Comparison of patient outcome for aortic valve replacement verses transcatheter aortic valve replacement

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Thesis

COMPARISON OF PATIENT OUTCOME FOR AORTIC VALVE REPLACEMENT VERSUS TRANSCATHETER AORTIC VALVE REPLACEMENT

by

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Submitted in partial fulfillment of the requirements for the degree of Master of Science 2014
DEDICATION

I would like to dedicate this work to my parents Hal and Sandy Goldberg. The support they have given me through life and all of my education has been absolutely incredible. It is because of them that I have found myself with the capabilities, drive and passion to pursue a Masters in Science.
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JOSHUA GOLDBERG

ABSTRACT

Aortic stenosis or narrowing of the aortic valve is the most common cause for surgical valvular replacement in the United States. The disease of aortic stenosis has a long asymptomatic latency period followed by a quickly progressing symptomatic phase. Symptoms of the disease include dyspnea, syncope, angina, and heart failure. The disease affects mostly the elderly and, as the United States population ages, and life expectancy increases, there is an increased prevalence of the disease. The main cause of aortic stenosis is calcification of the leaflets of the aortic valve. There are currently no pharmaceutical interventions to combat or slow the processes of the disease. The only treatment for the disease is the surgical replacement of the aortic valve. The original aortic valve replacement (AVR) was done in 1952, after that time this was the only surgical intervention until 2002 with the advent of transcatheter aortic valve replacement (TAVR). TAVR has since been approved by the Food and Drug Administration (FDA) for use in patients who are not candidates for AVR or who are at high risk for AVR.

The initial studies of TAVR showed an elevated risk of stroke in those undergoing surgery but it provided similar relief of symptoms, and similar patient mortality at one and two year follow up. With the increased risk of stroke there was evaluation of cause and mechanism of the cerebral events. After concluding that the
strokes were due to emboli released during mechanical movement during surgery, new technologies have begun to be developed to combat the stroke risk. One device that is used is a deflection device that ensures that an embolus does not have access to cerebral circulation.

Through the study of current literature it can be concluded that the patient long-term outcomes are much improved in TAVR verse AVR for the subgroup of the population who are not candidates for surgery. There are comparable patient outcomes for those who are at a high risk for surgery, but the risk for stroke with TAVR doubled compared to AVR, which continues to be investigated. TAVR carries the benefit of a less invasive surgery, shorter hospital stays and reported increased quality of life one-year post operation. This study demonstrates that there is still a need for further development of technology, surgical technique and long term patient follow up to ensure high quality outcome for those undergoing TAVR.
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LIST OF ABBREVIATIONS

AVR ............................................................ Aortic Valve Replacement
FDA ............................................................. Food and Drug Administration
TAVR ............................................................ Transcatheter Aortic Valve Replacement
INTRODUCTION

Aortic stenosis, a severe heart disease that once symptomatic, quickly leads to death if left untreated and is the most common cause for cardiac valve replacement in both Europe and North America (Cary & Pearce, 2013; Lester & Abbas, 2014). Aortic stenosis causes an obstruction of the left ventricular cardiac blood flow due to a reduction in area of the aortic valve opening. The symptoms include difficulty breathing (dyspnea), heart failure, chest pain (angina), and temporary loss of consciousness (syncope). Pharmaceutical intervention for symptomatic patients is very limited, and the gold standard of treatment is surgical aortic valve replacement (AVR). In recent years, the development of transcatheter aortic valve replacement (TAVR) was developed as an alternative to surgery for those who were at high risk for the standard surgical intervention (Carabello, 2013). Each technique has its own benefits, risk factors, and patient outcomes. Debate continues as to which method should be used for each individual patient case. This thesis will be comparing the specific patient outcomes of these two surgical techniques, providing insight into future development of the treatment of aortic stenosis.

The human heart’s main function is to receive deoxygenated blood from the venous side of the circulatory system, provide a pumping force to move the blood to the pulmonary system for oxygenation and then out of the heart back to the systemic circulation to satisfy tissue needs. The deoxygenated blood from venous circulation first enters the right atrium via the superior and inferior vena cava. The blood is then moved from the higher-pressure chamber of the right atrium to the lower-pressure chamber of
the right ventricle passing through the bicuspid valve. Each valve of the heart is designed to allow only one-way passage of blood in order to ensure a constant unidirectional flow of the circulation. Once the blood has reached the right ventricle, during systole or contraction, the blood is pumped through the pulmonary valve to the pulmonary system where oxygenation of the blood occurs. The blood flows from the pulmonary circulation to the left atrium where it then moves through the mitral valve into the left ventricle. The movement of blood from the left atrium to the left ventricle is carried out again by pressure differences of the two chambers, where the atrium initially has a higher pressure than the ventricle. Again during systole, the blood is pumped out of the left ventricle through the aortic valve and into the aorta where it is now free to enter the systemic circulation and provide oxygen to the tissues. Both the right and left atrium contract in unison during diastole, and the two ventricles contract simultaneously during systole. The coordinated cardiac contraction, chamber system, and valves allow for unidirectional flow of circulation. Any disturbance to this system can create severe symptoms or death (Morton, 2011).
**Figure 1: Cardiac blood flow** - The deoxygenated blood enters the heart through the inferior and superior vena cava. Blood enters from the right atrium (RA) to the right ventricle (RV), and to the pulmonary circulation for oxygenation. Oxygenated blood now enters the left atrium, to the left ventricle and finally out the aorta to the systemic circulation. Taken from Morton, 2011.

Stenosis in general is narrowing of an organ structure; therefore, aortic stenosis is a narrowing of the opening to the aortic valve. When aortic stenosis occurs it causes obstruction of blood flow from the left ventricle through the aortic valve out into the aorta. This obstruction increases the work load of the cardiac muscle and leads to the
symptoms mentioned above as the cardiac system attempts to compensate for this change (Cary & Pearce, 2013). First defined by Dr. Lazare Rivière in 1663, aortic stenosis was described during autopsy on a patient who was found to have ventricular enlargement and calcified obstruction to the left ventricular outflow through the aortic valve. The original belief was that the calcification was caused by an inflammatory response to a bacterial infection, known as endocarditis. In 1846, there was a challenge to this theory attributing the calcification to valvular degeneration (Leopold, 2012; Mylonakis & Calderwood, 2001). Since that time, both theories have been reevaluated and the current conclusion on the cause of calcification is that calcification is not a passive process, but is one that is due to active cellular infiltration of immune cells or other altered cells entering the normal tissue. During a normal immune response, immune cells such as macrophages or lymphocytes will enter or infiltrate the injured tissue in order to carry out their immune function. In aortic stenosis, this same immune cell infiltration mechanism can occur after injury to the valve leading to immune cell accumulation in the valvular tissue. The cause of aortic stenosis came only with the development and research of the cellular composition of the aortic valve itself and the cells that were present once aortic calcification had occurred (Alexopoulos et al., 2012).

A clear understanding of the specific anatomy and makeup of the aortic valve is necessary in order to have a better understanding of aortic stenosis and how the disease actively progresses. The aortic valve is located between the left atrium and the aorta, and consists of three avascular leaflets that meet in the center to form the valve. The leaflets ensure a one-way passage of blood from the left ventricle to the aorta. There are three
layers of cell types in the aortic valve providing the site for possible ossification and stenosis or narrowing of the valve opening. The cell type that faces the aorta is the fibrosa layer that consists of collagen fibers. The ventricularis layer is made of mostly elastic fibers and faces the ventricle aspect. The spongiosa layer is in the middle of three layers consisting of glycosaminoglycans and proteoglycans in order to minimize friction and stress between the two outer layers. The three layers respectively provide strength, elasticity in times of stretch, and cushion (Cary & Pearce, 2013). Cellular response to injury within these different layers causes cells to alter their function, which leads to calcification causing valvular hardening, and ultimately leads to aortic stenosis with its subsequent cardiac symptoms.

Figure 2: Cellular layers of aortic valve- The normal aortic valve consists of three layers, fibrosa, ventricularis and spongiosa. They provide strength, elasticity, and cushion respectively. Taken from Dweck et al., 2012.
The disease of aortic stenosis begins with aortic sclerosis or tissue hardening. This sclerosis gradually worsens to create a stenotic aortic valve or valve with less area for blood to pass through, gradually leading to partial blockage of the blood flow from the left ventricle to the aorta. Aortic sclerosis itself is present in 25% of those 65 years old, creating a decently large population that is at risk for developing aortic stenosis (Alexopoulos et al., 2012). However, this process of valve hardening takes many years, with only 10% of patients progressing from having aortic sclerosis to hemodynamically compromised aortic stenosis with changes in the normal blood flow that requires intervention (Cary & Pearce, 2013).

The majority of cases of aortic stenosis are due to calcification of the aortic valve leaflets. The leaflets of the valve begin to accumulate calcium deposits, eventually making them larger and decreasing the aortic valve opening or stenosis. Aortic stenosis has been linked to similar pathways of disease progression of atherosclerosis or lipid deposition in arteries and also to bone deposition with the presence of osteoblastic cells, whose cellular function is to lay down new-formed bone. During either process there is cellular deposit on the leaflet. In the atherosclerotic pathway, lipid deposition creates increased area that calcium can be further deposited upon. The calcification of the aortic valve causes over 80% of the cases of aortic stenosis and is termed calcific aortic valve disease (Rayner et al., 2014). Both calcified aortic stenosis and atherosclerosis have similar risk factors and cell infiltration processes. The risk factors include older age, male gender, hypertension, history of smoking, and elevated lipoprotein and low-density
lipoprotein levels. Genetics can also affect the onset of aortic stenosis. There is a direct relationship of genetic factors and the ossification load on the aortic valve that leads to stenosis (Alexopoulos et al., 2012).

The similarities between the cellular mechanisms of aortic stenosis and atherosclerosis are demonstrated by the observation of the similar cell types that infiltrate the tissue during either process. Atherosclerosis is a process that is initiated with cellular injury followed by inflammatory response with cellular infiltration, which in turn leads to eventual lipid deposition. During normal aortic tissue function there are very few inflammatory cells, macrophages or leukocytes, whereas during atherosclerosis and aortic stenosis there are very elevated levels of both these cell types, indicating the integration of the inflammatory response for both of the processes (Alexopoulos et al., 2012).

Originally, aortic stenosis was thought to be a passive process where calcification of the valve occurred over time, but it is now known that the process is active and due to cellular accumulation within the valvular tissue.
Figure 3: Calcification mechanisms—This diagram shows the different cellular pathways that can occur to lead to calcification of the aortic valve. Taken from Leopold, 2012.

The aortic valve cell types display aspects of functional plasticity and have the ability to change their utility due to certain stresses. This change in phenotype is the basis for the cells’ novel functional expression causing aortic stenosis, as the cells either now accumulate or actively deposit bone structure, or calcification.

Several mechanisms can cause this calcification to occur: cellular injury, improperly functioning regulatory cells or endothelial cells, or the presence of bone marrow derived cells.

Cellular injury can come from various factors including direct endothelial injury, lipid accumulation, or inflammatory cell infiltration into the endothelial lining. The initial injury or cellular accumulation (lipid, or inflammatory) causes a remodeling of the valvular interstitial cells which ultimately leads to the cells transforming their ability to
produce osteoid. This newly deposited osteoid, eventually causes calcification of the aortic valve as the processes occurs over time (Alexopoulos et al., 2012). The cellular transformation can cause deposition of lamellar bone with bone marrow, chondrocytes, cartilage, and endochondral calcification, which create calcific nodules. The majority of these calcific nodules occurs on the fibrosa layer of the valve, and often extends in to the aortic side of the valve. This placement of the aortic calcification ultimately causes the utility of the valve to function improperly, creating greater resistance of blood flow from the left ventricle to aorta, ultimately leading to aortic stenosis.

In addition to cellular injury and the subsequent transformation of cellular function that can lead to calcific nodules, improperly functioning regulatory cells can also cause aortic calcification. In normal functioning tissue, these cells regulate activation or inhibition of gene transcription factors leading to cellular replication, function transformation, or cellular activation. Poorly functioning regulatory cells can lead to an imbalance, with more cell deposition than inhibition, which ultimately leads to net calcification (Leopold, 2012).

In addition to the mechanisms of cellular injury or improperly functioning regulatory cells, a third mechanism of calcification involves the individual endothelial cells of the valve undergoing transition, requiring no infiltration of other cell types as was seen with the inflammatory response mechanism. This cellular transition ultimately leads to the same outcome as the inflammatory response, with the valve becoming calcified and hardened with a decreased area for the blood to flow through. In this transition, the individual endothelial cell differentiates into an osteoblastic like cell with a new ability to
deposit bone material. This change in cellular function is carried out through an endothelial-to-mesenchymal-transition where the cells lose their endothelial characteristics along with their adhesion properties. The endothelial-to-mesenchymal transition is believed to be caused by activation of cellular growth factors, transcription factors and signaling pathways, although the activation of these cellular pathways is still under investigation. The loss of adhesion that occurs during the transition allows the transformed cells to act as mesenchymal or myofibroblast cells and infiltrate other areas contributing to the fibrosis or hardening of the valve (Leopold, 2012).

Besides the cellular transitions described, a fourth factor that can contribute to aortic valve stenosis is the presence of vascularization to the valve. The healthy human aortic valve is avascular with no direct blood vessels, but during incidence of calcification the tissue surrounding the areas of inflammatory cell infiltration becomes vascularized. This occurs near the calcified nodules and beneath the border of the leaflet developing a direct blood supply to the tissue. The new vascularization now allows for a more rapid movement of additional inflammatory cells and other cellular signaling molecules that will leads to calcification (Leopold, 2012).

Each of these four different causes of active calcification and eventual narrowing of the heart’s ventricles (aortic stenosis) take a long time to develop. These processes are also generally asymptomatic until the calcification and subsequent narrowing of the aortic valves are significant enough to cause symptoms. As aortic stenosis worsens, it puts a greater strain on the heart’s overall functioning. The cardiac functional demand is increased as the disease progresses, requiring greater force to move blood from the
ventricle to the aorta. This decrease in the cardiac function can lead to symptoms of syncope, dyspnea, angina, and ultimately heart failure. By the time the patient is symptomatic, the cardiac function is already highly compromised and the prognosis is poor.

Due to the fact that aortic stenosis requires such a long time period to develop, up to twenty-five years, the elderly are often at the highest risk for disease. Due to compounding population factors, the disease burden of aortic stenosis is increasing in the United States (Figure 4). Aortic stenosis is most prevalent in those above the age of 65. As the elderly population in the United States begins to grow, and life expectancy continues to increase, the disease prevalence will continue to rise (Cary & Pearce, 2013).

This increasing disease burden is compounded by the fact that as of yet, there is no pharmaceutical preventative action that can be taken to combat the disease (Cary & Pearce, 2013). In the United States, there has been an increase in age-adjusted mortality secondary to aortic valve disease by 1.6% per year between 1978 and 2009 (Rayner et al., 2014). This increase in the disease prevalence and burden to the medical system shows the great need for more options for medical intervention, once patients are diagnosed. Preventive options currently exist, but must be initiated more effectively at earlier stages in order to reduce the long-term disease prevalence and burden of aortic stenosis. In 2012, aortic stenosis led to 28,000 deaths and 48,000 hospitalizations in the United States alone. Aortic stenosis is the most common valve pathology and accounts for 43% of patients who present with valvular disease (Leopold, 2012). The disease is present in 2-7% of the population that is greater than 65 years old (Alexopoulos et al., 2012).
Figure 4: Age distribution of aortic stenosis—The diagram above demonstrates the increase of aortic stenosis as the population ages. Taken from Nkomo et al., 2006.

Rheumatic fever and congenital defects are two other causes of aortic stenosis exist in United States populations that have a relatively minor impact on the population age groups most affected by the disease. Medical interventions for both of these causes, once the disease has progressed to symptomatic aortic stenosis, are the same as those with calcific aortic valve disease.
Rheumatic fever has the potential to lead to aortic stenosis and is caused by untreated pharyngeal infection. Rheumatic fever can lead to aortic stenosis in younger as well as older populations. Due to an easy treatment regimen of penicillin for streptococcal infection among children and adults as prevention for rheumatic fever, there are few cases of aortic stenosis caused by rheumatic fever in developed nations. This decrease in rheumatic fever cases has led to a shift in the age group of those who suffer with aortic stenosis to an older age population (Cary & Pearce, 2013).

The second mechanism for development of aortic stenosis is due to a congenital defect, occurring in 1% to 2% of the population, that causes an individual to have an aortic valve with two leaflets instead of three. There is no preventative measure for this congenital defect. The increased stress that these two leaflets must sustain causes on average a two-decade earlier onset of aortic stenosis. The cellular mechanism of stress and injury causing aortic stenosis for these two leaflet valves is consistent with the three leaflet valves described earlier (Cary & Pearce, 2013).

Limited options exist to prevent aortic stenosis. The disease has two stages: a long latent asymptomatic period followed by a fast progressing symptomatic phase that requires surgical intervention for a cure. There are currently no pharmaceutical interventions that are reliable at preventing or slowing the progression of the calcification of the aortic valve during its asymptomatic or symptomatic phase (Leopold, 2012). However, some behavior changes can be effective in preventing aortic stenosis. Due to the common association with atherosclerosis and aortic valve calcification, preventative measures that are used for atherosclerosis can be applied to prevention of calcific aortic
stenosis. For example, avoiding smoking, lowering one’s low-density lipoprotein levels, and lowering one’s blood pressure can assist in the prevention of aortic stenosis (Alexopoulos et al., 2012).

For patients who have asymptomatic aortic stenosis, it is normally not advised to provide surgery due to the low risk of sudden death caused by aortic stenosis, compared to the slightly higher risk factor that one faces during surgery. For those who have asymptomatic aortic stenosis, their sudden death rate is 0.5%-1% per year, while the risk of death during AVR surgery is less than 2.5% for those over thirty-five years old (Carabello, 2013). During surgery patients are at risk of thromboembolism, endocarditis, valve failure, bleeding and death. Consequently, this differential risk has led to the general practice to not operate on patients before they become symptomatic (Lester & Abbas, 2014).

In general practice, asymptomatic patients are not operated on during this period of disease progression. However, there is a subgroup of asymptomatic patients who are at higher risk of sudden death who will often be operated on, as their risk of surgical death is lower than the risk of sudden death. Those with transaortic jet velocities >4.0 m/s, indicating highly decreased area of the valve, those with severe left ventricular hypertrophy which indicates a greater work load on the cardiac muscle, those with extensive valve calcification, and those with abnormal exercise test results are all at an elevated risk of sudden death. With an indication of more than one of the above risk factors, decisions to operate in the asymptomatic phase are often taken to lower the risk of sudden death (Carabello, 2013; Dweck et al., 2012).
Due to the long latency period, many patients do not self-report their symptoms. The progression of hemodynamic status change, or change in the blood flow, is very slow. There is no abrupt change in status that would lead to symptoms that patients would notice easily. Instead, difficulty in breathing worsens or slow progressive decrease in exercise tolerance occurs that the patient may not notice (Cary & Pearce, 2013).

Detection of calcific aortic valve disease, therefore, commonly occurs either by the observation of a systolic murmur, evaluation of new onset atrial fibrillation or during a cardiac catheterization for a common comorbidity, symptomatic coronary artery disease, due to the association of stenosis with atherosclerosis.

Once the disease has become symptomatic, it progresses very quickly with a high risk of death of those affected. The classic symptoms of aortic stenosis are angina, exertional syncope, or congestive heart failure. Those who have developed angina pectoralis from aortic stenosis have a 50% mortality rate within five years of symptom onset without the use of valve replacement (Lester & Abbas, 2014).

As shown in the figure below, the latent period is followed by a rapid symptomatic decline that is followed by death without surgical intervention.
Figure 5: Clinical course of aortic valve stenosis - The disease is characterized by a long asymptomatic latent period followed by a rapid progressing symptomatic phase. Taken from Ross & Braunwald, 1968.

The classic symptoms of presentation for symptomatic calcific aortic valve disease are angina, syncope and heart failure with dyspnea. In those that are affected by aortic stenosis, about 35% of them present with angina as their initial symptom. Angina, or chest pain, is due to the myocardial tissue not receiving enough oxygenated blood. This lack of oxygenated blood is caused by decreased blood outflow due to obstructions caused by aortic stenosis, compounded by the need for more oxygenated blood by the hypertrophied left ventricle, due to the increased tissue mass (Carabello, 2013). This is further compounded by the fact that as the aortic stenosis severity worsens, the increase in wall thickness and hypertrophy is insufficient to compensate for the rising pressures.
requirements to eject blood through the stenotic valve. This results in a higher wall stress and a drop in ventricular function, ultimately leading to decreased cardiac output causing decreased blood to the myocardium and angina. Left ventricular hypertrophy is the most common physical finding for those suffering from calcific aortic valve disease (Lester & Abbas, 2014).

Syncope is a temporary loss of consciousness, most often due to brief disturbance in cerebral blood flow. It is still debated as the cause of hypotension associated with aortic stenosis, but it has been established that this hypotension is what causes syncope in the patient group. The syncope is most often associated with exercise due to the physiological changes that occurring during activity (Carabello, 2013). As the body begins to exercise, the normal response is to have peripheral vasodilation compensated by increased cardiac output, ultimately leading to increased blood pressure and increased blood flow to the tissues. In a calcific aortic valve diseased patient, the normal response of vasodilation has no ability to be compensated for with increased cardiac output due to a diseased heart (Cary & Pearce, 2013). The increased resistance in the stenotic valve, or the hypertrophied left ventricle, leads to a situation where the heart cannot increase its cardiac output to the levels needed. The vasodilation without compensative effects causes a drop in blood pressure and therefore syncope (Carabello, 2013).

The cause of dyspnea or shortness of breath associated with calcific aortic valve disease is still debated, but most likely is attributed to the systolic or diastolic heart failure that often accompanies aortic stenosis (Carabello, 2013). The symptom with the worst outcome for aortic disease is heart failure, resulting in death 11 months after
symptom onset, compared to 23 months in those with severe aortic stenosis who do not develop heart failure (Rayner et al., 2014).

There are two types of heart failure, systolic and diastolic. They have different mechanistic causes, but both lead to dyspnea or difficulty breathing. In general, as the heart begins to fail by either systolic or diastolic mechanism, there is a backup of fluid in the pulmonary system that causes difficulty in breathing. When heart failure occurs by diastolic mechanism, blood approaching from the pulmonary side of the circulation faces a higher than normal diastolic pressure in the left ventricle as its tissue is less compliant due to hypertrophy. This decreased pressure difference between the two chambers creates a condition where blood has more difficulty passing from a higher-pressure system of the pulmonary system to a lower-pressure system of the ventricles. The decreased passage from the pulmonary side to the left ventricle creates a backup of fluid into the pulmonary system, which leads to dyspnea (Carabello, 2013).

In the case of systolic dysfunction, the hypertrophied ventricle may not be able to create a great enough pressure to maintain the baseline cardiac output or ejection fraction as the increase in wall thickness is not adequate to combat the rising pressure of the ventricle (Lester & Abbas, 2014). As ejection fraction begins to fall, there is an increase in the preload of the cardiac ventricles, creating a condition where the atrium must generate higher pressures to move blood from the atrium to the ventricle. This same situation of high ventricular pressure can be caused by direct lack of contractility due myocardial ischemic damage and therefore decreased ejection fraction. In either case,
dyspnea is created due to the decreased movement of blood moving from the atrium to the ventricles causing pulmonary fluid back up (Carabello, 2013).

As we have just seen, the symptomatic phase of aortic stenosis can include a variety of onset symptoms that lead to cardiac evaluation and diagnosis of aortic stenosis. Once evaluation for aortic stenosis has begun, the most accurate and best test for confirming aortic stenosis is a 2-dimensional Doppler echocardiography (Cary & Pearce, 2013). Echocardiography is used to evaluate the rate and amount of fluid traveling through the aortic valve. An increased rate of flow indicates stenosis or narrowing of the valve, as the same amount of fluid must travel through a smaller opening, leading to increased flow rate. A great benefit of echocardiography is that it inexpensive, noninvasive and widely available. A major limitation in echocardiography comes with patients who have decreased left ventricular function that leads to underestimating the severity of the aortic stenosis. As the left ventricle looses its power to pump the blood through the stenotic valve, the rate of flow will decrease even with the narrowed valve. The decreased flow rate will lead to the conclusion that there is less severe stenosis than is truly present. As those with a weakened left ventricle and severe aortic stenosis are at an even higher risk for sudden death, such misinterpretation of the actual severity of aortic stenosis can have grave repercussions for surgical decision-making and patient health. However, while these patients with weakened left ventricles and severe aortic stenosis need cardiac surgical intervention, they also carry a higher surgical risk (Rayner et al., 2014).
While echocardiography can test for blood flow, other tests are needed to evaluate cardiac function and assist in the diagnosis of calcific aortic valve disease. Only a full picture of the state of a patient’s heart can provide the complete information needed to make appropriate decisions about the need for surgery and which type of surgery is best for that particular patient.

Various tests are used to evaluate cardiac function. Many of these tests help evaluate left ventricular hypertrophy, which is one of the greatest changes to the heart that has significant impact on cardiac function during aortic. As the aortic stenosis becomes more severe, the left ventricle requires more force to create a great enough pressure to move the blood from the ventricle through the stenotic or narrowed valve in to the aorta and on to the systemic circulation. Left ventricular hypertrophy begins when the cardiac tissue compensates to be able to provide increased force across the stenotic valve, which normally is capable of restoring baseline cardiac function. The heart begins to fail as the hypertrophy becomes severe enough that the increased wall thickness of the cardiac tissue begins to cause detrimental effects on the amount of pressure the muscle is able to provide. The wall thickness is inversely proportional to the amount of pressure that the ventricle can produce. In the beginning, the increased amount of cardiac tissue allows the wall to increase contractive ability, but eventually the increased wall thickness is too detrimental and creates failure (Carabello, 2013; Dweck et al., 2012).

The table below shows the different tests that are used to evaluate the cardiac function in assistance with the diagnosis of calcific aortic valve disease.
Table 1: Methods for diagnosing aortic stenosis - Each of the below studies are used to evaluate different aspects of associated symptoms, risk factors or clinical outcomes of aortic stenosis. Taken from Cary & Pearce, 2013.

<table>
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<th>Study</th>
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| Doppler echocardiography   | Estimation of severity of aortic stenosis, left ventricular size, and ejection fraction  
Estimation of pulmonary pressures, aortic valve gradient, aortic valve area  
Assessment of thickening of aortic valve leaflet, reduced leaflet motion, reduced valve opening |
| Cardiac catheterization    | Assessment of coronary arteries to determine need for simultaneous coronary artery bypass surgery and aortic valve replacement  
Direct measurement of left ventricular and ascending aortic pressures to determine aortic valve pressure gradient  
Determination of left ventricular systolic pump function quantified by measuring left ventricular end-diastolic and end-systolic volumes, and ejection fraction |
| 12-Lead electrocardiography| Evidence of left ventricular hypertrophy: Increased R-wave amplitude of the QRS complex in lead V6  
Increased S-wave amplitude in lead V1  
ST-segment depression and T-wave inversion in leads facing the left ventricle: I, aVL, V5 and V6 |
| Chest radiography          | Determination of heart size  
Detection of calcification in the aortic valve (lateral view)  
With heart failure, enlarged heart size from dilatation of left atrium and left ventricle, venous congestion, and pulmonary edema |
| Stress testing             | Determination of the degree of exercise tolerance  
Distinguish between asymptomatic and symptomatic aortic stenosis |
| Brain natriuretic peptide  | Determination of severity of increased left ventricular pressure and volume overload  
Distinction between cardiac and noncardiac dyspnea |

Another noninvasive test that is not listed in the above table that can be used to detect calcific aortic valve disease can be done in a routine physical utilizing cardiac auscultation. Calcific aortic valve disease can be diagnosed by observation of a systolic ejection murmur. The blood flowing through the narrowed stenotic valve causes an abnormal cardiac sound that is interpreted as a murmur (Rayner et al., 2014).

In 1897, there was the first description of association of a systolic murmur with calcific aortic valve disease by Dr. W. Hoship Dickinson (Dickinson, 1897). He was able to use the findings of auscultation to indicate aortic stenosis prior to the advanced diagnostic tools that are available today. He proved that the murmurs being heard by auscultation were not a mitral valve issue but truly an aortic valve issue. During autopsy
of patients who had presented to medical care with a systolic murmur, he noted ventricular hypertrophy especially in the left ventricle. He attributed the aortic valve blockage to rheumatic fever in one patient who had been infected when he was younger; in another patient, he attributed the stenosis to endocarditis. The thoughts at the time were in accordance with the belief that aortic stenosis in those without rheumatic fever infection was caused by mechanism of endocarditis (Dickinson, 1897).

In addition to the variety of tests available to diagnose aortic stenosis, a system for grading the severity of the disease is also needed, as this defines the course of action for treatment. This grading system is based on the jet velocity of the aorta, since it defines the severity of stenosis as blood travels from the left ventricle through the aortic valve to the aorta. As the severity of disease increases, the area of the valve decreases, leading to an increased jet velocity. The grade of aortic stenosis is mild, moderate, and severe with velocity at less than 3m/s, 3-4m/s, greater than 4m/s respectively. The aortic stenosis in a patient is defined as severe when the aortic stenosis and obstruction is causing symptoms, such as syncope, angina, dyspnea or heart failure (Cary & Pearce, 2013).

Once aortic stenosis has been diagnosed, using the tests and grading systems described above, treatment options can vary, based on the severity and stage of the disease. Treatments that have been tried to date include both pharmaceutical and surgical options.

Initially, for those in the early stages of aortic stenosis, pharmaceutical intervention for treatment have been tried in order to avoid surgical intervention with its
concomitant higher risks. Since many comorbidities exist with calcific aortic valve disease, such as atherosclerosis and high blood pressure, there has been a push to try to use the standard medications for these ailments in an attempt to slow the processes of calcification. Statins have been used to slow calcification, angiotensin-converting enzymes used to combat heart failure with ventricular hypertrophy, and bisphosphonates used to reduce bone deposition on the aortic valve. Unfortunately none of these drugs has provided a statistically significant effect on slowing the process of aortic stenosis (Salas et al., 2012). Without a reliable pharmaceutical intervention, there is a true need for surgical intervention to provide care.

Figure 6: Pharmaceutical strategies for combating aortic stenosis-The above diagram displays the association of other medical diseases that are also linked with aortic stenosis. Each pharmaceutical intervention that is used to combat the baseline ailment has been attempted to slow the process of aortic stenosis. Taken from Dweck et al., 2012
There are currently three options of surgical intervention for those patients with calcific aortic valve disease that require surgery. The first surgical intervention that is still the gold standard is AVR by open-heart surgery, the second developed surgery is balloon valvuloplasty and lastly, developed in 2002, is TAVR. Surgical AVR and TAVR will be discussed specifically in the following work.

As described in an overview in the table below, each surgical technique has its own indication. The indication for TAVR under current protocols only allows operating on those who are not surgical candidates for AVR and those at high-risk for AVR. Research is underway to determine if these protocols can be expanded. Balloon valvuloplasty will not be greatly discussed here because it is solely used as a temporary device in order to sustain a patient until it is time for AVR or TAVR. The procedure carries around a 10% mortality and or morbidity rate. Overall balloon aortic valvuloplasty has the same long-term results for the patient as they would have obtained through the natural course of the disease, with a recurrence of symptoms in 80% of patients one-year post operation (Bohula et al., 2013; Rayner et al., 2014).
**Table 2: Options of surgery for aortic stenosis**—The three surgical treatment options for aortic stenosis are AVR, TAVR or balloon aortic valvuloplasty. Each surgical option has different indications for use. Taken from Cary & Pearce, 2013.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Indication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve replacement</td>
<td>Symptomatic severe stenosis, Severe aortic stenosis with ejection fraction &lt;50%, Severe aortic stenosis and a need for any other heart surgery</td>
<td>Aortic valve is removed and a new valve (mechanical or biological) is sewn to the annulus of the native valve</td>
</tr>
<tr>
<td>Balloon aortic valvuloplasty</td>
<td>Bridge to aortic valve replacement in patients in unstable condition, Palliative to reduce symptoms when surgery is high risk</td>
<td>A balloon is placed across the stenotic valve and inflated and deflated several times per second to widen the valve annulus and reduce degree of stenosis</td>
</tr>
<tr>
<td>Transcatheter aortic valve implantation</td>
<td>Seriously ill patients who are not candidates for conventional aortic valve replacement surgery</td>
<td>Replacement valve inside a stent that is deployed over the diseased aortic valve annulus via a transapical or transcatheter approach</td>
</tr>
</tbody>
</table>

The first surgical intervention to combat aortic valve disease came in 1952 when Dr. Charles Hufnagel of Georgetown University implanted the first mechanical valve in a patient, placed in the descending thoracic aorta to combat severe aortic regurgitation. This set the precedent for future developments that would allow cardiac surgical intervention to combat aortic stenosis. The valve continued to function as the patient’s own valve would have, responding to pressure changes that caused the valve to open and close. After insertion of the first valves, outcomes included patient improvement of congestive heart failure, cardiac remodeling to decrease hypertrophy, and improvement in exercise tolerance (Butany et al., 2002).

In 1960, Dr. Dwight Harken placed the first mechanical ball-valve prosthesis in the anatomical location of the natural aortic valve (Roberts, 1985). This was the first intervention that could now provide assistance to those with aortic stenosis. The placement of the valve in the anatomical position only became possible after the advent
of cardiopulmonary bypass used in surgical interventions. Cardiopulmonary bypass allowed for surgeons to operate on any portion of the heart as the patients’ blood was oxygenated and pumped utilizing an external mechanical device. At the time of the publication of the article in 1985, Dr. Harken’s second patient was still alive. This indicated the promise of this then new intervention, since it showed, on only the second surgical attempt, an increase of at least 28 years in the patient’s life span with few complications (Roberts, 1985). This promising start continued in the first 61 patients with AVRs at the National Institute of Health, who had a hospital mortality rate of 16% and a later mortality rate of 10%. This was a significant improvement compared to the 30-50% mortality rate one year after symptoms presented for those who did not receive surgery (Bajona et al., 2014; Ross & Braunwald, 1968).

Today for those undergoing AVR, the peri-operative mortality rate is 1-3% in those under 70 years old and 4-8% of those above 70 years of age (Rayner et al., 2014). This great improvement in the peri-operative patient outcome has led to adoption of AVR as the general practice for those with aortic stenosis. The great patient outcome and improvement in post-operative health has led to an estimated 50,000 AVRs done in the United States per year (Bohula May & Faxon, 2013).

The establishment of a high quality surgical intervention has also led to standardizing the definition of who should be operated on and at what time during their clinical course. The American College of Cardiology/American Heart Association was tasked with creating a system that would classify patients for both diagnostic and therapeutic interventions. The classification system was based on who would benefit
from an intervention or diagnostic test. Class I was defined by findings and/or opinion that a specific intervention would be beneficial to the patient. Class II was for when there was differing evidence between if the intervention would be beneficial, IIa favoring the effectiveness and IIb when the usefulness is less clearly proven. Class III was used when there was established evidence or opinion the intervention is not useful and at times can put the patient at risk for harm (Bonow et al., 1998).

While these standardized classifications helped when creating guidelines for surgical intervention, the definitive definition of when to operate with the scaling system becomes more difficult when comorbidities and age are considered as well. Risk factors such as increased age or previous cardiac surgery, or comorbidities such as coronary artery disease, chronic lung disease, prior cerebrovascular accident, kidney failure, heart failure, or myocardial dysfunction increase the risk for those patients needing AVR (Bohula May & Faxon, 2013). This increase in risk can place these patients in the class III category. However, until 2011 with the advent of TAVR, there was no alternative to surgery for those in the class III category for AVR intervention. With no treatment available, these patients unfortunately would routinely die within three to five years after their aortic stenosis became symptomatic (Cary & Pearce, 2013).

TAVR was the first development that could be used as a technique for long-term benefit to those who were not candidates for AVR. Of the candidates requiring AVR, typically 30% of those with severe aortic stenosis would not undergo surgery due to comorbidities, left ventricular dysfunction or older age, but TAVR provided an option for these non-operable patients (Leon et al., 2010). The surgery approved by the Food and
Drug Administration (FDA) in 2011 is still reserved for use only when surgical AVR is either contraindicated or a high-risk option for the patient due to comorbidities, age, or previous surgical status (Aksoy et al., 2013).

TAVR is a procedure that is far less invasive than AVR as it does not require a median sternotomy or cardiopulmonary bypass. As it does not require direct entry into the cardiothoracic cavity or placing the patient on an external device for blood oxygenation, the patient recovery time is improved and the patient is at less direct surgical risk. The valve is implanted using minimally invasive techniques where the procedure can be done while the patient is under minimal anesthesia. The TAVR is done through standard catheterization techniques with a device that has a biological heart valve attached to a stent that can be expanded in place. The valve is guided from its entry location through the vasculature to the anatomical location where it is placed, expanding in order to displace the anatomical valve and assume its function.

There are three different approaches to the implantation that can be utilized: transvenous, transseptal or retrograde. Currently, the standard is the retrograde approach, where the device is placed retrograde starting at the femoral artery, guided by fluoroscope or echocardiography, and then positioned across the native aortic valve.
Figure 7: New surgical development-The placement of TAVR is depicted above with placement of the expanding valve across the anatomical aortic valve. Aortic stenosis is also depicted showing the hardening of the leaflets and decreased opening for blood flow. Taken from Smith et al., 2011.

The first device to be approved in the United States by the FDA was the Edwards SAPIEN valve, which consists of bovine pericardial tissue leaflets secured to a stainless steel frame stent that is expanded by use of balloon (Aksoy et al., 2013). The next valve, Medtronic CoreValve System, was approved for use in the United States on January 17, 2014 (“Recently-Approved Devices > Medtronic CoreValve System - P130021,” 2014).
Figure 8: Current valvular choices—The two above valves are those approved for use in the United States by the FDA. A is the Edwards SAPIEN valve, B is Medtronic CoreValve. Taken from Aksoy et al., 2013.

The first case of use of TAVR was performed on a 52 year-old patient in 2002 who was in need of a last-resort intervention to assist in his hemodynamic stability. Post-operatively at 48 hours he had decreased amounts of heart failure showing a great enough improvement that the patient was able to move from his bed. Following the initial recovery from surgery he had multiple non-cardiac related issues, including pulmonary embolism, septicemia and right leg ischemia that eventually led to his decline and death 17 weeks post-operation. The researchers conducting the study noted that further improvements to the technology and the techniques surrounding TAVR are needed. Nonetheless, this technology had the possibility of providing relief to those who were otherwise non-surgical candidates (Cribier et al., 2002).

While TAVR is still only approved for those that are in the high-risk category for AVR or those that have no surgical option, the fast progression of aortic stenosis once the
disease becomes symptomatic makes the approach a vital alternative surgery for those without AVR approval. In addition, the increased prevalence of aortic stenosis and an aging population with a substantial subset of patients who are not good candidates for standard surgical procedures, a variety of interventions are needed to provide care for those affected and TAVR provides a possibility for treatment option. As the utilization of TAVR continues there must be continued evaluation of the surgical outcomes in order to ensure the efficacy of the intervention compared to AVR. This study provides an evaluation of the current state of research that has been carried out on TAVR in order to evaluate the efficacy and safety of TAVR compared to AVR.
Specific Aims:

The interventions for aortic stenosis have seen many changes over the past twelve years with the advent of TAVR. These changes have been particularly rapid in the United States over the past three years, following FDA approval for its use in the general population. This thesis will look specifically at the two surgical techniques of AVR and TAVR to evaluate the patient outcome of the two procedures. The data regarding patients operated on with TAVR who are at lower risk for AVR is not available due to the lack of current approval for this patient group. The focus will be on patients who are at high risk for AVR and speculation of outcome for those that are lower risk for AVR.

The major risk that has been seen with TAVR over AVR is the risk of a cerebrovascular accident (stroke). This specific patient risk will be evaluated here. Lastly, current research is being conducted to combat this risk of stroke, improving overall outcome and there will be evaluation of what changes must be taken in order to lower the associated risks in the patients who are in need of TAVR. The thesis aims to show that TAVR will provide similar patient outcomes compared to those receiving AVR who are at high-risk for surgery, and provide insight to the future development of the newly developed technique.
PUBLISHED STUDIES

The first study carried out in the United States to evaluate the efficacy of TAVR on patients who were not candidates for surgical AVR was published in 2010 (Leon et al., 2010). The study conducted by Leon et al. was used to compare the outcome of TAVR to standard therapy for those who were not surgical candidates of pharmaceutical and balloon aortic valvuloplasty intervention. This trial was used to prove the safety and efficacy of TAVR over the current practice for this population. This study improved on previous retrospective studies by prospectively evaluating 358 subjects who were randomly assigned to either a surgical intervention or to classical intervention (Leon et al., 2010). During the surgical intervention, the Edwards SAPIEN bovine valve of Edwards Lifesciences, described earlier, was used. The study was conducted from May 11, 2007 to March 16, 2009 with patient evaluation and follow up at 30 days, 6 months and 1 year post operation (Leon et al., 2010). In the Leon et al. study, of the 173 patients who received TAVR, 11 (6.4%) died within 30 days compared to 2.8% of those receiving standard therapy.
Table 3: Patient clinical results TAVR verses standard therapy—Outcome at day 30 and 1 year post operation for TAVR verses classic treatment for those unable to undergo surgery.

Transient ischemic accident (TIA)
Transcatheter aortic valve implantation (TAVI).
Not Available (NA)
Taken from Leon et al., 2010.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>30 Days</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAVI (N=179) no. of patients (%)</td>
<td>Standard Therapy (N=179) no. of patients (%)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>9 (5.6)</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>From cardiovascular cause</td>
<td>8 (4.5)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Repeat hospitalization</td>
<td>10 (5.6)</td>
<td>18 (10.1)</td>
</tr>
<tr>
<td>Death from any cause or repeat hospitalization‡</td>
<td>19 (10.6)</td>
<td>22 (12.3)</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>12 (6.7)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>3 (1.7)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Major</td>
<td>9 (5.0)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Death from any cause or major stroke‡</td>
<td>15 (8.4)</td>
<td>7 (3.9)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vascular complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>55 (30.7)</td>
<td>9 (5.0)</td>
</tr>
<tr>
<td>Periprocedural</td>
<td>29 (16.2)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine &gt;3 mg/dl (265 μmol/L)§</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Renal replacement therapy†</td>
<td>2 (1.1)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>30 (16.8)</td>
<td>7 (3.9)</td>
</tr>
<tr>
<td>Cardiac reintervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon aortic valvuloplasty</td>
<td>1 (0.6)‡</td>
<td>2 (1.1)‡</td>
</tr>
<tr>
<td>Repeat TAVI†</td>
<td>3 (1.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td>0 (0.0)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>New atrial fibrillation</td>
<td>1 (0.6)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>New pacemaker</td>
<td>6 (3.4)</td>
<td>9 (5.0)</td>
</tr>
</tbody>
</table>

As described earlier there was great concern about stroke risk for the patients who were assigned to the TAVR group. At 30 days, TAVR verses standard therapy had a
stroke rate of 5.0% vs 1.1% respectively. The stroke rate at one year was also elevated in the TAVR population at 7.8% verses in 3.9% in the standard therapy approach. Analysis of outcome of those who survived surgery was much improved with TAVR compared to standard therapy. At the benchmark of 1 year, 30.7% of the TAVR group and 50.7% of the standard therapy group were deceased. Evaluation at one year showed that only 42.0% of those with standard therapy were asymptomatic compared to 74.8% in those receiving TAVR (Leon et al., 2010).

Figure 9: Cause of death curves and outcome period - The time from surgery to death is depicted for different causes of death. Taken from Leon et al., 2010.

As shown above in the represented graphs, the survival rate was much improved with the use of TAVR over the use of standard therapy, reducing death from any cause,
cardiovascular death and rehospitalization. The patients who did receive TAVR were at higher risk for surgical complications including stroke, vascular complications, and major bleeding which was seen in this population group as expected compared to the non-surgical group. For those who did survive the one-year follow up for both standard therapy and TAVR, the patients who received TAVR had greatly improved symptoms compared to standard therapy.

As part of the trial findings, the research team recognized some limitations to the new technology and surgical techniques. These included flaws in the initial TAVR system. These flaws included, requiring large femoral access, which likely led to vascular complications. The research team also recognized that the higher risk for cerebral events for those undergoing TAVR could be attributed to the use of the large catheters and equipment used for the valve replacement (Leon et al., 2010).

This initial randomized trial provided the basis for establishing the benefits and safety of TAVR and led to a further study comparing the outcomes of high-risk patients undergoing TAVR verses AVR. This surgical comparison study, published in 2011 by Dr. Smith et al., was conducted in conjuncture with the Leon, 2010 study. The 699 patients that were enrolled were high-risk patients originally screened for the Leon, 2010 study but were found to be candidates for surgical intervention. The 699 patients were randomly assigned to either undergo TAVR or surgical AVR and were followed up for their survival rate, post-operative complications and disease relief. The study evaluated patient outcomes at 25 surgical centers, 22 located in United States, two in Canada and a single site in Germany. The study defined patients to be at high risk for surgery if the
patients’ health status and comorbidities afforded a 15% chance of death within 30 days prior to surgery.

In this trial the patients that received a TAVR also had a Edwards SAPIEN valve implanted either by transfemoral or transapical approach (Smith et al., 2011). Although Edwards Lifesciences, the company that developed the valve, funded the study an independent statistics firm was utilized to analyze the data to ensure a lack of bias and confirm the accuracy of the results. Those that were treated with AVR had an 8.0% death rate at 30 days post operation compared to 5.2% in those receiving TAVR. The death rate at one year was 24.2% and 26.8% for TAVR compared with AVR respectively. There was a far higher rate of neurologic events in patients undergoing TAVR than AVR with 5.5% verses 2.4% at 30 days, and 8.3% verses 4.3% at 1-year post operation.
**Table 4: Patient clinical results in TAVR vs. AVR-** Outcome at day 30 and 1 year post operation for TAVR verses AVR. Taken from Smith et al., 2011.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Transcatheter Replacement (N=348)</th>
<th>Surgical Replacement (N=351)</th>
<th>P Value</th>
<th>Transcatheter Replacement (N=348)</th>
<th>Surgical Replacement (N=351)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30 Days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td>12 (3.4)</td>
<td>22 (6.5)</td>
<td>0.07</td>
<td>84 (24.2)</td>
<td>89 (26.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>Death</td>
<td>From any cause</td>
<td>11 (3.2)</td>
<td>0.90</td>
<td>47 (14.3)</td>
<td>40 (13.0)</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>From cardiac causes</td>
<td>15 (4.4)</td>
<td>0.64</td>
<td>58 (18.2)</td>
<td>45 (15.5)</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Repeat hospitalization</td>
<td>25 (7.2)</td>
<td>0.24</td>
<td>120 (34.6)</td>
<td>119 (33.9)</td>
<td>0.73</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>Either</td>
<td>19 (5.5)</td>
<td>0.04</td>
<td>27 (8.3)</td>
<td>13 (4.3)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Transient ischemic attack</td>
<td>3 (0.9)</td>
<td>0.33</td>
<td>7 (2.3)</td>
<td>4 (1.5)</td>
<td>0.47</td>
</tr>
<tr>
<td>Stroke</td>
<td>Minor</td>
<td>3 (0.9)</td>
<td>0.34</td>
<td>3 (0.9)</td>
<td>2 (0.7)</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>Major</td>
<td>13 (3.8)</td>
<td>0.20</td>
<td>17 (5.1)</td>
<td>8 (2.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Death from any cause or major stroke</td>
<td>24 (6.9)</td>
<td>28 (8.2)</td>
<td>0.52</td>
<td>92 (26.5)</td>
<td>93 (28.0)</td>
<td>0.68</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>2 (0.6)</td>
<td>0.16</td>
<td>1 (0.4)</td>
<td>2 (0.6)</td>
<td>0.69</td>
</tr>
<tr>
<td>Vascular complication</td>
<td>Any</td>
<td>59 (17.0)</td>
<td>&lt;0.001</td>
<td>62 (18.0)</td>
<td>16 (4.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Major</td>
<td>38 (11.0)</td>
<td>&lt;0.001</td>
<td>39 (11.3)</td>
<td>12 (3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>Creatinine &gt;3 mg/dl (265 μmol/liter)</td>
<td>4 (1.2)</td>
<td>0.95</td>
<td>12 (3.9)</td>
<td>8 (2.7)</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>Renal-replacement therapy</td>
<td>10 (2.9)</td>
<td>0.95</td>
<td>18 (5.4)</td>
<td>20 (6.5)</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td>32 (9.3)</td>
<td>&lt;0.001</td>
<td>49 (14.7)</td>
<td>85 (25.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Endocarditis</td>
<td>0</td>
<td>0.32</td>
<td>2 (0.6)</td>
<td>3 (1.0)</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>New-onset atrial fibrillation</td>
<td>30 (8.6)</td>
<td>0.006</td>
<td>42 (12.1)</td>
<td>60 (17.1)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>New pacemaker</td>
<td>13 (3.8)</td>
<td>0.89</td>
<td>19 (5.7)</td>
<td>16 (5.0)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Evaluating other factors that did not include stroke or death found that TAVR and AVR had variable advantages and disadvantages for patient outcomes. TAVR had a significant increased amount of vascular complication with 11.0% complication compared to 3.2% in AVR. TAVR was better at avoiding major bleeding, 9.3% compared to 19.5% or new-onset atrial-fibrillation 8.6% compared to 16.0% in AVR. Evaluating recovery time and quality of symptom relief, at 30 days TAVR patients were able to walk further in a 6-minute walk test compared to the AVR group patients, and were out of the intensive care unit two days earlier than the AVR patients, who averaged
a five day stay and also had an overall average 8 day hospital stay compared to 12 in the AVR group. The one-year evaluation showed similar clinical symptom outcome improvement between the two groups (Smith et al., 2011). These findings of improved patient recovery time are of great advantage to the overall patient outcome as long hospital stays often lead to poorer long-term outcomes, given the risk of nonsurgical related infection, especially in the elderly population with weakened immune systems (Vincent et al., 2009).

Another large difference in outcomes between the two surgical techniques was with moderate or severe paravalvular regurgitation. This was present in 12.2% of TAVR patients compared to 0.9% in AVR patient at 30 days, and 6.8% in TAVR compared to 1.9% in AVR patient group. Aortic regurgitation is when the blood that was intended to go in a unidirectional flow, travels backward from the aorta to the ventricle. Paravalvular regurgitation is when blood is able to flow around the implanted valve backwards from the aorta to the left ventricle, showing faults in the implanted valve as blood travels in a non-intended direction. Although paravalvular regurgitation was a subsequent finding in the study, this study’s main goal was to prove that patients at high-risk for surgical complication had comparable survival one-year post operation using either AVR or TAVR (Munir & Schreiber, 2014; Smith et al., 2011).

As mentioned above, the greatest concern for patient outcome in those receiving TAVR is risk of cerebrovascular accident or stroke. Further evaluation is needed regarding this stroke risk, because the stroke rate for TAVR is significantly higher than for those operated on in AVR. Analysis of these two risks must be considered while
comparing patient outcomes (Smith et al., 2011). A possible cause for this higher stroke rate could be due to the mechanics of the valve implant and the manipulation of calcified valve, which can create possible debris that can move to smaller vessels and cut off blood supply. In a study of 50 subjects, the use of an examination device, Doppler, during surgical implantation showed that the most common cause of cerebral event occurred during surgically advancing the catheter internally over the aortic valve, balloon valvuloplasty, or during actual valve placement. Doppler, which uses sound for examination, was utilized to evaluate for signals of ischemia or lack of blood supply during the seven portions of the surgical intervention that were most at risk for creating an embolus. Lowered rates of stroke were the result of catheter advancement at the site of catheter entry point (Drews et al., 2011). These findings provide a target for improved treatment and insight into new technologies that could be developed and implemented to combat the current surgical stroke rate. These will be discussed further in the next section.

As the comparison of the two surgical techniques continues, there must be confirmation that the benefits of the new technology have long lasting positive outcomes. This evaluation must consider the extended benefit of TAVR beyond one-year post operation. Consequently, Kodali et al. conducted a study in 2012 to evaluate patient outcomes between the two surgical techniques at two years post operation. The patients that were evaluated in this study were the same 699 patients who received either TAVR or AVR in the Smith et al. 2011 trial. In the patient group, 244 patients were treated with a transfemoral approach, 104 were treated using a transapical approach and 351 were
treated with surgical AVR. In the time period between one year follow up and the second year, the TAVR group had 32 additional deaths compared to 25 additional deaths in the AVR group. However, this difference in mortality between the two treatment approaches was not significant, with TAVR and AVR having a death rate of 33.9% and 35.9% respectively (Kodali et al., 2012a). Both groups suffered four additional strokes, along with two transient ischemic attacks occurring in the transcatheter aortic valve implantation group and one in the AVR group between year one and year two follow up. This resulted with TAVR continuing to have a higher stroke rate at 11.2% compared to 6.5% in AVR group (Kodali et al., 2012a).

**Figure 10: Comparing AVR to TAVR patient outcomes** - The above graphs show the survival percentages as a function of time between those receiving TAVR and AVR. Taken from Kodali et al., 2012a.
Stroke as a cause of death was comparable in the two groups at two years with 36.4% in the AVR group and 37.1% in the TAVR group. Importantly for patient overall outcome, there were similar values of rehospitalization in the two groups over the two year follow up period, and also similar clinical outcome benefit between the two groups of those patients who survived. Mortality is often associated with stroke, with 31% mortality in those that suffering a stroke in less than 24 hours after surgery and 14% mortality in those suffering a stroke past 24 hours after surgery compared to only a 4.6% mortality rate of those receiving AVR who did not suffer a stroke. This same association was seen in the TAVR cohort where the 1-year mortality was 66.7% in those who did suffer a stroke compared to 27.7% in those who did not (Daneault et al., 2011; Kodali et al., 2012a).

In addition to risk of cerebrovascular accident causing death, aortic valve regurgitation with associated mortality was found to be elevated in the two year follow up of TAVR verses AVR. Aortic regurgitation even when mild was associated with poor patient outcomes and death. The aortic regurgitation that was observed was caused by valvular error from incomplete circumferential apposition of the valve insertion to the fibrous rings that surround the valvular opening. This lack of apposition was found to be caused by the positioning of the valve, correct sizing of the valve, and specific calcific build up on the native valve that caused incomplete seal. Without complete apposition to the walls of the opening, there is room for blood to leak backwards from the aorta to the left ventricle. Moderate regurgitation was defined as 10% of blood flowing in the incorrect direction and was present in a low frequency during the two-year follow up
study. The aortic regurgitation that was noted was stable between the year one and year two follow up without worsening of symptoms. Approximately 40% of patients at the two-year evaluation had mild paravalvular regurgitation that puts them at a higher risk for death. Those without any or with trace regurgitation had a much higher survival rate at the two-year follow up point (Kodali et al., 2012a).

**Figure 11:** The role of aortic regurgitation on patient mortality - The presence of aortic regurgitation had a higher association with mortality than those who did not suffer regurgitation. Taken from Kodali et al., 2012b.

In addition to stroke, another common neurovascular event that one is at risk for during surgery is cerebral ischemia or lack of blood supply to the brain, which is often
asymptomatic. These events may not cause immediate cognitive decline, but over time can have very detrimental effects, including decrease in neurocognitive function and increased rates of dementia. The Kodali et al. and Smith et al. trials only evaluated the post-operative death rate, and rate of cognitive decline strokes during the two surgeries. The trials did not evaluate potential longer-term negative impacts from cerebral ischemia with or without cognitive decline (Kodali et al., 2012b; Smith et al., 2011)

A study published in 2010 by Kahlert et al. evaluated the incidence of clinical silent cerebral ischemia associated with TAVR (Kahlert et al., 2010). During TAVR, patients are at higher risk for cerebral ischemia due to the risk of dislodging micro debris either during the catheter insertion or through direct manipulation of the calcified aortic valve. This debris has the potential to cause embolic stroke, which in turn causes cerebral ischemia.

The study compared the outcome of 32 patients undergoing TAVR to the outcome of 21 patients undergoing AVR. Patients were analyzed for cognitive function prior to the procedure, immediately after anesthesia was completely reversed and at three months post operation. Whole body magnetic resonance imaging was also used at each of these time intervals to evaluate the presence of any embolic lesion (Kahlert et al., 2010). On neurologic evaluation, a fully reversible neurologic event that lasted less than 24 hours was considered a transient ischemic attack, while an event with neurologic deficit lasting over 24 hours was considered a stroke.

Between the two subject groups no neurologic deficits were seen in the first evaluation of the patients post-operatively, but the AVR surgical group had one left-
hemispheric stroke that presented in the second day post operation. During post
procedural imaging evaluation, the TAVR group had 84% of patients suffering new
lesions with restricted diffusion compared to 48% in the AVR group. The lesions that
were present in the TAVR patient were consistent with embolic lesions. An embolic
lesion is caused by ischemia to a portion of tissue due to some type of embolus blocking
blood flow to an area of tissue. The embolus can be a blood clot, air bubble, atheroma, or
other physical material such as calcified debris that moves through the circulation system
with the potential to block blood flow, causing damage to any down stream tissue, with
brain tissue being particularly susceptible to this risk. Any damage to the brain also
causes proportionately more potential negative impact to patient outcomes and quality of
life. However, in the three month evaluation there were no addition imaging findings in
either group along with no neurological deficits recorded, and 80% of the foci detected
postoperatively had resolved with no residual deficits found. Besides the single stroke
recorded in the AVR group, each patient had no change to their neurological outcome
post operation (Kahlert et al., 2010).

The researchers attributed the cause of the elevated level of lesions in the TAVR
group to the higher level of atheromas or fat deposits on arterial walls in the patients who
received this treatment. These atheromas have the potential to dislodge and create an
embolism. With any cardiac intervention using catheterization there is risk for atheroma
disturbance and subsequent embolism. This embolism can occur even with the smallest
size of catheters. Those used during TAVR are significantly larger in size than most
catheters used due to the initially collapsed valve that must be guided into place (Kahlert et al., 2010).

In 2010, an additional study looked solely at stroke outcome in patients receiving TAVR. The study enrolled 30 patients for evaluation of cerebral embolism and ischemia using magnetic resonance imaging; 22 were able to be fully evaluated according to the study protocol. In those that were evaluated, 72.7% of patients developed new silent cerebral embolism, with only 3.6% of the patient population experiencing neurologic deficit three months post operation (Ghanem et al., 2010). This study had similar findings to the Kahlert 2010 study, which showed an elevated level of cerebral lesions detected with magnetic resonance imaging, but a similar low incidence of long-term neurologic deficits. Continued evaluation of these patients is recommended in order to monitor the long-term effects that these silent cerebral lesions may have on patient outcomes. Both studies confirmed that, in those patients who suffered new cerebral lesions, these lesions were caused by the mechanism of debris embolism. This confirmation of embolism as the causal agent for these legions showed the importance of reducing embolus for this type of surgery. New devices have been developed to focus on combating the risk of embolism and subsequent stroke for those undergoing TAVR (Ghanem et al., 2010).

As the thirty-day postoperative stroke rate during TAVR is still twice as high as undergoing AVR, prevention of stroke is a key priority in providing greater benefit to those undergoing TAVR. One method that is being developed to assist in the prevention of stroke are devices that are implanted in the vasculature during surgery to deflect or capture embolus material in order to prevent cerebral ischemia and stroke. The devices
are in the early stages of development and testing but have shown benefit during their use during surgery. One device that was developed is the SMT Embolic Deflection Device, with publication of its first use in 2012. The device was tested on 15 patients undergoing TAVR. The device is placed at the aortic arch using catheterization and acts to deflect any microdebris that may be traveling in the vasculature toward the cerebral circulation. The device does not act to capture or remove the debris but deflects the emboli/debris to other portions of the circulation where they are less likely to cause harm (Onsea et al., 2012). To test the effectiveness of the device, ten patients had baseline magnetic resonance imaging exams followed by one week follow up imaging after the surgical intervention. During the follow-up imaging, there was an average of 3.2 new lesions in the patient group with device implementation compared to 7.2 new lesions from a previous similar trial without using the deflection device. In follow up of the patients clinically, there was no development of new neurologic deficits in any patient besides one patient who had a transient ischemic attack two days post operation (Onsea et al., 2012). This study showed promise in the development and utilization of deflection devices in order to prevent strokes in those undergoing TAVR. Larger clinical trials are needed in order to fully prove its efficacy. Reducing the risk of stroke would provide a great improvement to the clinical outcomes of those patients undergoing TAVR.

Although there has been a large focus on clinical outcomes related to patient survival, in order to evaluate the full patient outcome, attention must also be placed upon the patient’s quality of life after TAVR and AVR. While an operation may lengthen a patient’s life, it is important to determine if the operation also led to an improved quality
of life, not simply to survival. The first study that was conducted to access this in the United States was done to evaluate quality of life improvements in those who underwent TAVR verses those non-surgical candidates who underwent standard treatment in the Leon study. This prospective quality of life study evaluated 358 patients at baseline before surgery, at 1, 6, and 12 months post operation or post standard treatment (Reynolds et al., 2011). The research team used two different evaluation scores to evaluate the patients: the Kansas City Cardiomyopathy Questionnaire and the Medical Outcomes Study Short-Form Health Survey. The Kansas City Cardiomyopathy Questionnaire focuses on heart failure, monitoring patient quality of life and symptoms due to this ailment on a scale of 0-100, with higher scores being more positive. The Medical Outcomes Study Short-Form Health Survey was used to evaluate general health status of the patient on a scale of 0-50, also with the highest score being the most positive outcome. The evaluations monitored improvement of patients’ quality of life and also the cardiac symptoms they were suffering from prior to the intervention. The quality of life improvement is significantly higher in the patients that underwent TAVR verses standard therapy (Reynolds et al., 2011).
Table 5: Quality of Life Scales - The quality of life for patients undergoing TAVR verses AVR are compared in order to ensure the positive benefits of TAVR. KCCQ (Kansas City Cardiomyopathy Questionnaire), SF-12 (Short-form 12 General Health Survey). Taken from Reynolds et al., 2011.

<table>
<thead>
<tr>
<th>Scale/Time Point</th>
<th>TAVR Group</th>
<th>Control Group</th>
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<tbody>
<tr>
<td></td>
<td>Mean (±SD)</td>
<td>Mean Δ vs Baseline</td>
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<tr>
<td>KCCQ summary</td>
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</tr>
<tr>
<td>1 mo</td>
<td>61.6±26.2</td>
<td>24.8</td>
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<tr>
<td>6 mo</td>
<td>70.7±23.0</td>
<td>33.5</td>
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<tr>
<td>12 mo</td>
<td>69.4±25.3</td>
<td>31.8</td>
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<tr>
<td>KCCQ total symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>69.4±23.3</td>
<td>20.8</td>
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<tr>
<td>6 mo</td>
<td>77.2±18.9</td>
<td>29.2</td>
</tr>
<tr>
<td>12 mo</td>
<td>75.3±22.8</td>
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<tr>
<td>KCCQ physical limitations</td>
<td></td>
<td></td>
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<tr>
<td>1 mo</td>
<td>53.3±31.5</td>
<td>15.2</td>
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<tr>
<td>6 mo</td>
<td>57.4±39.8</td>
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<tr>
<td>12 mo</td>
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<td>16.8</td>
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<tr>
<td>KCCQ social limitation</td>
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<tr>
<td>1 mo</td>
<td>55.7±36.7</td>
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<tr>
<td>KCCQ quality of life</td>
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<td>SF-12 physical</td>
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<td>5.9</td>
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<tr>
<td>12 mo</td>
<td>53.3±10.0</td>
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In each evaluation the mean difference from baseline was much more improved in the TAVR patient group than in the standard therapy group. This initial evaluation showed the benefit of not only patient symptoms, but also the quality of life that the patient is afforded after TAVR verses standard therapy.

Another important study by Kala et al. in 2013 also compared quality of life the quality of life for those patients undergoing AVR verses TAVR (Kala et al., 2013). The
study was an observational randomized study conducted at a single site and evaluated changes in the quality of life for 45 high-risk patients. The patients were evaluated at baseline, day 30, day 90 and day 365 using a standardized EQ-5D three level questionnaire that evaluated quality of life. At baseline there was no difference found in the quality of life between the two patient groups, and both groups reported similar health outcomes at day 30 and 90 (Kala et al., 2013). At the one-year evaluation, while the group that underwent standard AVR experienced less anxiety/depression and displayed an upward trend in increase of general health, this upward trend was not found to be statistically significant. For those who received TAVR surgery, however, their general health was significantly improved. In fact, the greatest improvements in quality of life scores were seen in the transcatheter aortic valve implantation group, with improvements in physical functioning ability. This study was able to prove with a small subset of patients that not only was TAVR comparable to AVR in patient symptomatic outcome, but that the quality of life for those receiving TAVR was improved over those receiving AVR (Kala et al., 2013).
DISCUSSION

As the medical field continues to advance and new technologies are implemented, each new technology must be assessed individually to ensure quality health outcomes for the patients involved. Such quality is defined not only by patient survival, but also by relief of patient symptoms and improvement to their quality of life. For many of the technologies being developed currently, there is already a known and effective intervention but the new technologies hope to build off of current practice to further improve the clinical outcome of the patients treated.

This is the case with the development and practice of AVR and TAVR. AVR has been an effective treatment for those suffering aortic stenosis that are capable of undergoing surgical intervention. TAVR was originally developed to assist those who were non-surgical candidates without recourse to treatment. This new technology improved patient access to lifesaving treatment through a much less invasive procedure. With any new technology there are predicted risks and unforeseen complications that must be compared to the previous technique and those evaluations have been undertaken by the studies above.

The study done by Leon et al. 2010 was the first study conducted in the United States to evaluate the baseline safety of TAVR compared to standard therapy for patients who would not be candidates for AVR (Leon et al., 2010). This was a pivotal study as it showed the first case where there was a surgical intervention option that had high success rates for those who were not candidates for AVR. As mentioned above, without the reliable pharmaceutical intervention for those suffering aortic stenosis, this was the first
true treatment for the non-surgical candidate subgroup. This study met its main goal of proving that the use of TAVR would afford a better outcome for those patients with aortic stenosis than the current pharmaceutical standard therapy approach for those who cannot undergo surgery. The mortality rate at one and two-year follow up was much higher in the group that had standard therapy compared to TAVR.

However, the researchers did find a higher rate of stroke in the TAVR patients. Smith et al. who compared the outcomes of high-risk patients undergoing TAVR vs. AVR found similar findings of elevated stroke rates in the TAVR group. In both studies, the increased stroke rate was attributed to surgical complication due to either device technology or surgical technique. The Smith trial proved that the outcome of TAVR vs. AVR was comparable when evaluating for mortality rate. Although the stroke rate was elevated in the Leon and Smith studies, the new technology provided better or comparable outcomes for patients and the studies led to FDA approval for the use of TAVR on patients who were not candidates for surgical AVR, and approval for TAVR in high-risk patients respectively. The two studies were well executed with a large sample size in both studies, using 21 and 25 different surgical sites in Leon and Smith trials, respectively, and using a randomized control for patient selection. Utilizing different sites ensured that the safety of the device was not dependent on the surgeon, the hospital, or the assisting staff. Patient randomization further ensured against potential operational biases that can occur, such as specific patient selection. Although both studies were funded by Edwards Lifescience, the company who developed the device, there was a
separate co-principal investigator and an executive committee not associated with the companies that helped ensure the validity of the study (Leon et al., 2010).

In order to fully evaluate the risk of stroke in patients undergoing TAVR and AVR, Kahlert et al. and Ghanem et al. used MRI evaluation to monitor for any sign of cerebral ischemia. This type evaluation was not carried out in both the Smith and Leon studies.

Cerebral ischemia is lack of blood flow to the brain; this can be symptomatic for a stroke or can be asymptomatic with no neurologic cognitive deficits. The researchers hypothesized that if there were elevated levels of strokes in TAVR patients there is likely elevated asymptomatic cerebral ischemia as well. Although asymptomatic ischemia can pose no issue to the patient at the time of development, it has the potential to cause detrimental neurologic effects later on in the patients’ life. Both Kahlert and Ghanem documented a significant increase in the incidence of cerebral ischemia in patients undergoing TAVR. Further studies are needed to assess this increased level of cerebral ischemia in long-term patient evaluations to monitor its effect on cognitive decline.

A limitation of both of these studies was the small sample size; the Kahlert study had 32 patients in their TAVR group and the Ghanem study, 30 patients. Although these study samples were small, the findings were still significant in showing the increased incidence of cerebral ischemia, and demonstrated further need for its evaluation.

Due to the high risk of stroke that has been documented in TAVR, there has been increased research to minimize this risk. As one of the first steps in finding a solutions
for the increased rate of stroke in TAVR patients, Drew et al. utilized Doppler screening during surgery to find the cause of stroke. The investigation was carried out as surgeries were being performed and the researchers found that there was an elevated risk of stroke due to microdebris being dislodged and becoming an embolus during surgery. Patients were at highest risk during catheter advancement over the aortic valve, balloon valvuloplasty, or during the aortic valve expansion (Drews et al., 2011).

In parallel with the findings of Drews that stroke was caused by embolisms often due to the surgical operation itself, devices have been developed to attempt to limit such embolus and concomitant cerebral ischemia. Onsea et al. established a device that was capable of deflecting embolus away from cerebral circulation. During the study, there was no neurologic deficit seen in any patient and there was a large decrease in the amount of cerebral ischemia found (Onsea et al., 2012). The embolus deflection technology may provide key advancements in preventing the incidence of stroke, but the technology is still in its early development and must be further investigated.

Another key aspect to limiting the rate of stroke in TAVR will be the development of surgical techniques and further technology advancement. Kodali, Smith and Leon all attributed many of the risks with stroke to the large catheters that must be used for implantation of the prosthetic valve. The design must continue to be evaluated to try to eliminate this size limitation that can lead to stroke in patients undergoing TAVR. Regardless of the technology advancement, surgeon familiarity with the devices should provide improvement of the TAVR outcome overall, including stroke risk. It was documented that it took 25 to 30 TAVR procedures to become proficient with the
techniques and with further experience there will hopefully be a decrease in surgical stroke complications (Alli et al., 2012). This must be evaluated later in time as many surgeons are still in early practice with the surgical technique.

In addition to increased risk of stroke, Leon, Smith and Kodali all found increased risk of paravalvular regurgitation in those undergoing TAVR with associated increased mortality (Kodali et al., 2012b; Leon et al., 2010; Smith et al., 2011). There needs to be development of surgical techniques, device improvements, or patient selection criteria to find ways to combat the increased rate of mortality. This risk of paravalvular regurgitation was associated with valvular sizing issues and placement issues, both of which can hopefully be improved with the surgeon learning curve as mentioned above. As the findings of paravalvular regurgitation were associated with mortality, reduction in this surgical issue could provide great advancements for TAVR patient outcomes.

The studies above were capable of comparing TAVR and AVR in short-term, thirty day, one and two year follow up, but the next challenge is comparing the surgical techniques on a long-term basis. Although the overall mortality and symptom relief statistics for those undergoing TAVR are comparable to AVR at two years post operation as shown by Kodali et al., without further follow up there cannot be a full evaluation of the patient outcomes (Kodali et al., 2012b). The long-term evaluations should monitor cardiac and neurologic effects of the device in order to ensure a comprehensive patient follow up of both survival and quality of life. In the short term, thirty day and one year follow up, quality of life was proven by Reynolds to be higher in the TAVR patients. The increase in the asymptomatic cerebral ischemia is a major issue that needs to be
monitored to ensure that the patients do not have long-term neurologic effects due to TAVR that could highly affect their quality of life and change the findings of Reynolds. Lacking these long-term evaluations it is impossible to make a full comparison of patient outcomes between the two techniques.

Another large issue with the field lacking these long-term studies is that there is no long-term follow up on the newly developed valves and evaluation of their device lifespan. Biological valves have an increased risk of degeneration, with device failure presenting a large risk to patients, and this evaluation must be continued in order to compare the long-term patient outcome. However, the risk of device failure when using TAVR is a greater risk to younger patients, who are less likely to undergo this surgery, than is the risk to older patients. In older patients the device is implanted toward the end of life, and so the device will more likely remain functional for the remainder of patients lives. The risk of device failure becomes significantly more important if TAVR is approved to be used on low-risk patients who tend to be younger and may have the device fail in their lifetime, requiring repeat surgery with its inherent risks (Bajona et al.;, 2014).

The biggest limitation of all of the studies above in comparing the outcomes of those undergoing TAVR versus AVR is the patient groups that were utilized during the studies. The studies were able to prove that patients undergoing TAVR who were not approved or at high-risk for AVR had comparable outcomes, but the studies lacked the ability to make conclusions on those at low-risk for surgical intervention. This is compounded by the fact that the older patients who are normally at high-risk for AVR are
also at increased risk for stroke at baseline. The findings of increased stroke rate in the studies are based upon a patient group that carry higher levels of comorbidities and a higher risk for stroke. In order to make a better evaluation of the overall outcome of TAVR, studies of low-risk patients must be conducted. The same investigators that conducted the Smith and Leon trials are now carrying out a trial to compare the outcome of AVR verses TAVR in intermediate-risk surgical patients. This is the next large advancement that must be made in order to evaluate the outcomes of TAVR (“The PARTNER II Trial: Placement of AoRTic TraNscathetER Valves - Full Text View - ClinicalTrials.gov,” 2014).

When looking at the two surgical techniques overall, both techniques have comparable overall survival in high-risk patients. TAVR carries increased risk of stroke, asymptomatic cerebral ischemia, vascular injury and paravalvular regurgitation. AVR has increased risk of bleeding, decreased improvement to the quality of life and increased hospital stay length with its attendant risks.

With nearly twice the high risk of stroke for individuals undergoing TAVR verses AVR, it cannot definitively be stated that TAVR is a better option than AVR for all aortic stenosis patients despite comparable survival outcomes. TAVR provides a drastic improvement in survival for patients that are unable to undergo surgery who would otherwise be limited to standard pharmaceutical therapy. The benefit begins to blur as one debates AVR or TAVR for those at high risk for surgery, instead of those who are unable to undergo surgery. Without long term follow up, the increased risk of stroke and comparable outcomes for TAVR must be considered on an individual patient case basis.
To further the science and improve patient treatment options and outcomes, more studies need to be conducted to look at TAVR compared to intermediate and low risk surgical patients. Further study is also needed to create or strengthen surgical techniques and devices that lower the incidence of stroke. Continuations of the surgical learning curve, decreased catheter size, and embolus blocking devices may provide significant improvements in lowering the stroke rate and increasing positive patient outcomes.

There is currently not enough information to conclude that overall, for the population of patients with aortic stenosis, TAVR has similar outcomes as AVR. AVR should continue to be the gold standard for those at low or intermediate surgical risk. TAVR should continue to be used in patients that are not surgical candidates as proved by the extreme improvement of patient outcome. Both techniques must be evaluated on a per patient basis when operating on those with high surgical risk as TAVR continues to carry a much larger stroke risk.

The development of TAVR is a promising field, given its benefits as a less invasive surgery with decreased recovery time. Further research is needed with a focus on long-term patient outcome as time passes. Without these follow up studies, a comprehensive comparison of patient outcomes, from survival to quality of life, cannot be made. As the science of TAVR continues to progress and subsequent strategies are developed, the options for those suffering from aortic stenosis will continue to increase, providing better outcomes for those affected.
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Recently-Approved Devices > Medtronic CoreValve System - P130021.


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• Worked directly with Emergency Medical physicians to assist in completing patient charts and expedite emergency room patient care.
• Monitored patient’s progress during visits and followed any diagnostic studies to assist physician and ensure accurate charting.

Rwanda Heart Foundation - Kigali, Rwanda
September-October 2011

Technical Specialist
Set up a database system which provided a method to follow patients who had received open-heart surgery at King Faisal Hospital in Kigali, Rwanda.
• This database can now be used to collect data, and provide information for future studies of surgical prevalence treatment options and outcomes in Rwanda.
• Utilized the knowledge of treatment results to develop standards for the evolving independent Rwandan Heart Surgery Program.

Team Heart Rheumatic Heart Disease Screening - Kigali, Rwanda

September 2011

Volunteer

Assisted in the research project to screen for Rheumatic heart disease in children from 6-18 years old by performing 2800 echocardiograms on asymptomatic individuals.

- Prepped patients for screening
- Assisted in set up and take down of screening rooms
- Provided assistance to sonographers
- Served as team photographer

Step Up Spokane Internship - Spokane, WA

June 2010 – June 2011

(A citywide initiative to encourage positive life style change through exercise tools and nutrition choices)

Social Network Development and Consultant

- Developed both Facebook and Twitter for the program creating an online community and presence
- Provided input for program development

Global Medical Brigades, Eastern Panama Medical Immersion Trip

March 2010

Volunteer

Responsible for assisting in medical treatment in rural village

- Triaged patients
- Aided patients in medicine descriptions – instructed patients on correct regimen for the medicine prescribed
- Assisted physicians in translation and description of medical problems