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Severe aortic stenosis in the young, with or without bicuspid valve: is transcatheter aortic valve implantation the first choice?

Igor Belluschi[1], Nicola Buzzatti[1], Alessandro Castiglioni[1], Michele De Bonis[1], Matteo Montorfano[2], and Ottavio Alfieri[1]*

[1]*Department of Cardiac Surgery, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy*
[2]*Department of Interventional Cardiology, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy*

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During the last decade, transcatheter aortic valve implantation (TAVI) has represented a valid alternative to surgical aortic valve replacement in patients with aortic stenosis and elevated surgical risk. Recent randomized clinical trials reported excellent results also for patients at low surgical risk, but in clinical practice, the mean age of the patients treated remain over 75 years, and the presence of a bicuspid aortic valve still represents an important exclusion criteria. Today, aortic valve replacement with a mechanical prosthesis remains the treatment of choice for young adults with aortic stenosis, although the desire to avoid oral anticoagulants drives more patients younger than 65 years of age towards biological prostheses. Furthermore, despite the follow-up of patients after TAVI is still limited to a few years, the opportunity of a second percutaneous treatment (TAVI-in-TAVI), extends the scope of percutaneous strategy. In the next few years, TAVI has to face many challenges to become a valid alternative to surgery in the younger patients as well.

Introduction

A recent epidemiological analysis has shown that the incidence of aortic stenosis in young adults (between 20 and 65 years) varies between 10 and 75 individuals/100 000 per year. Surgical aortic valve replacement still represents the gold standard for the treatment of severe symptomatic aortic stenosis, with long-term results well-validated in subjects of different ages. After being introduced for the treatment of inoperable or high-risk patients, thanks to the technological development that has allowed the introduction of increasingly safe and effective devices, in the last 15 years transcatheter aortic valve implantation (TAVI) has been progressively adopted in patients with reduced surgical risk. In fact, in low-risk patients undergoing TAVI with a balloon-expandable prosthesis, the PARTNER III study demonstrated a composite rate of death, stroke, and rehospitalization at 1 year lower than surgery [8.5% vs. 15.1%; absolute difference −6.6%; 95% confidence interval (CI): −10.8, −2.5; $P < 0.001$ for non-inferiority].[1] Overlapping results also emerged in the Evolut R Low Risk study for self-expanding TAVI devices (5.3% vs. 6.7% at 2 years; difference −1.4%; 95% BCI: −4.9, 2.1).[2]

Despite the decrease in the overall operating risk profile, the vast majority of patients undergoing TAVI has so far remained characterized by advanced age and a reduced life expectancy, as evidenced by the Guidelines in place until 2019 which favoured the transcatheter approach compared to surgery over 75 years.

Only recently, in light of the good results obtained in the context of low risk, the application of TAVI in younger patients with greater life expectancy is becoming increasingly concrete.[3] Similarly to coronary angioplasty, TAVI promises patients minimal invasiveness, the absence of

*Corresponding author. Email: alfieri.ottavio@hsr.it

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anticoagulant therapy, and the possibility of a percutaneous reintervention. However, there are several aspects of TAVI that are still unclear, which in the context of young patients with long life expectancy become crucial.

Surgery in the young

Aortic valve replacement for aortic stenosis in a young patient is one of the simplest operations in cardiac surgery, with a low mortality rate and complications. However, it is known that aortic valve replacement *per se*, regardless of the type of prosthesis adopted, leads to a reduction in life expectancy compared to the general population.[4] This phenomenon can be explained in large part by the 'intrinsic' long-term complications of prostheses: degeneration and reintervention for bioprostheses; while thrombosis vs. bleeding for mechanical valves.

Over the years, there has been a continuous expansion of the use of biological prostheses in increasingly younger patients, in order to avoid oral anticoagulant therapy.[3] This trend was also confirmed by data: results from the most recent and largest study available, on over 25 000 patients, confirm a reduced mortality rate with the use of mechanical prostheses in an aortic position compared to the biological one, only up to 55 years of age.[5]

It should also be remembered that all prostheses (mechanical and biological) can be subject to other common problems that can negatively impact long-term results, such as the prosthesis–patient 'mismatch' and infectious endocarditis.

First TAVI results in patients <75 years of age

The most recent randomized clinical trials have considered low-risk patients undergoing TAVI, but in most cases, they are still patients with an average age of 75–80 years (*Figure 1*).

The evidence available in the literature in younger patients are still scarce and inconclusive, due to the small number of patients treated and the absence of long-term data. Some sporadic cases of TAVI in patients even in their 20s are already available with good results, but with follow-up of only 1 year. A retrospective and 'propensity matched' analysis of 2018 compared the in-hospital results of 528 patients aged <65 years undergoing TAVI with those of similar patients undergoing surgery. In this study, mortality rates (2.7% vs. 3.2%, $P = 0.12$) and stroke (0.57% vs. 1.76%, $P = 0.24$) were similar; however, in the TAVI group, there was a greater number of pacemaker implants (8.1% vs. 4%, $P = 0.02$).[6] However, despite encouraging data, the follow-up duration of the few published studies still remains limited to 1 year.

Are we ready for TAVI in young people

The aspects that remain open today and that represent cause for concern towards the expansion of TAVI in the young can be grouped into three macro-categories:

- Acute results
- Durability
- Bicuspid valves

Acute results?

Despite the great improvement over the years, the immediate results of TAVI remain somewhat 'imperfect' compared to surgery. Various degrees of paravalvular leaks (PVLs) still affects many TAVI patients. Although this 'modest' regurgitation has been commonly considered irrelevant in the high-risk elderly patients treated so far, its evolution and impact in patients with long life expectancy are unknown. Recently also the 'landmark analyzes' over

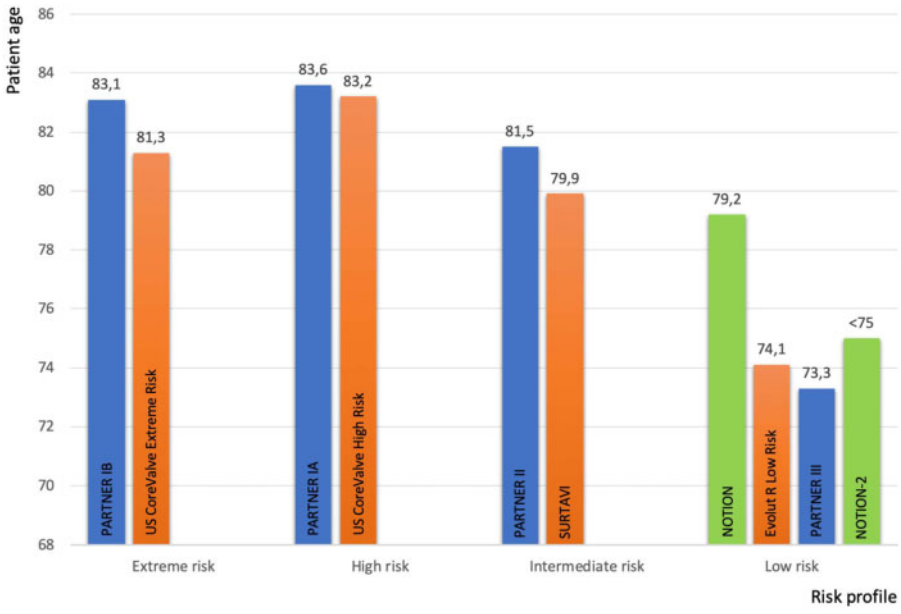


Figure 1 Risk profile and mean age of randomized TAVI patients in comparison. The graph represents the risk profile (on the abscissa axis) and the average age (ordinate axis) of the TAVI patients enrolled in the main randomized studies. As can be seen, in all studies (even in low-risk ones), with the exception of NOTION-2 (which enrolls patients aged <75 years), the average age of the subjects remains high.

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Table 1 Promises and caveats of TAVI in young patients

Promises	Caveats
Less invasivity	Residual aortic regurgitation (PVLs)
Less patient–prosthesis mismatch	Conduction disorders
No anticoagulant	Durability
Repeatability (TAVI-in-TAVI)	Repeatability (TAVI-in-TAVI)

2 years of PARTNER 2 (intermediate-risk patients treated with old-generation prostheses), have underlined that in order to obtain a survival similar to surgery it was important not to leave residual aortic insufficiency after TAVI.[7]

Similarly, a significant number of patients still have conduction disorders (from new-onset left bundle branch block to advanced blocks with the need for pacemaker implantation).[8] The long-term consequences of these drawbacks after TAVI in young subjects are still to be confirmed, however, the data currently available seem unfavourable in terms of progression towards more advanced conduction blocks, left ventricular dysfunction and mortality.

It must be underlined that currently the type of implanted prosthesis has an important impact on these complications and that technology, together with the adequate selection of patients, has the potential to be able to determine a further improvement, both from the point of view of PVLs, and of conduction disturbances (*Table 1*).

Durability

The durability of bioprostheses implanted through transcatheter procedures remains an unknown to date and it will take several years before certain results can be obtained in this regard.

Recently, the flourished debate about the durability of TAVI has underlined how in the past, especially in surgical experiences, too often the heterogeneity of the definitions used to evaluate the long-term results of aortic valve replacement does not allow to accurately evaluate the real 'degeneration' of bioprostheses and made comparisons difficult. To overcome this need, in 2017 a Consensus Document was published by the European Society of Cardiology (ESC), European Association for Cardio-Thoracic Surgery (EACTS), and European Association of Percutaneous Cardiovascular Interventions (EAPCI), to define the durability of a valve prosthesis.[9] In this document, structural valve deterioration (SVD) is defined as the irreversible intrinsic changes of the prosthesis (such as perforations, calcifications of the cusps etc.) that lead to degeneration and/or haemodynamic dysfunction, determining stenosis or valve insufficiency. In contrast, the term bioprosthetic valve failure should be used to consider the clinical manifestations.

In the past, numerous studies have been published showing excellent results in terms of haemodynamics and durability of TAVI bioprostheses with a follow-up of almost 5 years.[7] Furthermore, in a large meta-analysis on over 8000 patients, Foroutan *et al.*[10] reported that prosthetic degeneration is infrequent in the first 5 years after TAVI (28/10 000 patients/year). Finally, in a group of 241 patients treated with TAVI, Blackman *et al.*[11] reported a severe SVD rate of 0.4% ($n=1$) and moderate SVD of 8.7% ($n=21$) at almost 6 years of follow-up. However, it should be emphasized that these first data relating to the durability of the TAVI concern patients with an average age of 80 years, so the impact of percutaneous bioprosthetic degeneration in young subjects has yet to be truly clarified, although, similarly to what happens for surgery, it is legitimate to hypothesize that the faster metabolism of young people could speed up SVD even in TAVI. In addition, as underlined in the work by Capodanno *et al.*,[9] we will have better clarifications on the durability of bioprostheses—both surgical and percutaneous—, when we comply with the recently introduced definitions, preferring the term of bioprosthesis failure, thus avoiding the overestimation due to patients with asymptomatic prosthetic degeneration.

It should also be considered that an intervention with aortic bioprosthesis at a young age implies the need, in most cases, to subsequently perform other procedures (percutaneous or surgical) to treat the degeneration of the valve or for other indications (e.g. coronary or others).

TAVI-in-TAVI procedures have already been performed in a very limited number of cases,[12] but with the expansion of transcatheter technology in patients with longer life expectancy, they are expected to increase in the coming years. Theoretically, depending on the age of the patient, it is possible to speculate repeated TAVI procedures that could allow to avoid the use of mechanical prostheses in case of cardiac surgery or even to never have the need for surgery (*Figure 2*).

However, in addition to the previously discussed problem of durability, there are other important aspects that must be taken into consideration and which could make it difficult or inadvisable, and in some cases impossible, to repeat TAVI procedures in the same patient.

(1) *Haemodynamics*: The positioning of a second or third transcatheter prosthesis within the previous degenerate valve, inevitably leads to the reduction of the valve area ('Effective Orifice Area'), with the consequent risk of prosthesis–patient 'mismatch' and the impossibility in supporting optimal haemodynamics.

(2) *Coronary*: While normally access to the coronary arteries after TAVI is maintained through the stent which is 'free-flow', in the case of TAVI-in-TAVI the new prosthesis will stretch and squeeze the flaps of the previous device along its stent, covering it and preventing coronary catheters from crossing it. This mechanism can compromise both perfusion and access to the coronary arteries, but the exact prevalence of the problem remains to be clarified,[13] depending on both the size of the native aorta and the device implanted first.

(3) *Clampability and post-TAVI aortotomy*: Finally, it is still debated by the scientific community whether the presence of TAVI prostheses with a long and bulky stent can make any aortic manipulation difficult in case of surgery.

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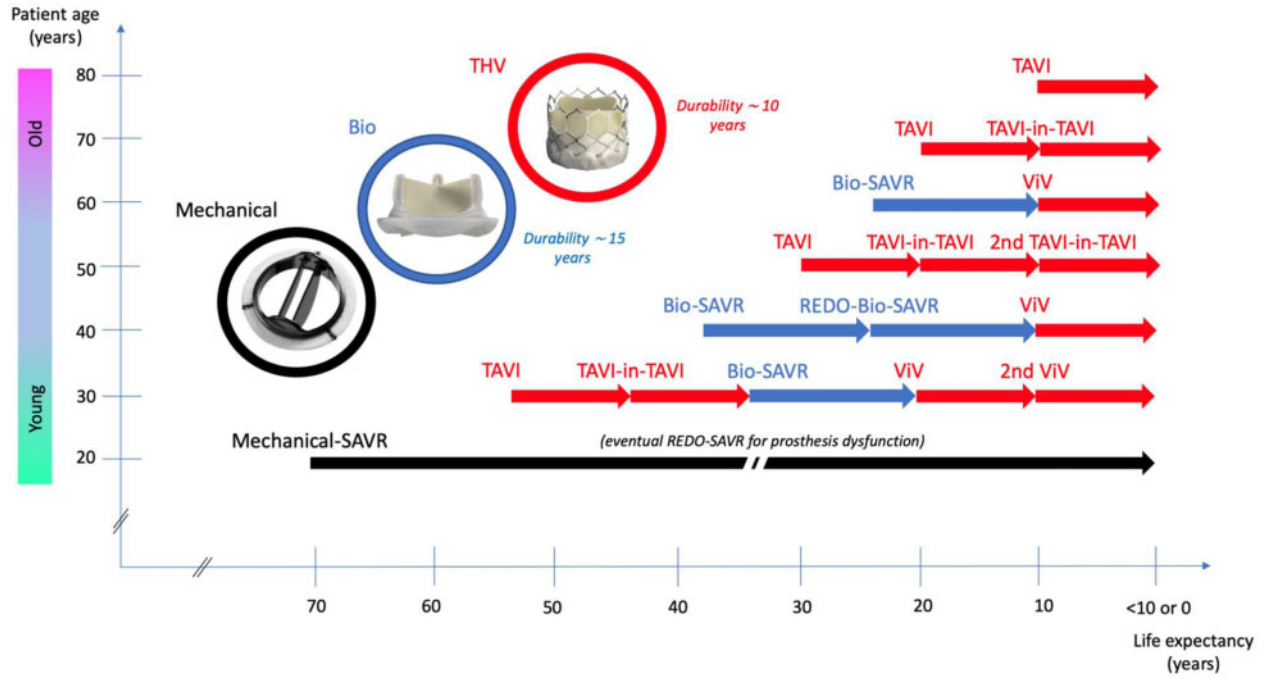


Figure 2 Surgical vs. percutaneous strategy. The graph shows the different strategies (surgical and percutaneous) in the treatment of aortic stenosis in young and elderly patients. With an expected durability of approximately 10 years for transcatheter prostheses (THV, transcatheter heart valve), in young patients the possibility of a single or double TAVI-in-TAVI (in red) could theoretically replace the surgical strategy of valve replacement with mechanical prosthesis (in black) or biological ones (in blue) followed by reintervention.

Bicuspid aortic valve

With decreasing age, the incidence of congenital bicuspid valve increases, i.e. the most common reason for aortic stenosis in young subjects. Indeed, in patients 75 years of age suffering from aortic stenosis, the incidence of bicuspid valve appears to be high (about 30–50% from autopsy series). Randomized studies on TAVI have always excluded patients suffering from bicuspid valve, whose intrinsic anatomical anomaly would have been an important confounding factor. Bicuspid valve also represents a continuum of different anatomical valve phenotypes to which various clinical correlates and procedural results correspond. In clinical practice, bicuspid valve determines greater technical complexity than tricuspid valve to perform a TAVI: bicuspids are often larger valves, with a high amount of calcium, and which typically cause an elliptical and/or asymmetrical expansion of the prosthesis for which the correct measurement and implant height are still debated, also associated with an intrinsic weakness of the aortic wall. For these reasons, a more careful selection of patients and of the device are fundamental to obtain good results.

In a 2018 meta-analysis of 13 studies involving a total of 758 patients, Reddy *et al.*[14] showed that TAVI in patients with bicuspid aortic valve is not associated with an increase in short-term mortality (3.7%; 95% CI 2.1–5.6%), which appeared comparable with that of patients with tricuspid valve. However, moderate–severe PVL and pacemaker implantation rates were relatively high (12% and 18%, respectively).

Similarly, also in the recent study by Makkar *et al.*,[15] from the comparison between 2691 TAVI patients with bicuspid valve and as many with native tricuspid valve, it emerged that there are no differences at 1 year in terms of mortality [10.5% vs. 12%; hazard ratio (HR) 0.90; 95% CI 0.73–1.10; $P = 0.31$] and PVL (3.2% vs. 2.5%; aRD 0.7%; 95% CI −1.3, 2.7), despite a higher surgical conversion rate (0.9% vs. 0.4%; aRD 0.5%; 95% CI 0–0.9) and 30-day stroke (2.5% vs. 1.6%; HR 1.57; 95% CI 1.06–2.33; $P = 0.02$) in the bicuspid group.

Furthermore, recent studies have shown that an asymmetric expansion of the valve stent could be associated with an increased risk of subclinical thrombosis. This condition, in some cases addressed with anticoagulant, manifests itself as thickening of the valve cusps visible on computed tomography scan and can subsequently evolve causing a reduction in motility of the flaps, up to a proper prosthetic degeneration. In addition, an alteration of the geometry of the prosthesis could affect its haemodynamics and, consequently, its long-term durability.

Finally, it must be emphasized that many of the young patients with bicuspid aortic valve suffer from valve insufficiency rather than stenosis, in some cases also associated with dilatation of the ascending aorta. These latter aspects pose further ‘anchoring’ and indication difficulties for which there are not yet sufficient data to recommend the use of the TAVI with respect to surgery.

Therefore, bicuspid aortic valve does not represent, by itself, a contraindication to TAVI, but some specific anatomical features could be (‘sizing’, aneurysm of the

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ascending aorta, etc.) and therefore a careful selection is very fundamental in this context.

Conclusions

In recent years, TAVI has provided increasingly encouraging results until it can be considered a valid solution, equal or superior to surgery, for patients adequately selected on the basis of anatomy, suffering from aortic stenosis with limited life expectancy.

The lack of long-term data, however, still represents an imponderable, which currently limits the safety with which TAVI can be recommended as a first choice in young patients with long life expectancy and without contraindications to surgery. Selected cases, based on the specific anatomy, clinical characteristics, and patient awareness are possible, but in this context, TAVI represents today rather a bet.

Conflict of interest: none declared.

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