets or points as in bicuspid valve.
- **bioprosthetic heart valve substitute** - man-made heart valve replacement made of biological material.
- **Brucella endocarditis** - Brucella: a genus of gram-negative, aerobic coccobacilli or short, rod-shaped bacteria of uncertain affiliation, made up of nonmotile cells that require biotin, niacin, thiamine, and sometimes serum for growth. Endocarditis: exudative and proliferative inflammatory alterations of the

endocardium, characterized by the presence of vegetations on the surface of the endocardium or in the endocardium itself, and most commonly involving a heart valve, but sometimes affecting the inner lining of the cardiac chambers or the endocardium elsewhere.

- **cannula** - a tube for insertion into a duct, blood vessel or cavity; during insertion its lumen is occasionally occupied by a trocar.
- **cardiac catheterization** - passage of a small catheter through a vessel in an arm, leg or the neck and into the heart, permitting the securing of blood samples, determination of intracardiac pressures, and detection of cardiac anomalies and coronary disease.
- **case series study** - a study which reports on a group of patients who all have a certain condition or disease. One group of patients is compared with another group of patients afflicted with the same condition but separated perhaps by time or location. Often a prospective group of patients is compared with a retrospective group of patients.
- **case control study** - a study in which the risk factors of people with a disease are compared with those without a disease. It is an epidemiological method that begins by identifying persons with the disease or condition of interest (the cases) and compares their past history of exposure to identified or suspected risk factors with the past history of similar exposures among persons who resemble the cases but do not have the disease or condition of interest (the controls). The relationship of an attribute to the disease can therefore be examined by comparing affected and non-affected individuals with regard to the frequency or levels of the attribute in each group.
- **coagulation** - the sequential process by which the multiple coagulation factors of blood interact, ultimately resulting in the formation of an insoluble fibrin clot; it may be divided into three stages: stage 1, the formation of intrinsic and extrinsic prothrombin converting principle; stage 2, the formation of thrombin; stage 3, the formation of stable fibrin polymers.

- **collagen** - the protein substance of the white fibers (collagenous fibers) of skin, tendon, bone, cartilage, and all other connective tissues; composed of molecules of tropocollagen, it is converted into gelatin by boiling.
- **co-morbidities** - the presence of coexisting or additional diseases with reference to an initial diagnosis or with reference to the index condition that is the subject of study. Co-morbidity may affect the ability of affected individuals to function and also their survival; it may be used as a prognostic indicator for length of hospital stay, cost factors, and outcome or survival.
- **congenital** - existing at, and usually before, birth; referring to conditions that are present at birth, regardless of their causation.
- **congestive heart failure** - a clinical syndrome due to heart disease and characterized by breathlessness and abnormal sodium and water retention, resulting in edema, usually pulmonary edema. The congestion may occur in the lungs or in the peripheral circulation, or both, depending on whether the heart failure is right-sided, left-sided, or global.
- **controlled clinical trial** - a study whereby patients are assigned to experimental and nonexperimental arms based on fulfilling a set of pre-determined criteria.
- **cryopreservation** - the maintaining of viability of excised tissue or organs by storing at very low temperatures.
- **dehiscence** - a splitting open or separation especially of a structure repaired together such as a surgical wound.
- **diastolic** - of or pertaining to the diastole. (The dilatation or period of dilatation of the chambers of the heart, especially of the ventricles; it coincides with the interval between the second and the first heart sound).
- **echocardiography** - a method of graphically recording the position and motion of the heart walls or the internal structures of the heart and neighboring tissue by the echo obtained from beams of ultrasonic waves directed through the chest wall. Also called ultrasonic cardiography.
- **effective orifice area** - calculated area of the inner orifice of a prosthetic valve by the cross-sectional area of the column of blood that is allowed to pass through.

- **elastin** - a yellow scleroprotein, the essential constituent of yellow elastic connective tissue; it is brittle when dry, but when moist is flexible and elastic.
- **embolize** - the sudden blocking of an artery or vein by a clot (thrombus), air, fat or foreign object that arrives at the site of lodgment by the blood current.
- **endocarditis** - exudative and proliferative inflammatory alterations of the endocardium, characterized by the presence of vegetations on the surface of the endocardium or within the endocardium itself, and most commonly involving a heart valve, but sometimes affecting the inner lining of the cardiac chambers or the endocardium elsewhere. It may occur as a primary disorder or as a complication of or in association with another disease.
- **endocardium** - the endothelial lining membrane of the cavities of the heart and the connective tissue bed on which it lies.
- **endoscopy** - visual inspection of any cavity of the body by means of an endoscope. (endoscope - an instrument for the examination of the interior of a hollow viscus, such as the bladder).
- **epidemiology** - the science concerned with the study of the factors determining and influencing the frequency and distribution of disease, injury, and other health-related events and their causes in a defined human population for the purpose of establishing programs to prevent and control their development and spread.
- **etiology** - the study or theory of the factors that cause disease and the method of their introduction to the host; the cause or origin of a disease or disorder.
- **fibrillation** - a small, local, involuntary contraction of muscle, invisible under the skin, resulting from spontaneous activation of single muscle cells or muscle fibers. (Atrial fibrillation - atrial arrhythmia characterized by rapid randomized contractions of the atrial myocardium, causing a totally irregular, often rapid ventricular rate).
- **fibrosis** - the formation of fibrous or scar tissue; fibroid or fibrous degeneration.
- **glutaraldehyde** - chemical name: pentanedial. A disinfectant effective against vegetative gram-positive, gram-negative, and acid-fast bacteria, bacterial spores, some fungi, and viruses; used in aqueous solution for sterilization of endoscopic

equipment, thermometers, and plastic, rubber, or other non-heat resistant equipment. It is also used topically as an anhidrotic and may be used in the manufacture of heart valves.

- **glycosaminoglycan** - any carbohydrate containing amino sugars occurring in proteoglycans such as chondroitin sulfate or hyaluronic acid that may be sulfated.
- **hemodynamic** - pertaining to the movements (as related to pressure and volume) involved in the circulation of the blood.
- **hemorrhage** - the escape of blood from the vessels; bleeding.
- **heart failure** - a clinical syndrome characterized by distinctive symptoms and signs resulting from disturbances in cardiac output or from increased venous pressure. Most often applied to myocardial failure with increased pressures distending the ventricle and a cardiac output inadequate for the body's needs; often sub-classified as right or left-sided heart failure depending on whether the systemic or pulmonary veins are predominantly distended respectively.
- **heart murmur** - A sound generated by disturbed blood flow through the heart manifested as "turbulence". Turbulence is an irregular condition of motion caused by local vibrations of the wall of a vessel or heart chamber. Heart murmurs are usually detectable in ventricular outflow obstruction and in various types of heart valve disease and are differentiated from heart sounds, a physiological concept.
- **homograft** - a graft of tissues between individuals of the same species but of disparate genotype; called also allogeneic graft and allograft.
- **hypertrophy** - the enlargement or overgrowth of an organ or part due to an increase in size of its constituent cells.
- **infarction** - the formation of an infarct which is an area of tissue death due to lack of oxygen.
- **interstitial** - pertaining to or situated between parts or in the interspaces of a tissue.
- **laparoscopic** - examination of the interior of the abdomen by means of a laparoscope, an instrument comparable to an endoscope which, when inserted into

the peritoneal cavity, permits it to be inspected.

- **left ventricular mass regression** - left ventricular enlargement (increase in both mass and wall thickness) is caused by aortic valve disease. When surgical intervention is used to correct the problem there should be a regression the left ventricular mass if the replacement valve has effectively relieved the obstruction and/or leakage created by its damaged predecessor.
- **Marfan's syndrome** - a congenital disorder of connective tissue characterized by abnormal subluxation of the optic lens, cardiovascular abnormalities (commonly dilatation of the ascending aorta), and valvular dysfunction. It is an autosomal dominant trait with a variable degree of phenotypic expression.
- **mastectomy** - surgical excision of the breast.
- **meta-analysis** - a quantitative method of combining the results of independent studies (usually drawn from the published literature) and synthesizing summaries and conclusions which may be used to evaluate therapeutic effectiveness or to plan new studies. With application chiefly in the areas of research and medicine, it is often an overview of clinical trials. It is usually called a meta-analysis when a statistical analysis is possible and should be differentiated from descriptive systematic reviews of the literature.• **myocardial infarction** - gross necrosis of the myocardium, as a result of interruption of the blood supply to the area, as in coronary thrombosis.
- **myocardium** - the middle and thickest layer of the heart wall composed of cardiac muscle.
- **non-randomized studies** - studies where the subjects are assigned to the control and experimental arms by a selection process that is not a purely mathematically random act.
- **open cholecystectomies** - surgical removal of the gallbladder by the traditional open method of surgery.
- **pericardium** - the fibroserous sac that surrounds the heart and the roots of the great vessels comprises an external layer of fibrous tissue and an inner serous layer. The base of the pericardium is attached to the central tendon of the

diaphragm.

- **physiologic** - normal, not pathologic; characteristic of or conforming to the normal functioning or state of the body or a tissue or organ.
- **presyncope** - syncope: a temporary suspension of consciousness due to generalized cerebral ischemia, a faint or swoon.
- **prosthesis** - an artificial substitute for a missing or dysfunctional body part e.g. a replacement for a cardiac valve.
- **randomized control trials** - clinical trials that involve at least one test treatment and one control treatment, concurrent enrollment and follow-up of the test- and control-treated groups, and in which the treatments to be administered are selected by a random process, such as the use of a random-numbers table. Treatment allocations using coin flips, odd-even numbers, patient social security numbers, days of the week, medical record numbers, or other such pseudo- or quasi-random processes, are not truly randomized and trials employing any of these techniques for patient assignment are designated simply controlled clinical trials.
- **rheology** - the science of the deformation and flow of matter, such as the flow of blood through the heart and blood vessels.
- **rheumatic fever** - a febrile disease occurring as delayed sequelae of infections with group A hemolytic streptococci and characterized by multiple focal inflammatory lesions of the connective tissue structures, especially of the heart, blood vessels and joints, and by the presence of microscopically identified Aschoff bodies in the myocardium and skin. Typically, the onset is signaled by the sudden occurrence of fever and joint pain, followed by manifestations of heart and pericardial disease, abdominal pain, skin changes, and chorea. Atypical manifestations, particularly in adults are not uncommon.
- **Ross operation** - first described by Donald Ross, entails replacement of the patient's aortic valve and root with a pulmonary autograft (patient's own pulmonary artery and valve conduit), then using an allograft in the pulmonary position. Rationale is increased long-term durability of the pulmonary autograft compared with an allograft in the aortic position.

- **stenosis** - narrowing or stricture of a duct or canal. For example, aortic stenosis is a narrowing of the aortic orifice of the heart or of the aortic valve itself.
- **supine** - lying with the face upwards.
- **syncope** - syncope: a temporary suspension of consciousness due to generalized cerebral ischemia: a faint or swoon.• **systolic** - pertaining to or produced by the systole; occurring along with the ventricular systole. Systole, the contraction, or period of contraction, of the heart, especially that of the ventricles; sometimes divided into components, as pre-ejection and ejection periods, or isovolumetric systole, usually premature, not associated with pulsation of a peripheral artery.
- **teratogenicity** - the ability to cause defects in a developing fetus. This is a distinct form of mutagenicity that causes genetic mutations in sperm, eggs or other cells. Teratogenicity is a side effect of many drugs.
- **thoracotomy** - surgical incision of the wall of the chest.
- **thrombectomy** - excision of a thrombus from a blood vessel.
- **thromboembolism** - obstruction of a blood vessel with thrombotic material carried by the blood stream from the site of origin to plug another vessel.
- **thrombosis** - the formation, development, or presence of a thrombus. Thrombus, an aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causes vascular obstruction at the point of its formation.
- **venous** - of or pertaining to the veins.

APPENDIX M: One Year Review of Journals

Obstacles Summarized: Table 1

The Journal of Thoracic and Cardiovascular Surgery					
Study	**Group**	**Survival**	**Late Mortality**	**Thromboembolism**	**Primary Tissue Valve Failure**
E. Butchart, et al., June 2001 J Thorac Cardiovasc Surg 2001; 121: 1090-1100 Portland, Oregon, USA	Medtronic Hall valve	AVR: 64 % 10 years MVR: 58 % 10 years DVR: 47 % 10 years	AVR: 211 deaths MVR: 325 deaths DVR: 95 deaths	AVR: 0.6 %/yr MVR: 0.6 %/yr DVR: 0.6 %/yr	Not Stated
Khan et al., August 2001 J Thorac Cardiovasc Surg; 122: 257-269 Los Angeles & Santa Monica, CA, USA	Tissue valve (Hancock, Carpentier-Edwards porcine, Carpentier-Edwards pericardial) St. Jude mechanical Valve	No significant differences in survival were seen between tissue and mechanical valves after stratifying by the presence or absence of coronary artery disease.	Not Stated	Not individually stated	Not individually stated
K. Lim, et al., January 2002 J Thorac Cardiovasc Surg; 123: 21-32 Bristol & Cardiff, UK	CarboMedics (CM)	82.4 % +/- 2.6 %	28	2	Not Stated
	St Jude Medical (SJM)	79.9 % +/- 2.8 %	36	3	Not Stated
N. Vitale, et al., October 2001 J Thorac Cardiovasc Surg; 122: 691-698 Bari, Italy	St Jude Medical HP Valve (HP) St Jude Medical standard cuff valve (SC)	3.5 % Early mortality	2 Deaths	Not Stated	Not Stated

Annals of Thoracic Surgery					
Study	**Group**	**Survival**	**Late Mortality**	**Thromboembolism**	**Primary Tissue Valve Failure**
M. Banbury et al., May 2002. Ann Thorac Surg 2002; 73: 1460-5 Cleveland, OH, USA	267 patients: Carpentier-Edwards aortic pericardial bioprosthesis	16 % (n=267) alive at 15 years 6 % alive at 16 years	Not Stated	Not Stated	Not Stated
M. Banbury et al, September 2001 Ann Thorac Surg 2001; 72: 753-7 Cleveland, OH, USA	267 patients received an aortic Carpentier-Edwards stented bovine pericardial prosthesis	Risk-unadjusted survival at 10 and 15 years was 52% & 26%	Risk-unadjusted chance of a patient remaining alive to experience prosthesis explant overall was 0.4%, 3.9%, and 10.4% at 5, 10, and 15 years.	Not Stated	Not Stated
G. Cohen et al., March 2002 Ann Thorac Surg 2002; 73: 767-78 Toronto, Canada	53 patients: stented CE pericardial valve (CE).	Early mortality: 2 patients	Not Stated	Not Stated	Not Stated
	46 patients: Toronto Stentless Porcine valve (SPV).	Early mortality: 2 patients			

Annals of Thoracic Surgery					
Study	**Group**	**Survival**	**Late Mortality**	**Thromboembolism**	**Primary Tissue Valve Failure**
I. Goldsmith, et al., May 2001 Ann Thorac Surg 2001; 71: 1471-6 Cleveland, UK	Aspire Porcine Bioprosthesis	Overall survival at 8 years: 45.6 % +/- 6.8 %	15 late valve-related deaths	1.9 % per patient year	Not Stated
E. Jamieson, et al., May 2001. Ann Thorac Surg 2001; 71: S282-4 Vancouver, Canada	53 - Carpentier-Edwards supra-annular porcine valve (CE-SAV)	Not Stated	Not Stated	Not Stated	Not Stated
	48 - pericardial valve (CE-P)				
	98 - Medtronic Mosaic porcine bioprosthesis (MM)				
A. Milano et al., January 2002. Ann Thorac Surg 2002;73: 37-43 Pisa, Italy	229 consecutive patients underwent aortic valve replacement with 19 mm (group 1, 53 patients) or 21 mm St. Jude Medical standard prostheses (group 2, 176 patients)	3.5 % +/- 0.9 % per year	10 patients	5 patients	Not Stated
		3.3 % +/- 0.5 % per year	31 patients	12 patients	
A. Milano, et al., July 2001. Ann Thorac Surg 2001; 72: 33-8 Pisa, Italy	Group 1: 37 patients with a 21mm aortic annulus received either an Edwards Perimount or a St. Jude Toronto bioprosthesis.	Not Stated	Not Stated	Not Stated	Not Stated
	Group 2: 47 patients with a 23mm aortic annulus received a Medtronic Mosaic or an Edwards Prima bioprosthesis.				
S. Silberman et al., October 2001 Ann Thorac Surg 2001; 72: 1217-21 Jerusalem, Israel	Toronto stentless porcine valve (TSPV), n=13	Not Stated	Not Stated	Not Stated	Not Stated
	Medtronic Freestyle (FR), n=11				
	Sorin Bicarbon (SOR), n=11				
	St. Jude Medical (SJM), n=10				
	Normal native aortic valves (NOR), n=10				

Obstacles Summarized: Table 2

The Journal of Thoracic and Cardiovascular Surgery						
Study	**Group**	**Bacterial Endocarditis**	**Reoperation**	**Structural Valve Deterioration**	**LV Mass Regression**	**NYHA Class I, II, III, IV**
E. Butchart, et al., June 2001 J Thorac Cardiovasc Surg 2001; 121: 1090-1100 Portland, Oregon, USA	Medtronic Hall valve	AVR: 5 MVR: 2 DVR: 3/2	AVR: 22 MVR: 25 DVR: 11	Not Stated	Not Stated	90 % of patients I or II
Khan et al., August 2001 J Thorac Cardiovasc Surg; 122: 257-269 Los Angeles & Santa Monica, CA, USA	Tissue valve (Hancock, Carpentier-Edwards porcine, Carpentier-Edwards pericardial)	Not Stated	AVR: 8.4 % 10 years MVR: 12.3 % 10 years	Not Stated	Not Stated	Not individually stated
	St. Jude mechanical Valve		AVR: 1.3 % 10 years MVR: 2.5 % 10 years			
K. Lim, et al., January 2002 J Thorac Cardiovasc Surg; 123: 21-32 Bristol & Cardiff, UK	CarboMedics (CM)	1	3	0	Not Stated	47, 45, 16, 4 At 5 years
	St Jude Medical (SJM)	4	4	0	Not Stated	45, 30, 16, 12 At 5 years
N. Vitale, et al., October 2001 J Thorac Cardiovasc Surg; 122: 691-698 Bari, Italy	St Jude Medical HP Valve (HP)	Not Stated	Not Stated	Not Stated	Not Stated	Not Stated
	St Jude Medical standard cuff valve (SC)					

Annals of Thoracic Surgery						
Study	**Group**	**Bacterial Endocarditis**	**Reoperation**	**Structural Valve Deterioration**	**LV Mass Regression**	**NYHA Class I, II, III, IV**
M. Banbury et al., May 2002. Ann Thorac Surg 2002; 73: 1460-5 Cleveland, OH, USA	267 patients: Carpentier-Edwards aortic pericardial bioprosthesis	Not Stated	Not Stated	Not Stated	Not Stated	120, 88, 26, 6
M. Banbury et al, September 2001 Ann Thorac Surge 2001, 72: 753-7 Cleveland, OH, USA	267 patients received an aortic Carpentier-Edwards stented bovine pericardial prosthesis	Not Stated	36 explants performed	27 patients	Not Stated	Not Stated

Annals of Thoracic Surgery						
Study	**Group**	**Bacterial Endocarditis**	**Reoperation**	**Structural Valve Deterioration**	**LV Mass Regression**	**NYHA Class I, II, III, IV**
G. Cohen et al., March 2002. Ann Thorac Surg 2002; 73: 767-78 Toronto, Canada	53 patients: stented CE pericardial valve (CE).	Not Stated	2 patients (for bleeding)	Not Stated	22.3 g/m2	Not Stated
	46 patients: Toronto Stentless Porcine valve (SPV).		3 patients (for bleeding)		23.8 g/m2	
I. Goldsmith, et al., May 2001 Ann Thorac Surg 2001; 71: 1471-6 Cleveland, UK	Aspire Porcine Bioprosthesis	5 patients	2 patients - aortic position	None	Not Stated	98 % I or II
E. Jamieson, et al., May 2001. Ann Thorac Surg 2001: 71: S282-4 Vancouver, Canada	53 - Carpentier-Edwards supra-annular porcine valve (CE-SAV)	Not Stated	Not Stated	Not Stated	Not Stated	Not Stated
	48 - pericardial valve (CE-P)					
	98 - Medtronic Mosaic porcine bioprosthesis (MM)					
A. Milano et al., January 2002. Ann Thorac Surg 2002; 73: 37-43 Pisa, Italy	Group 1: 19 mm St. Jude Medical standard prostheses	Not Stated	2 patients	Valve related complications: 15 patients	18 +/- 9 %	1.8 +/- 0.8
	Group 2: 21 mm St. Jude Medical standard prostheses		3 patients	Valve related complications: 47 patients	22 +/- 9 %	1.3 +/- 0.5
A. Milano, et al., July 2001. Ann Thorac Surg 2001: 72; 33-8 Pisa, Italy	Group 1: 37 patients with a 21mm aortic annulus received either an Edwards Perimount or a St. Jude Toronto bioprosthesis.	Not Stated	Not Stated	Not Stated	Group 1 patients showed a significant reduction of peak gradient during follow-up with a statistically significant difference between 1 month versus last follow-up.	Not Stated
	Group 2: 47 patients with a 23mm aortic annulus received a Medtronic Mosaic or an Edwards Prima bioprosthesis.				Group 2 patients showed similar results as group 1.	
S. Silberman et al., October 2001. Ann Thorac Surg 2001: 72; 1217-21 Jerusalem, Israel	Toronto stentless porcine valve (TSPV), n=13	Not Stated	Not Stated	Not Stated	Not Stated	Not Stated
	Medtronic Freestyle (FR), n=11					
	St. Jude Medical (SJM), n=10					
	Normal native aortic valves (NOR), n=10					

Financial Information – One Year Journal Review Summary

The Journal of Thoracic & Cardiovascular Surgery: 2001-2002									
Study	**Support Not Indicated**	**Funding Indicated**			**Unclear Type of Support**	**Sources of Financial Support**			
		Specific	**General**	**Unclear**		**Foundations Charities Associations Societies**	**Labs Pharmaceutical Companies**	**Agencies, Government Departments**	**Unclear**
E. Butchart, et al., June 2001 J Thorac Cardiovasc Surge 2001; 121: 1090-1100 Portland, Oregon, USA	-	X	-	-	-	-	X	-	-
Khan et al., August 2001 J Thorac Cardiovasc Surg; 122: 257-269 Los Angeles & Santa Monica, CA, USA	-	-	-	X	X	-	-	-	X
K. Lim, et al., January 2002 J Thorac Cardiovasc Surg; 123: 21-32 Bristol & Cardiff, UK	-	X	-	-	-	-	X	-	-
N. Vitale, et al., October 2001 J Thorac Cardiovasc Surg; 122: 691-698 Bari, Italy	-	-	-	X	X	-	-	-	-

The Annals of Thoracic Surgery: 2001-2002										
Study	**Support Not Indicated**	**Funding Indicated**			**Unclear Type of Support**	**Sources of Financial Support**			
		Specific	**General**	**Unclear**		**Foundations Charities Associations Societies**	**Labs Pharmaceutical Companies**	**Agencies, Government Departments**	**Unclear**
M. Banbury et al., September 2001. Ann Thorac Surg 2001; 72: 753-7 Cleveland, OH, USA	-	-	X	-	-	-	-	-	X
M. Banbury et al., May 2002. Ann Thorac Surg 2002; 73: 1460-5 Cleveland, OH, USA	-	X	-	-	-	X	-	-	X
G. Cohen et al., March 2002. Ann Thorac Surg 2002; 73: 767-78 Toronto, Canada	X	-	-	-	-	-	-	-	-
Goldsmith, et al., May 2001 Ann Thorac Surg 2001; 71: 1471-6 Cleveland, UK	X	-	-	-	-	-	-	-	-
E. Jamieson, et al., May 2001. Ann Thorac Surg 2001: 71: S282-4 Vancouver, Canada	X	-	-	-	-	-	-	-	-
Milano et al., January 2002. Ann Thorac Surg 2002; 73: 37-43 Pisa, Italy	X	-	-	-	-	-	-	-	-
Milano, et al., July 2001. Ann Thorac Surg 2001: 72; 33-8 Pisa, Italy	X	-	-	-	-	-	-	-	-

The Annals of Thoracic Surgery: 2001-2002									
Study	Support Not Indicated	Funding Indicated			Unclear Type of Support	Sources of Financial Support			
		Specific	General	Unclear		Foundations Charities Associations Societies	Labs Pharmaceutical Companies	Agencies, Government Departments	Unclear
S. Silberman et al., October 2001. Ann Thorac Surg 2001: 72; 1217-21 Jerusalem, Israel	X	-	-	-	-	-	-	-	-

APPENDIX N

GUIDELINES FOR DESIGN OF A SURGICAL TRIAL: COMPARING TWO BIOPROSTHETIC HEART VALVES

N.1 Preamble

Although several approaches may have been used to develop a set of guidelines, the U.K. Medical Research Council (M.R.C.) guidelines, as adapted by the Canadian Institutes of Health Research, was deemed the most suitable for our purposes. This set of guidelines was extremely important in clarification of the many hurdles encountered by surgeons conducting trials.

Surgical trials that are well controlled and randomized present a unique array of problems in terms of their design and implementation. Their complexity entails attention to the co-ordination, monitoring and accumulation of data for these studies. Hence, they are quite rare and costly to perform. A set of guidelines follows based on the framework proposed by the CIHR and the United Kingdom MRC. They were developed to ensure that well designed surgical trials would be formulated to avoid the biases and shortcomings of other types of study design.

The guidelines were applied to develop a specific study protocol, which are provided below. The study protocol is designed for evaluating two bioprosthetic stented heart valves (Carpentier-Edwards Perimount Magna versus Medtronic Mosaic Porcine).

N.2 Abstract

A concise and structured outline divided into the subheadings of: background, objectives, study design, setting, study population, interventions, outcomes, sample size, duration

and mode of follow-up, and time line.

N.3 Statement of the Problem

This paragraph will address the surgical issue of interest and how the intervention will address it. It requires an overview of the burden of disease and complications relative to the surgical procedure. If possible, it should also address morbidity, mortality, and the natural history of the illness especially in situations where the surgical procedure is not performed. Any differences between the surgical and the non-surgical or control population should be addressed. These differences mainly relate the demographics, associated co-morbidities and long-term medical management of both groups. If for some reason it is ethically impossible to have a non-surgical or control population, then specific reasons must be given and a careful evaluation of differences between the two subgroups should be documented.

N.4 Practice Variation

Substantial differences in how a particular operation is conducted exist between surgeons and between centres. Although the art of performing certain highly specialized operative procedures can vary substantially depending on the surgeon performing it, there are often several factors that are kept constant between one centre and another and occasionally between surgeons. Level of expertise will determine outcomes between centres and as well between surgeons. A surgeon with a special aptitude may be designated to do a particular procedure. This information will have to be documented and standardized for all centres involved in the study. This will also affect study recruitment.

N.5 Background

The epidemiology and incidence of the surgical disease should be reviewed with particular focus made to regional, national and international variations. Specific data pertaining to cause of death and morbidity for treated and untreated illness should be discussed.

A summary of the health care delivery systems, population demographics, type of surgical practice, and post-operative care should be discussed. For example, patients that are treated in a group practice of a tertiary health care hospital may expect a different level of health care delivery than those treated in a primary care facility. Access to associated specialists, home care, critical care, and follow-up will likely be different and should be described in detail. The number and expertise of necessary staff before, during and after surgery should also be reported.

The impact of the trial on application of subsequent surgical techniques, prosthesis selection, and patient selection should be described. Potential risks, benefits and long-term effects should be discussed.

N.6 Hypothesis

A clearly stated hypothesis that identifies the clinical benefit from a new surgical procedure is necessary. For example, when comparing the performance of a new bioprosthetic device with one that is currently being used in practice there would be an expectation of benefit of a decreased trans-valvular gradient or left ventricular mass regression over a specific length of time in the newer device. If there is an expectation of increased long-term survival then documentation of the length of follow-up should be made. A standardization of the periods is necessary for comparison with other studies. For example, follow-up at one, five and ten years would be useful.

N.7 Study Objectives

The following clinical objectives are proposed for a comparison between two bioprosthetic heart valve substitutes. Based on the systematic review of bioprosthetic heart valves, several primary and secondary objectives should be stated.

N.7.1 Operational Objectives

Should be to perform a randomized controlled trial comparing two bioprosthetic heart valves that would maximize the degree of blinding and minimize the amount of bias thereby overcoming the two major problems in conducting surgical trials. This would involve implementation of a variety of strategies that would address the difficulties encountered by other surgical investigators.

N.7.2 Clinical Objectives

Should be to perform a randomized controlled trial comparing two bioprosthetic heart valves that would identify a clinically significant difference in performance reflected in morbidity, mortality, long-term survival and complications. Important to the design of such a study would be the reproducibility of the results in other centers and ideally by the hands of most surgeons in clinical practice. Thus, the results would be applicable to other populations of patients.

Primary Objective

A comparison of two bioprosthetic heart valve substitutes used in the treatment of aortic valve disease in the human adult. Differences in hemodynamics, extent and rate of left ventricular mass regression, and long-term survival will be examined.

Secondary Objective

To compare morbidity and operative mortality associated with the two surgical approaches. An additional secondary objective would be measurement of the cost effectiveness of either prosthesis.

N.8 Experimental Methods

N.8.1 Study Design Overview

A brief summary of the proposed trial design (for example, double blind, crossover, cohort, and so on) and the planned surgical procedure for both the experimental and the control groups should be discussed. This may be a comparison of an existing heart valve substitute or surgical procedure with a new device or technique. These features may not be possible in certain types of surgical procedures. Informed consent should be standardized.

N.8.2 Participating Surgeons, Groups and Centres

The enthusiasm of a particular surgeon will be as important as his expertise for a particular procedure. The surgeon's experience will not only determine complication rates, operative success, and expertise but it will also affect patient recruitment rates. Surgical team group dynamics will determine whether a single surgeon should be designated to accept all cases of a particular surgical nature or whether expertise should be diluted among group members. A high success rate of a particular surgeon will produce better results with an inferior new bioprosthetic heart valve or surgical procedure when compared with a surgeon or group that generally does not perform this procedure. Hence, application of such a device or procedure could potentially be difficult to introduce to the general population of surgeons outside the study setting. External

validity of the study would need separate evaluation before the procedure or prosthetic device could be allowed for general implementation. This would also introduce the issue of whether surgeons with different skills would become part of the study. In addition to a surgeon's preference for one of the experimental procedures or heart valve substitutes is the fact that other members of the surgical team need to be evaluated in terms of their skills. For example, whether a single anesthetist or a group is used, whether specific surgical assistants or a group is used, and whether a standardized critical care approach is implemented or not will all need clarification. If a learning period is necessary, then technical failures, complications or variations in the protocol should be reviewed by the steering committee with the group surgeons in a discrete manner to implement the appropriate correction measures. The run-in period is useful to determine if the planned intervention can be delivered.

Major differences between centres may be encountered with regard to the availability of human resources, financial support, and patient demographics. Variations related to patient referral patterns, and timing of surgery may well affect outcomes and introduce bias.

N.8.3 Study Groups

Protection against bias such as blinding or masking should be described in detail. Allocation of participants to the trial groups by randomization must be documented. Factors that are chosen for stratification or minimization should be identified and the reasons documented. Ultimately, the goal is to produce comparable study groups that are large enough and representative of the actual population in question. Age, gender, pre-operative functional capacity, co-morbidities, biophysical parameters, and left ventricular function are carefully documented pre-operatively.

N.8.4 Recruitment

Inadequate recruitment of large numbers of patients for both control and experimental arms often interferes with achieving adequate sample sizes. This significantly hinders adherence to the period established for the study. Also, with rapid advances and changes in surgical technique and technology there could be significant improvements in the standardization of techniques for patients entering the study at the beginning compared with those entering later on in the study.[33] The resources necessary to achieve the required recruitment need to be clearly established, including promotion of the trial to generate interest from the referring specialists, participating surgeons, and possible patients. The popularity of the intervention amongst referring specialists is essential. The surgeon's level of enthusiasm is as important as the patient's anxiety about entering such a study.[33] Psychological barriers need to be overcome, as patients often do not wish to be 'guinea pigs' to procedures that are performed on them. A study nurse is necessary to thoroughly educate the patient, and address costs and inconveniences incurred to the patient, and as some may choose an established therapy over a new technique because of ignorance.[33]

Failure in recruitment is as likely to be related to patient anxiety and fear of the unknown as it can be due to the reluctance of a surgeon to engage in a novel procedure.[33] Inclusion and exclusion criteria may have to be relaxed to allow more patients to become eligible.[33] Patient instability and severity of illness are fundamental factors affecting the decision to operate and may therefore result in selection bias during the recruitment stage of a study. This potential for bias should be accounted for in the study design and subgroup analysis should take the pre-operative status of the patient into consideration.

N.8.5 Inclusion and Exclusion Criteria

Inclusion criteria for enrolling patients should include the following:

1) Adults 19 years and over with aortic valve disease undergoing first time replacement of the aortic valve;
2) a bioprosthetic valve substitute is the chosen option for the patient;
3) patient undergoing aortic valve replacement and concomitant coronary artery bypass grafting;
4) patient undergoing aortic valve replacement with or without coronary artery bypass grafting who has undergone previous bypass surgery.

Exclusion criteria would encompass patients who:

1) are less than 19 years of age;
2) have refused consent (refusal is from the patient or the surgeon);
3) are suffering from a terminal illness with a life expectancy of less than six months;
4) have previously been enrolled in the study;
5) are currently enrolled in another surgical intervention study;
6) are unable to receive blood products (such as patients who are of the Jehovah's Witness faith, inability to receive a blood product, previous severe transfusion reaction, or cross-matching technical difficulties);
7) undergo primary or re-operative surgery for adult congenital heart procedures;
8) would be unable to return for clinical and echocardiographic follow-up.

N.8.6 Surgical Intervention Protocol

Recruiting a large number of eligible patients, which are relatively homogeneous, for a randomized controlled trial on aortic valve replacement in a given amount of time may be exceedingly difficult due to the varied set of symptoms these patients typically exhibit. Therefore, it is very important to minimize the differences between the two study arms by standardizing anesthetic protocol, operative technique, surgical personnel, critical care support and medications. One possible approach for a double-blind trial would be to

have two or more surgeons implant both the bioprosthetic heart valve substitutes and then have an independent surgeon who remains blinded, review all patients and their hemodynamic data. Assigning a specific surgeon to implant each device for the duration of the study may ensure a standardization of surgical technique and help account for the propensity for varying degrees of enthusiasm, preference and skill the surgeons may have. The experimental arm of the study should encompass a "learning phase" so that the surgeon may familiarize himself with the device in question. Once the surgeon is comfortable with implanting the device there is a greater chance that his operative technique will not be subject to a learning curve bias through out the study. This will, however, seriously limit generalizability of the study results and will hinder the adoption of a new device or surgical procedure or technique.

An alternative, and possibly better approach, entails having a group of surgeons assigned to implanting one device and another group of surgeons within the same centre implanting the other device. A cluster trial would achieve this goal. Once again, the group of surgeons implanting the experimental device should be given an adequate amount of time to become familiar with implantation to avoid less optimal results or a lack of enthusiasm prior to enrolling patients into the study. The advantage of this second approach is a substantial reduction in the amount of bias, individual preference, and skill of the surgeon from influencing the variables, thus enabling the results of the study to be more applicable to other centres and other groups of surgeons.

It is important to note that if any specific measures are necessary for implantation of a new bioprosthetic heart valve, all operative and post-operative personnel should have attained the minimum standard of skill because this would affect operative time and duration of post-operative support. An educational and information session should be conducted prior to obtaining approval from nursing, anesthesia and critical care staff.

Multiple centres may be enrolled to achieve adequate recruitment. Although a specific surgeon at each centre could be assigned to implant the valve for the control group and another surgeon the valves for the experimental group, this could reduce recruitment

substantially.

N.9 Outcomes

Primary Outcomes

Assessment of the hemodynamic differences between two bioprosthetic valve substitutes may be performed by echocardiography at specified intervals. Evidence from previous work recommends serial echocardiography to measure not only the hemodynamics of the implanted valve but also the left ventricular mass regression at six months, one year, three years and five years. The longer the post-operative duration is then the more attributable left ventricular mass regression is related to the hemodynamic differences between the two bioprosthetic valve substitutes. Accurate records of other hemodynamic parameters such as blood pressure, pulse and concomitant medications are necessary to ensure that there is no undue influence from these factors. Clinical follow-up should be combined with serial echocardiography to ascertain secondary outcomes. Survival rate as a primary outcome such as a ten year follow-up (to assess valve durability and effect) will provide useful information but may be difficult to achieve, as patients are lost to follow-up. Some patients may move away, others expire and some may refuse to answer requests for follow-up. These directly affect survival statistics.

Secondary Outcomes

1) ***Mortality***

   Mortality may be determined as perioperative (less than 30 days) and long-term mortality. These are classified as being cardiac or non-cardiac related.

2) ***Functional Status***

   Measurement of pre-operative and post-operative functional status to determine the degree of improvement in symptomatology between the two study groups should be determined at specified intervals.

3) ***Complications***

Complications previously described can be recorded at intervals coinciding with echocardiographic and clinical follow-up through a questionnaire.

4) ***Structural Valve Degeneration***

The incidence and extent of prosthetic stenosis, insufficiency, paravalvular leakage and so on, may be documented but would require follow-up at more extended times such as ten years and beyond the surgical date.

N.10 Data Collection

A protocol for data collection in bioprosthetic heart valve implantation should include how the data will be collected, processed and analysed. The study nurse will collect much of this data during hospitalization of the patient for surgery. Specific intervals for assessing left ventricular mass and hemodynamics by echocardiography should be clearly delineated. Based on the natural history of left ventricular mass regression from successful aortic valve replacement, suggested intervals for follow-up would be baseline assessment in hospital, at six months, one year, five years, ten years and fifteen years. The purpose of five-year intervals would be to standardize the time frame so that studies can be compared between centres. Longer term follow-up is difficult through a trial. Ideally, these data can be captured through a database set-up similar to that used in orthopedic surgery. The six-month follow-up would be based on the fact that a significant amount of left ventricular mass regression would have occurred by this time. The left ventricular mass regression would be compared to baseline assessment pre-operatively and post-operatively while in hospital. Feasibility of such a study would be determined by the financial resources available, the methods employed in tracking the patients and the facilities to assess them. These would be problematic in the scope of an RCT. The study nurse would accumulate other data such as survival, late mortality, thromboembolism, echocardiographic assessment of tissue valve failure, and other events

as documented in the outcomes tables. An interim analysis at one year may be performed on any accumulated data and may potentially influence subsequent trial design and compilation of the trial data. Assessment of data by an independent observer or surgeon and report of the statistical analysis to the safety board is crucial.

N.11 Randomization and Blinding

Failure to randomize patients may lead to the creation of unbalanced treatment and experimental arms. Therefore, factors such as patient and surgeon preference, surgeon's experience, exclusion of patients from the experimental group due to safety concerns, systematic exclusion of patients from the trial for ill-defined reasons, need to be accounted for wherever randomization is not possible. When randomization is possible, then some control over the selection bias may prevent the participants from being entered into the trial because of anticipated treatment assignment. Accidental bias may still arise if the randomization process fails to achieve balance on risk factors or prognostic covariates. In the small studies typical of surgical trials, allocation procedures such as simple randomization are more vulnerable to accidental bias producing an imbalance. Blocked randomization ensures that imbalance in allocation will be minimized during the entire recruitment of these surgical patients. If inclusion of a learning phase into the study design is necessary for the study valve so that the surgeons have a trial period to become comfortable, then perhaps these patients should be excluded from the study. This would unfortunately lead to less recruitment. Educating the referring physicians would also reduce referral bias that could be generated through uncertainty and ignorance of what the procedure entails.

In addition, the surgeon or investigator involved in retrieval and analysis of data would be blinded enabling at least single blinding of the study. For ethical reasons it is usually not possible to blind the patient or the surgeon who is implanting the valve. The surgical technique must usually be tailored to the specific valve as related to sizing of the annulus and the recommended suture approach to implantation of the device. The patient needs

to know what operation was performed and full disclosure is mandatory. Blinding of as many health care personnel as possible will reduce bias. This would include anesthetists, clinical perfusionists, intensive care unit physicians and nurses, and most importantly study nurses and statisticians.

N.12 Management of Bias

Bias plays an important role in collection and assessment of data in clinical trials that are not double-blinded. As bias is complex and difficult to eliminate in surgical trials, every attempt must be made to at least blind the participants and whenever possible the surgeons as well. Although it is difficult to conceal the type of procedure from the patient, a blinded investigator should assess the outcomes. In the majority of situations when the experimental arm is receiving a procedure or device as a therapy it is impossible for the other participants to receive a placebo. Administration of a placebo may only be possible if the new intervention or the placebo is added to standard surgical therapy without replacing it. Another situation where a placebo-control trial may be justified is when there is no standard intervention that is clearly superior to the placebo.

Although a single blind trial will bring some degree of control to the bias caused by the patient, preconceived notions from the surgeon also need to be addressed, as the surgeon is usually fully aware of the intervention in question. To treat this form of bias the investigator should be unaware of what procedure has been performed by which surgeon.

Referral patterns and treatment that the referring physicians are expecting their patients to receive also determines the allocation of patients to a particular surgeon (referral bias). Ideally, randomization should ensure that the groups are comparable although generalizability will be affected by the referral pattern. Referral bias may be operating within the inclusion and exclusion criteria such that the full range of patients may not be entered into the study but only the best candidates. As a result, the outcomes one would expect in the planning of the study and the differences in the outcomes considered for the

minimum clinically important difference (which would be used for the sample size calculations) would not be realized in this more restricted population. Hence, it is important to ensure that the surgeons are willing to enrol the full range of patients described by the inclusion and exclusion criteria.

Factors that can be incorporated into the study design to take this into account include the following:

i) An independent assessment of each patient by a trained study nurse to determine the suitability of the patient for the study and to include the subject in the randomization process, which is particularly important if neither the surgeon nor the patient can be blinded to the surgical treatment (treatment being assessed).

ii) Determine whether referral patterns to specific surgeons may be altered and broken during the process of randomization of subjects in the study.

iii) Determine whether someone can assess the acuity of the patients' medical condition preoperatively other than the surgeon so that randomization can be done independently from the referral process.

iv) Consideration of a training period to compensate for the learning phase for all participating surgeons so that less emphasis is given to a specific surgeon's ability and more emphasis on patient factors for determination of patient treatment.

N.13 Statistical Analysis

Consideration of the statistical methods vary based on different types of measurements of the outcomes. For example, Student's t-test for continuous outcomes, Kaplan-Meier method for time-to-event, and Chi-square for binary events are identified. Secondly, for the same level of measurement, the method varied because of the distributional projection. For example, normal shaped distributions will usually require the t-test, but highly skewed ones utilize the Wilcoxon. While most authors used the Student's t-test, the Kaplan-Meier method, Chi-square and the Fisher's exact test, the Student's t-test was

the preferred method of analysis by most authors, and they determined the preferred method.

N.14 Funding

The source of funding for a study comparing two heart valve substitutes is essential as these devices are quite costly and industry funding has historically been the major source for conducting such studies. The number of patients allocated to the two arms in the study, the number of prosthetic devices necessary, the labour required for follow-up investigations as well as development of a valve clinic that would continue for at least ten to fifteen years to follow the patients would be necessary to be accountable. If the valves are supplied to the hospital as a deal by the manufacturer, disclosure and terms of the agreement would need to be made available as part of the study. Appendix K summarizes sources of funding for the papers. Most papers in the survey did not report details and those that did were not specific about the actual amounts provided.

N.15 Time line

Developing a time line for a comparative study of two bioprosthetic heart valves is problematic based on a cost factor and because of ongoing loss to long-term follow-up and attrition from mortality. In general, bioprosthetic heart valves tend to degenerate more rapidly in anywhere from eight to fifteen years from the date of implantation although occasionally premature structural valve degeneration can occur prior to this time. Subtle differences between two bioprosthetic valves will probably not be apparent between three and eight years following implantation. Many of the studies evaluated in the systematic review that were either retrospective or prospective did not exceed eight to ten years of follow-up. Hence, it would be vital for the time line to extend up to fifteen years at a minimum to identify major differences in attrition by death, incidence of re-operation, and decline in functional status related to recurrence of heart failure. For such

an extended follow-up, an institutionally based cardiac valve follow-up clinic would be able to track patients better and retain them in follow-up even if the surgeons were to relocate. With changes in surgical technique, movement of patients away from the centre of therapy, and even movement of investigators, factors such as the number of centres involved in the study, frequency of follow-up and arrangements for surveillance through a valve clinic would be important in determining whether a time line could be continued for such duration. If attrition becomes a major problem for the extended follow-up, this may lead to missing data and the data will need to be imputed. The problems of imputation of data will then become an issue in the analysis.

N.16 Summary

The computer search results identify the surgical literature as being composed of mostly non-randomized studies without control groups. There are numerous comments, editorials, case series and reviews. Many small pilot studies demonstrate negative findings when two devices are compared. These studies often recommend full RCTs to be performed but it is difficult to identify such studies. The reasons for this are not made explicit but certainly a lack of resources may be a factor. A lack of methodological expertise on the part of surgical scientists, the ethical dilemmas previously discussed and possibly even inadequate regulatory guidelines for introducing devices into clinical practice may be factors. The lack of understanding of the importance of randomization or possibly the difficulty to randomize such patients is noted in the fact that this issue is usually poorly addressed in most of the comparative studies reviewed. Ethical dilemmas are not discussed in detail simply because it has been traditionally inconceivable that procedures would be allowed to be performed with a risk of operative morbidity or mortality without disclosure to either the patient or their surgeon. Finally, from the studies reviewed, it was never evident what government guidelines or regulations were being followed such that a device could pass them.