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REVIEW ARTICLE

Should Patients with Low to Moderate Surgical Risk be Offered TAVI Instead of Conventional Aortic Valve Replacement in the Management of Symptomatic Aortic Stenosis?

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ABSTRACT

Introduction: Surgical aortic valve replacement (AVR) is the current gold standard treatment for symptomatic aortic stenosis. Without surgical intervention, patients experience a period of rapid clinical worsening, with 50% mortality within two years. However AVR in itself carries considerable risk and many patients may be considered too high risk and therefore not candidates for surgery. Transcatheter Aortic Valve implantation (TAVI) was conceived in 2002 which showed comparable results to AVR in patient are at high surgical risk. TAVI is indicated for high risk patients and in patients that are contraindicated to surgery. Due to increasing public interest there is demand for TAVI to be used within lower risk patients. This is currently being assessed through the large SURTAVI and PARTNER A trials.

Aim: The aim of this review is to appraise the current indications surrounding the use of TAVI in potentially low-moderate surgical risk patients and inform its readers about the history of TAVI and its future direction. This paper also addresses the pathogenesis, epidemiology, management and prognosis of aortic stenosis from the most up to date research studies.

Methods: A systematic review was conducted. Databases searched included MEDLINE, Embase, AMED, Science Direct, UPTODATE and the British Journal of Cardiology for papers published from the period of January 1990-present. Combinations of the following terms were used: 'tavi, 'transcatheter aortic valve implantation', 'aortic stenosis', 'treatment of aortic stenosis', 'aortic valve replacement' 'avr' 'Medtronic core valve' 'bioprosthetic heart valves', 'edward sapien bioprostheis' and 'treatment of aortic stenosis'. All papers were from the most up to date sources and all information was cross referenced with NICE guidelines and the UPTODATE database.

Results: 37 papers were selected for review. The main findings included: the incidence of aortic stenosis is rising due to advances in medical treatment resulting in an aging population; AVR is the current gold standard treatment for aortic stenosis; TAVI is superior to medical therapy alone; TAVI is indicated in high surgical risk patients and those that are contraindicated to surgery; TAVI is comparable to AVR in high risk patients; studies have shown comparable result comparing TAVI with AVR in low- moderate risk pateints; the wide SURTAVI and PARTNER A trials are currently assessing the use of TAVI in low-moderate risk patients.

Conclusions: TAVI has revolutionized an alternative way of thinking towards the management of symptomatic aortic stenosis. TAVI is indicated in patient whom are at high surgical risk and in cases where surgery is contraindicated. AVR remains the gold standard treatment in low-moderate surgical risk patients. TAVI may be considered as an alternative method to surgical AVR following the results of the PARTNER 2 and SURTAVI trials.

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Introduction

Surgical aortic valve replacement (AVR) is the current "gold standard" treatment for symptomatic aortic stenosis. Without surgical intervention, patients experience a period of rapid clinical decline, with 50% mortality within 2 years. However AVR in itself carries considerable risk and many patients may be considered too high risk for surgery. Until recently, these patients were managed with best medical therapy, which mildly alleviated symptoms but did not alter the disease's natural progression. Since its introduction in 2002, transcatheter aortic valve implantation (TAVI) has offered an alternative for these patients, showing prognostic results comparable with AVR.

Following the results of the PARTNER (Cohort B) study, which showed considerable reductions in mortality for TAVI compared with best medical therapy, TAVI has become the mainstay treatment in patients deemed too high risk for AVR. TAVI has recently been compared with AVR in high-risk patients who are surgically eligible, through the US-PIVOTAL and PARTNER (Cohort A) trials. Both trials showed comparable results in both treatment options and TAVI has since been updated and is licenced as an alternative to AVR in high-risk patients. This paper will explore the current guidelines surrounding indications for TAVI and surgical AVR in the treatment of aortic stenosis based on the findings of the PARTNER (Cohorts A and B) and US-PIVOTAL studies. This paper will also appraise the type of valves used in TAVI, the best access points undertaken, their potential use in low- to moderate-risk groups, and also the main reasons why the population may prefer TAVI over AVR.

Background

Aortic stenosis is a chronic inflammatory and fibrotic process of the aortic valve resulting in abnormal narrowing of the aortic orifice and subsequent impediment of left ventricular ejection.[1] It is the most prevalent valve-related heart disease in the Western world affecting 4% of the population over 75 years of age and is one of the leading causes of morbidity and mortality.[2] This condition has multiple aetiologies, the most common including senile calcific, bicuspid, rheumatic, and congenital.[3,4] The most common of these is calcific aortic valve disease (CAVD), which is most prevalent in elderly populations.[5]

Pathophysiology

A number of mechanisms have been postulated regarding development of CAVD. One of these theories involves transformation of interstitial cells within the valve leaflets from a regular reparative state, to a more active proliferative state following mechanical stress or injury secondary to disease. When in their active state, these interstitial cells upregulate osteoblasts and myofibroblasts, which then induce calcification.[6]

Another mechanism suggests a role for T lymphocytes, monocytes, and low-density lipoproteins in initiating inflammation and calcification within the aortic leaflets, following damage to their basement membranes through mechanical stress.[7] Bicuspid-related aortic stenosis is the most prevalent cause in younger populations as mechanical stress exerted on the valve leaflets is distributed amongst two leaflets instead of three, thereby accelerating damage mediated via mechanical stress.[8] These processes of calcification result in progressive thickening and stiffening of the aortic leaflets, leading to impaired leaflet motion and subsequent narrowing of the aortic orifice.

As the aortic orifice continues to narrow, the left ventricle exhibits chronic resistance during systole, resulting in a systolic pressure gradient between the aorta and left ventricle.[9] In an attempt to overcome this increase in afterload, the musculature of the left ventricle undergoes concentric hypertrophy.[10] This is where the muscular walls of the left ventricle thicken approximately equally through the replication of parallel sarcomeres. This compensatory process strengthens left ventricular contraction and aids in the maintenance of stroke volume and cardiac output, but at the expense of reduced diastolic compliance.[11]

As aortic stenosis persists, the left ventricle continues to hypertrophy resulting in elevation of left ventricular end-diastolic pressure. When this increase is sufficient, it evokes an equivalent increase in pulmonary capillary arterial pressures and subsequent reductions in cardiac output secondary to diastolic dysfunction. Cardiac output may be impaired further by systolic dysfunction, whereby myocardial elasticity and thus contractility are reduced as a consequence of left ventricular hypertrophy.[12]

Presentation

The natural history of aortic stenosis is that of a long, dormant, relatively asymptomatic period, followed by a sharp decline in survival following the onset of symptoms.[13] As aortic stenosis progresses, the left ventricle eventually succumbs to the chronically elevated ventricular pressures and begins to dilate. Ventricular dilatation reduces ejection fraction and cardiac output leading to symptoms of heart failure.[14] Backwards pressure is exerted on the pulmonary system, leading to pulmonary venous hypertension, reactive pulmonary vasoconstriction, and dyspnoeic symptomatology. Angina and syncope are frequently experienced due to inadequate coronary blood flow and the larger oxygen demand of the overexerted, hypertrophied left ventricle. Calcific infiltrates from the aortic valve may extend to the conduction system resulting in atrial arrhythmias, atrial-ventricular blockade, and left bundle branch block.[15] As a result, untreated patients with aortic stenosis are at increased risk of heart failure, dilated cardiomyopathy, arrhythmias, and sudden death. With an ageing population, aortic stenosis is becoming increasingly prevalent and represents a significant global health problem.

Methods

A systematic review of the literature was conducted. Databases searched included MEDLINE, Embase, AMED, Science Direct, UpToDate, and the British Journal of Cardiology for papers published from the period of January 1990–present. Combinations of the following terms were used: "tavi", "transcatheter aortic valve implantation", "aortic stenosis", "treatment of aortic stenosis", "aortic valve replacement", "avr", "Medtronic core valve", "bioprosthetic heart valves", "Edward Sapien bioprosthesis", and "treatment of aortic stenosis". All papers were from the most up-to-date sources and all information was cross-referenced with NICE guidelines and the UpToDate database.

Surgical valve replacement

Patients with aortic stenosis experience a rapid period of clinical deterioration with more than 50% of people dying within 2 years of symptom onset if surgical intervention is not initiated.[16] AVR is currently the "gold standard" treatment for symptomatic aortic stenosis. However, despite continual improvements in operative mortality rates, AVR still poses considerable risk in certain patient subsets including the very elderly, frail, and poly-morbid.[17] This created a paradox whereby patients who are most in need of surgery were deemed inappropriate or too high risk, and were managed medically. This equated to approximately 30–40% of patients with symptomatic severe aortic stenosis that were not candidates for surgery.[18]

Transcatheter aortic valve implantation

In 2002, Cribier *et al.*[19] established a less invasive alternative approach to surgical AVR in an effort to manage the growing unmet clinical need of high-risk patients ineligible for surgery. The TAVI procedure involves percutaneous implantation of a stent-based biological prosthesis into the diseased native aortic valve, which offers lower peri-procedural risk than conventional open valve replacement. There are currently two prostheses in wide commercial use; these include the self-expanding Medtronic-CoreValve bioprosthesis and the balloon expandable Edwards-Sapien bioprosthesis. Advancement of these biological prostheses can be undertaken via a transfemoral, subclavian or direct aortic approach by means of a retrograde catheter or introduction of an anterograde catheter via the transapical route.[20]

TAVI versus best medical therapy

In 2010, Leon *et al.*[21] conducted the large multicentre placement of aortic transcatheter valves (PARTNER Cohort B) trial. This trial compared the outcomes of best medical therapy against those of TAVI in patients with severe aortic stenosis who were too high risk for conventional AVR. The natural progression of aortic stenosis remained unchanged in the best medical therapy arm, which showed 50.7% and 44.6% mortality rates at 1 year from any cause and cardiovascular causes respectively. Transfemoral TAVI was associated with a 20% reduction in mortality rates as well as reductions in symptoms and level of recurrent hospitalizations. The haemodynamic performance of the bio-prosthetic valves was followed up 1 year post-TAVI with echocardiography, which revealed no signs of deterioration. TAVI was, however, associated with an increased risk of major vascular complications, paravalvular regurgitation and stroke.

It was concluded that the higher level of vascular events occurred as a result of gaining percutaneous access with large diameter delivery catheters.[22] The

higher levels of stroke were caused by atherothrombotic emboli liberated from the aortic valve during implantation.[23] Current studies are therefore evaluating the use of smaller valves, catheters and support systems as well as devices to protect from cerebral emboli in an attempt to reduce future complications. Following results of the PARTNER (Cohort B) trial, TAVI has been shown to be a superior approach for the best medical therapy in patients who are too high risk or not medically fit for surgery.

TAVI versus AVR

Due to the promising results of the PARTNER (Cohort B) trial, the potential role of TAVI was further investigated among high-risk patients who were nevertheless viable candidates for surgery. Numerous trials including PARTNER (Cohort A)[24] and the US-PIVOTAL[25] trials were initiated with the aim of comparing outcomes of TAVI with that of standard surgical AVR. PARTNER (Cohort A) compared outcomes using the balloon expandable Edwards-Sapien bioprosthesis, whereas the US-PIVOTAL study used the self-expanding Medtronic-CoreValve bioprosthesis. Each of these trials utilized both transfemoral and transapical methods and thus secondary outcomes included approach risk.

The results of the PARTNER (Cohort A) trial showed comparable mortality rates at 30 days, 1 year and 2 years for both TAVI and AVR groups, respectively. Patients treated with TAVI experienced quicker recovery times and greater amelioration of their symptoms but were similar to surgical patients at the 1 and 2 year marks. There are inherent differences in complications between the two approaches. Surgical AVR was associated with higher rates of new-onset atrial fibrillation and life-threatening bleeding, whereas TAVI was associated with higher risk of vascular and athero-embolic complications. In this study, TAVI was associated with a greater risk of stroke, TIA, paravalvular regurgitation, and vascular complications at 30 days, 1 year and 2 years.[26]

The results of the US-PIVOTAL trial showed lower mortality rates in the TAVI group than the AVR group. Periprocedural and postoperative complications were relatively consistent with the PARTNER (Cohort A) trial, reporting higher levels of major bleeding and new onset atrial fibrillation in the surgical group, with higher risk of vascular complications, TIAs, and stroke within the TAVI group. TAVI was also associated with a higher incidence of conduction system disruption necessitating permanent pacemaker implantation. In this trial, the risk of stroke or TIA within the first 30 days was initially highest among the TAVI group. However, after this period, this risk reduced and was equal with the surgical group at the 1- and 2-year marks. This higher incidence in stroke and TIA may reflect the liberation of atherothrombotic debris from the aorta or valve during the procedure, resulting in embolization.[27] Despite the higher incidence of stroke at 30 days, the composite mortality rate in both TAVI and surgical arms from major stroke or any other cause, were comparable amongst both groups at 30 days and 1 and 2 years. Following the results of these studies, TAVI is now licensed in patients with severe symptomatic aortic stenosis who are not candidates for surgery or as an alternative in high-risk patients.[3]

TAVI access routes

With regards to approach, numerous trials have reported significantly higher complication rates among transapical or subclavian access routes in comparison with those performed transfemorally.[24,28,29] Patients, however, were not randomized beforehand and many of those who received transapical or subclavian approaches possessed higher risk profiles than those who underwent transfemoral approaches. Therefore, it is difficult to say whether the higher mortality rates observed in these two approaches were due to higher procedural risks or simply a reflection of these patients' increased risk profiles. A large study has since adjusted for potential confounders and confirmed transfemoral approach as superior to transapical and subclavian routes, which are associated with increased mortality rates and adverse events at 30 days, 1 year and 2 years.[30] The transfemoral approach is now the standard route undertaken, however both transapical and subclavian routes remain integral measures of the TAVI armamentarium where femoral access may not be feasible due to excessive tortuosity, peripheral vascular disease, or small vessel calibre.[31]

Medtronic CoreValve versus Edwards-Sapien bio-prostheses

The UK TAVI registry[32] has concluded no significant differences in mortality rates among patients treated with the Edwards-Sapien or the Medtronic CoreValve bioprostheses. There was however a

higher incidence of paravalvular aortic regurgitation and need for permanent pacemaker implantation in those managed with the CoreValve system, which is consistent with most studies. This however has not equated to differences in mortality rates between both systems, but the need for further study regarding aortic regurgitation on future outcomes is justified.[30]

Future of TAVI

Due to the effectiveness of TAVI, more patients with symptomatic aortic stenosis classed as low to moderate risk are demanding percutaneous therapy over the well-established AVR option. There are many reasons why patients may prefer TAVI over AVR, including: quicker recovery times, reduced number of repeat hospital admissions, faster amelioration of symptoms, reduced risk of life-threatening bleeding and new-onset atrial fibrillation, it is less invasive, and it avoids sternal scarring. Presently, TAVI has not been compared with AVR in patients who are of low to moderate risk and is therefore not indicated for this subgroup. Before TAVI can be recommended as an alternative approach to open heart surgery in lower risk patients, additional evidence regarding long-term procedural outcomes is imperative, including strategies to reduce complications.

The long-term complications post-TAVI are currently unknown, with data rarely exceeding 4 years of follow-up.[33] Mortality rates, complications, and bio-prosthetic longevity must be established through longer periods of study before TAVI can be used in low- to moderate-risk patients. The established complications, such as higher rates of stroke, vascular events, and conduction system impairment should be minimized. As regards minimizing stroke risk, cerebral embolic protection devices and greater detection of possible embolic debris should be facilitated.[34] The higher rates of vascular complications may decrease with future developments such as use of more discreet devices, superior screening and better closing devices.[35] The higher level of permanent pacemaker implantation and aortic regurgitation, particularly in the Medtronic CoreValve bioprostheses should be addressed through enhanced device engineering, positioning, sizing, and dilatation post-TAVI.[36] Current guidelines recommend dual antithrombotic therapy post-TAVI. This is currently being evaluated in order to determine if only one antithrombotic drug would suffice, which is prudent in elderly patients or those on chronic anticoagulant regimens.[37] The future usage of TAVI in low- to moderate-risk patients is currently being investigated through the PARTNER 2 and SURTAVI trials.[38,39] These long-awaited studies will help evaluate the need for TAVI in low- to moderate-risk patients.

Limitations of current literature

There is limited data encompassing the use of TAVI in the low- to moderate-risk surgical patients. Only a few studies investigating this have been conducted thus far. As TAVI has only been around for 13 years, long-term follow up is not yet available, restricting discussion of long-term complications to conjecture. There are few studies comparing the current bioprosthetic valves available, their complications and how they compare with surgical AVR among patients with different surgical risk levels.

Conclusions

Since its conception in 2002, TAVI has revolutionized the approach to the management of symptomatic aortic stenosis. In patients who are too high risk for surgical AVR or where surgery is contraindicated, TAVI has shown superlative results in relation to best medical therapy. TAVI has also shown promise amongst high-risk patients who are eligible for surgery, demonstrating comparable outcomes in terms of mortality. As a result, TAVI is now considered in patients where surgery is not appropriate and also in patients with high surgical risk. Despite the recent success of TAVI, AVR remains the "gold standard" treatment in low- to moderate-risk patients. Due, in part, to its minimally invasive approach, TAVI may well become a logical alternative among low- to moderate-risk patients, however longer follow-up studies are a necessity. Despite future innovations, one absolute is the need for a multidisciplinary approach, where every case is taken on its own merit and managed as such.

With continual improvements in engineering, patient selection, techniques and pending the results of the zealously anticipated PARTNER 2 and SURTAVI trials, a paradigm shift in the management of symptomatic aortic stenosis may be closer than we thought. Surgical AVR may ultimately be utilized in patients only when TAVI is contraindicated.

Summary points

- TAVI has revolutionized the approach to the management of symptomatic aortic stenosis.
- TAVI is indicated in patients at high surgical risk and in cases where surgery is contraindicated
- AVR remains the "gold standard" treatment in patients with low to moderate surgical risk.
- TAVI may be considered as an alternative method to surgical AVR following the results of the PARTNER 2 and SURTAVI trials.

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