Clinical Conundrum: Lifetime Management of Aortic Stenosis in Young Patients

Editor's Pick

For this year's edition of *EMJ Cardiology*, my editor's pick is 'Clinical Conundrum: Lifetime Management of Aortic Stenosis in Young Patients' by Kipshidze et al. This feature discusses an important issue in modern healthcare: the long-term outcomes of transcatheter aortic valve replacement (TAVR) in patients under 65. With current guidelines favouring surgical aortic valve replacement, yet more young patients undergoing TAVR; this article addresses a growing area of concern. Kipshidze et al. delves into the complexities of this evolving landscape and highlights the key challenges that remain unresolved.

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Abstract

The management of aortic stenosis (AS) in younger patients presents significant clinical challenges. While transcatheter aortic valve replacement (TAVR) offers a minimally invasive approach with favourable short- and mid-term outcomes, its long-term efficacy in patients under 65 years remains uncertain, particularly given the extended life expectancy of these patients. Current guidelines favour surgical aortic valve replacement for younger individuals due to concerns about the durability of TAVR valves. However, an increasing number of younger patients are opting for TAVR, drawn by its shorter hospital stay and reduced operative complications, revealing a disconnect between clinical practice and established guidelines. This discrepancy underscores the need for alternative strategies. Emerging technologies such as novel implant-free devices, show promise in extending valve life and delaying the need for TAVR. Additionally, ongoing research into pharmaceutical interventions, including RNA-based therapies and anti-calcification drugs, aims to slow the progression of AS. As the field evolves, there is a growing emphasis on developing strategies that balance immediate patient benefits with long-term outcomes, ultimately enhancing the quality of life and survival rates for younger individuals with AS.

This review highlights the necessity of innovative approaches tailored to the unique needs of this population, emphasising the importance of continued research and adaptation of clinical practices.

Key Points

1. Transcatheter aortic valve replacement (TAVR) is increasingly being used for younger, lower-risk patients with longer life expectancies compared to those treated at the start of the TAVR era, making long-term durability data crucial. The implications include concerns regarding lifelong coronary access, valve longevity, and the potential need for repeat TAVR procedures in the future.

2. There is a significant unmet need for innovative non-implant technologies that could delay the need for transcatheter aortic valve implantations in younger patients who are more likely to require multiple valve implants over their lifetime, or even eliminate the need for transcatheter aortic valve implantations in some patients altogether.

3. Future research should focus on valve design and materials that can enhance durability. Additionally, exploring medical therapies that utilise new drugs to slow the progression of valve degeneration and/or developing no-leave-behind technologies that may extend the time to initial operation and improve valve longevity could help address this clinical challenge.

INTRODUCTION

The number of transcatheter aortic valve replacements/implantations (TAVR/TAVI) has nearly equalled that of the number of surgical aortic valve replacements (SAVR) among patients under the age of 65 years with severe isolated aortic stenosis (AS) in the USA.[1] The substantial growth in TAVR procedures can be attributed to the growing preference to treat younger patients through minimally invasive means. In fact, growing evidence has demonstrated that patients exhibited superior outcomes during their hospital stay when undergoing TAVI as opposed to SAVR. Furthermore, TAVI was linked to reduced odds of in-hospital death, stroke, acute renal damage, and significant bleeding.[2] Although TAVI is recommended for individuals across a spectrum of surgical risk, current guidelines in the USA uphold that SAVR should be the preferred option for patients who are under the age of 65 years or those with a life expectancy of more than 20 years at the time of their valvular intervention.[3] Despite guidelines and expert consensus, the trends show a clear deviation from official recommendations, which reveals a gap in the long-term management of younger patients who undergo TAVR.[4] The implications encompass concerns regarding lifelong coronary access, the longevity of the valve, and the possibility of repeat TAVR procedures in the future. Although 5- and 10-year follow-up studies have shown positive results, there is a paucity of long-term evidence on the durability of these valves.[5-9]

DISCUSSION

While studies assessing the motivations among patients choosing TAVI over SAVR remain sparse, current evidence suggests that patients cite a desire for a minimally invasive procedure with shorter in-hospital stays.[10] Nevertheless, it remains the case that a significant number of patients continue to get the discouraging message that they do not meet the age criteria for TAVR. Individuals below the age of 65 years will probably surpass the lifespan of their transcatheter aortic valve (TAV) due to the progressive degradation of the valve tissue, necessitating further replacement. At the same time, untreated AS is associated with a substantially increased mortality risk, regardless of the severity degree.[11] Given that TAVR represents a comparatively recent therapeutic alternative, there is currently a dearth of extensive clinical investigations that can substantiate the long-term efficacy of this procedure for younger individuals necessitating numerous valve replacements.

Furthermore, regulatory bodies (under International Organization for Standardization [ISO] standards) dictate that *ex vivo* durability testing for transcatheter heart valves run for a minimum of 200 million cycles, equivalent to approximately 5 years.[12,13] Recently, the SAPIEN 3 THV (Edwards Lifesciences, Irvine, California, USA) was tested up to 1 billion cycles (equivalent to 25 years) and demonstrated promising durability results at the bench side.[14] The most extensive data on *in vivo* durability are derived from the NOTION randomised controlled trials study, which demonstrates favourable durability outcomes for both SAVR and TAVI over an 10-year period.[15] As the frequency of TAVI rises among individuals below the age of 65 years, it is important to acknowledge that the average age seen in the NOTION study was 79.1 years. In two randomised controlled trials involving individuals with moderate risk, the average age of the participants surpassed 80 years.[5,6] Nevertheless, there remains an association between the age of a patient receiving a surgical replacement of biological valves and the rate of valve failure, with younger patients experiencing a somewhat higher likelihood of accelerated valve deterioration.[16]

A prudent strategy would involve opting for open-heart surgery while considering ongoing developments in other medical technologies and therapies at the time of the procedure. However, it is important to bear in mind that the performance of redo surgery or transcatheter intervention in older individuals is not without its own inherent risks. Regrettably, the existing medical therapy for AS is presently confined to symptom management and enhancing the patient's quality of life. At the same time, TAVR treatment delays have been linked to mortality rates of 3.8% and 23.3% at 1 and 6 months, respectively, with the 2019 USA national average being around 7 weeks from intake to treatment.[4,17]

There is a significant unmet need for innovative non-implant technologies that have the potential to delay the need for TAVI in younger patients who are more likely to require numerous valve implants over the course of their lifespan, or even eliminate the requirement for TAVI in some patients entirely. It may be advantageous to reconsider the utilisation of balloon aortic valvuloplasty (BAV), a previously overlooked technology, as a temporary measure to significantly extend the effectiveness of BAV treatment until a more definitive approach can be implemented.[18,19] The function of BAV, on the other hand, is conditional on the particular clinical situation. Patients who have significant AS and a congenital bicuspid valve may be candidates for this therapy as a definitive treatment option.[18,20]

New BAV involves the application of high-pressure inflations, which may lead to the prominent occurrence of intra-leaflet fractures within calcified nodular deposits. The increased flexibility of valve leaflets may be further enhanced by the process of calcification softening. Accurate balloon sizing by the utilisation of preprocedural transthoracic echocardiography or CT is imperative in order to mitigate the potential risks associated with high-pressure inflations. It should be noted that high-pressure inflation has the potential to damage the valve with protrusion into the left ventricle and induce aortic regurgitation. A low-profile (5F) BAV device was designed for trans-radial applications, utilising high-pressure inflations. The FIM study for this device is scheduled to commence in the fourth quarter of 2024. The authors' present research focuses on exploring the application of reinforced (scoring-like) valvulotomy balloons as a viable technique for the treatment of calcified leaflets. These balloons have the potential to alter calcified leaflets by reducing inflated pressure requirements, hence improving safety. Furthermore, it is possible that the utilisation of modified intravascular lithotripsy catheters could potentially offer benefits in the treatment of deteriorated valves.[21]

There exists the potential for the application of several anti-restenotic drugs, including sirolimus, paclitaxel, dexamethasone, colchicine, antifibrotics, anti-calcification substances, matrix metalloproteinases, and new anti-inflammatory chemicals, to have the potential to be used in BAV coating.[22-25] Furthermore, an option for balloon

valvuloplasty is the utilisation of a novel device called Leaflex (Pi-Cardia, Rehovot, Israel) in patients who may be considered too old or feeble for TAVI, or even improve the outcomes of TAVI in patients who have severely calcified aortic valves and bicuspid aortic valves. The Leaflex device is a transfemoral transcatheter tool that employs a pair of mechanical components to assess and score calcification in the aortic valve. The system comprises a patented expander that is inserted into the left ventricular outflow canal, elevating the aortic leaflets to make contact with the frame. Additionally, there are three scoring arms positioned in the aortic root. In essence, the process involves the alteration of leaflet motion through the deliberate exertion of force, which effectively scores the calcification present inside the leaflets while ensuring that the calcium particles do not get embolised. One notable benefit of this approach is the facilitation of enhanced mobility of the valve leaflets, rendering them more flexible and expanding the flow area.[26]

Beyond surgical intervention, current pharmaceutical therapies are incapable of reversing the stenosis of the aortic valve. In recent times, there has been significant progress in establishing the connections between inflammation and AS, as well as between lipoprotein(a) and PCSK-9.[27-29] Multiple research groups, including the author's, are actively engaged in studying the primary and secondary prevention of AS. Although lipoprotein(a) has been associated with the calcification of the aortic valve, the progression of AS is a gradual process that spans many years. The implementation of clinical studies aimed at preventing or delaying the evolution of AS would likely entail greater time and financial resources compared to trials focused on atherosclerotic cardiovascular disease, which typically observe benefits within a maximum follow-up period of 5 years or less. The CHIANTI study is currently in progress aiming to obtain primary endpoints by the year 2025. In addition, the authors' research group is currently engaged in the development of therapeutic RNA and/or peptide vaccines aimed at mitigating chronic inflammation, which is recognised as a primary catalyst for the degradation of valve leaflets.[30-33]

Most recently, there has been promising research on the use of osteopontin to stabilise and slow amorphous calcium phosphate, which is believed to be a primary driver of human aortic valve leaflet calcification.[34]

The field of focused ultrasound is experiencing rapid advancements, offering a non-invasive therapeutic approach that has promise for enhancing patients' quality of life and reducing healthcare expenses associated with calcifications on heart valves. Pulsed cavitation-focused ultrasound, also known as histotripsy, is employed to administer mechanical energy to the calcium deposits on the valve at the point of beam convergence. This intervention enhances blood circulation and augments the functionality of the valves in terms of their capacity to open. This procedure bears resemblance to lithotripsy, a medical intervention commonly employed for the treatment of kidney stones. The primary indication is for individuals diagnosed with severe and symptomatic AS.[35,36]

Returning to surgical interventions, the existing choices for prosthetic valve replacement, including bioprosthetic and mechanical heart valves, are constrained by the occurrence of structural valve degeneration, which necessitates further surgical intervention or the lifelong administration of anticoagulant medications. Over the past decade, many strategies, such as advanced calcium-blocking tissue technology, have been proposed to potentially enhance the durability of valve leaflets and decrease the need for further interventions.[37-41] It should be noted that recent research investigating the mechanisms of TAV degeneration demonstrated TAV function can be severely impacted by both non-calcific and calcific mechanisms of tissue degeneration. This study highlights the importance of considering non-calcific factors in TAV degeneration.[14] Interestingly, Sato et al.[42] provide a histopathological evaluation of one THV that had been explanted 2 months after a TAVR procedure. The THV was severely deteriorated and showed microvessels originating from the animal pericardial tissue used for the bioprosthetic leaflets.

The new growth of blood vessels, known as neovascularisation, indicated a possible reason for the valve's dysfunction.[42]

Additionally, a number of novel polymer technologies have been devised with the aim of developing an optimal alternative for polymeric heart valve substitutes, thereby addressing the aforementioned drawbacks.[43,44]

The utilisation of drug-eluting heart valves in clinical practice remains limited and not yet widespread. Although drug-eluting stents and drug-eluting balloons have been widely used in cardiovascular procedures, the utilisation of drug-eluting technology in heart valves is now being explored and developed. The drug-eluting heart valve concept entails the integration of pharmaceutical substances within the valve structure or coating to mitigate concerns such as calcification, pannus formation, tissue degeneration, or inflammation, which may result in valve dysfunction or failure in the long run. The medicine would seek to mitigate these effects and maybe extend the longevity of the valve. Numerous preclinical investigations are currently being conducted to examine the viability and possible advantages of drug-eluting heart valves. Recently, first-in-human results were reported with nitric oxide coated TAVR.[45]

Various procedures are now being investigated, encompassing the utilisation of coatings for local drug delivery, tissue engineering methodologies, and gene therapy techniques. There continues to be progress in the realm of TAVR, with the investigation of drug-eluting TAVR valves currently an area of active exploration. The potential advantages associated with drug-eluting TAVR would be comparable to those observed with drug-eluting stents or drug-eluting balloons. These advantages entail the targeted administration of medication to enhance the long-term efficacy and robustness of the implanted device. The application of drug-eluting technology in TAVR has the potential to mitigate issues associated with valve degeneration, calcification, and inflammation, which can adversely affect the long-term durability and functionality of the prosthetic valve.

The administration of medication directly to the valve has the potential to mitigate or postpone these issues, enhancing the durability of the valve and diminishing the necessity for subsequent procedures. Nevertheless, it is crucial to acknowledge that the advancement and clinical implementation of drug-eluting TAVR is currently in the exploratory phases.

CONCLUSION

With the increasing use of TAVR among persons under the age of 65 years, the optimal care of these patients has received less attention. Furthermore, as life expectancy in most high-income nations has increased since the introduction of these valves, the subject of long-term durability of implantable valves, whether surgical or transcatheter, has become more relevant for a variety of age groups. Future research should look into design and materials that can help these valves last longer. Thus, medical therapy research utilising new medicines to decrease the evolution of valve degeneracy and/or no-leave-behind technologies that may lengthen the time to index operation as well as improve valve longevity may aid in resolving this clinical quandary.

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