Chapter

Valve-in-Valve Transcatheter Aortic Valve Replacement: Challenges for Now and the Future

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Abstract

The recent years have seen a huge expansion in the number of bioprostheses implanted, and this number is likely to increase further in the future. This is likely to lead to a pandemic of patients requiring reoperation/re-intervention for structural deterioration of the valve. Valve-in-valve transcatheter aortic valve replacement (ViV-TAVR) has become a safe and effective alternative to redo aortic valve surgery and has gained approval for use in high-risk patients with prohibitive operative risk. ViV-TAVR is a complex procedure requiring rigorous planning, technical expertise and patient anatomical appreciation. In this chapter, we examine the evidence supporting the use of ViV-TAVR along with the primary technical issues surrounding this procedure such as: elevated postprocedural gradients, coronary obstruction and valve-related thrombosis. TAVR use is also expanding towards an increasingly young patient profile with extended life expectancy, likely to outlive the implanted bioprosthesis. We therefore also examine the huge current challenge of establishing what is the best lifetime strategy for the management of aortic valve disease in younger patients.

Keywords: transcatheter aortic valve replacement, valve-in-valve, structural valve deterioration, bioprosthetic valve failure, redo surgical aortic valve replacement

1. Introduction

The global burden of aortic valvular disease continues to rise due to an increasingly aged population [1]. The traditional treatment of aortic valve disease involved surgical aortic valve replacement (SAVR). However, with the arrival of transcatheter aortic valve replacement (TAVR), the therapeutic landscape has dramatically changed. SAVR is often precluded in patients at a very high risk for surgery, for example, frailty, extreme obesity, porcelain aorta, severe pulmonary hypertension, severe right ventricular dysfunction, severe liver disease, severe lung disease, poorly controlled diabetes and impaired renal function [2]. TAVR's indication has now been expanded to intermediate and low-risk patients [3]. This is based on a series of clinical trials comparing TAVR with SAVR [4–9]. Thus, TAVR is now approved for all patient risk profiles, representing a therapeutic option for all patients regardless of age [3].

However, in young, low-risk patients with severe aortic stenosis, current guidelines recommend shared decision making, centred around patient preferences and beliefs [10, 11].

Of note, recent years, have seen an ever-increasing number of bioprostheses being implanted [12, 13]. More than 85% of implanted SAVRs are bioprosthetic [14]. This will inevitably lead to an enlarging population and potential future pandemic of patients requiring reoperation/reintervention for structural valve deterioration. Valve-in-valve transcatheter aortic valve replacement (ViV-TAVR) is a safe and effective alternative to redo SAVR and is currently approved for higher-risk patients deemed inoperable.

In this chapter, we examine the literature in detail and study the major reported technical issues with ViV-TAVR, the evidence supporting its use and the critical issue of what is the current optimum lifetime treatment strategy for aortic valve disease, particularly in younger patients. The advent of wider TAVR implantation in increasingly younger patients, having a longer life expectancy than the expected longevity of the bioprosthesis, has mandated a focused discussion of this issue. This is because the primary aortic valve intervention significantly influences subsequent valve therapies and what is best strategy, if indeed there is a single best strategy, is not yet established.

1.1 Structural valve degeneration

Bioprosthetic valve dysfunction is simply categorised as either (A) non-structural valve deterioration: valve thrombosis or endocarditis, paravalvular regurgitation, patient-prosthesis mismatch, *or* (B) structural valve deterioration: irreversible permanent degenerative intrinsic valve alterations [15, 16].

Of note, there is a wide variation in structural valve deterioration definition in the literature, leading to similar variations in reported valve failure incidences. The majority of SAVR studies define valve failure based on the need for reintervention. This likely underestimates the true incidence of structural valve deterioration, which is heavily dependent on manufacturer and prosthesis type.

2021 Valve Academic Research Consortium 3 (VARC-3) guidelines use 3 stages to define bioprosthetic valve failure: (1) any bioprosthetic valve dysfunction with clinically expressed criteria dysfunction, (2) valve intervention and (3) valve-related death [16, 17].

The optimum treatment of structural valve deterioration is yet to be defined and is likely to be bespoke and personalised according to anatomical, original valve- and patient-risk-related criteria. Approaches broadly compete between (A) traditional or (B) minimally invasive redo-SAVR and (C) ViV-TAVR valve.

1.2 Valve in valve TAVR versus redo SAVR: the evidence

There are no randomised controlled trials studying the best treatment of structural valve deterioration. There is also an obvious scarcity of long-term data on ViV-TAVR. Most studies are less than 5 years' duration, and there are no head-to-head comparison studies with redo-SAVR.

At present, ViV-TAVR is the treatment of choice for patients with structural valve deterioration considered high risk for redo-SAVR. However, redo-SAVR remains the first choice among patients at low-intermediate surgical risk unless unfavourable anatomies are present, for example, calcified aortic root or hostile chest.

Several meta-analyses demonstrate lower incidence of post-operative complications and 30-day mortality and similar 1-year and mid-term mortality rates for ViV-TAVR versus redo SAVR [18–20].

Pompeu et al. analysed 12 studies with 16,207 patients, comparing ViV-TAVR with redo-SAVR, published between 2015 and 2020. In their pooled analysis, ViV-TAVR was associated with significantly lower rates of 30-day mortality, major bleeding and shorter hospital stay. However, patients receiving ViV-TAVR were 4 times more likely to have severe patient prosthesis mismatch [18]. No difference in mortality was seen at 1 year. Thandra et al. analysed 9 observational studies with 2891 patients and a mean follow-up of 26 months. They too demonstrated significantly lower 30-day mortality, bleeding and length of stay but higher post-operative gradients with ViV-TAVR compared with redo-SAVR [19]. Saleem et al. analysed 11 studies including 8326 patients and showed similar findings. At 30-days, the risk of all-cause mortality, cardiovascular mortality and major bleeding were significantly lower with ViV-TAVR. At up to a 5-year follow-up, no significant difference in all-cause mortality, cardiovascular mortality and stroke was seen. However, again, ViV-TAVR showed a higher risk of patient prosthesis mismatch and greater transvalvular pressure gradients [20]. Hirji et al. looked at more than 3000 US patients, comparing ViV-TAVR versus redo-SAVR using the National Readmissions Database. Using propensity score matching, VIV-TAVR showed superiority over redo-SAVR in terms of 30-day mortality, 30-day morbidity, bleeding and hospital length of stay [21].

In the absence of good randomised control trials, later published meta-analyses draw similar conclusions [22–24]. Raschpichler et al. analysed 15 studies and 8881 patients; 50.2% underwent ViV TAVR and 49.8% redo-SAVR. Short-term mortality was 2.8% with ViV-TAVR compared with 5.0% with redo-SAVR, and again, mid-term mortality did not significantly differ (maximum follow-up 5 years). Again, significant, prosthetic valve regurgitation was 4 times more likely with ViV-TAVR, and severe patient prosthesis mismatch was 3 times more likely [22].

Formica analysed 12 studies with 3457 patients. The redo-SAVR group included 1783 patients and ViV-TAVR 1764. Redo-SAVR showed a higher incidence of all-cause mortality within 30 days with no difference observed between 30 days and 1 year and at a 5-year follow-up [23].

Bruno et al. analysed 11 studies with 8570 patients, 4224 undergoing ViV-TAVR and 4346 redo-SAVR. The studies focussed on intermediate-high-risk patients. 30-day all-cause and cardiovascular mortality were significantly lower with ViV-TAVR. At a mean follow-up of 717 days, there was no mortality difference between techniques. Major bleeding and new-onset atrial fibrillation were significantly lower with ViV-TAVR [24].

1.2.1 Limitations

These meta-analyses include non-randomised retrospective studies and are vulnerable to the inherent weaknesses of observational data. Therefore, results are to be interpreted with caution. In addition, clinically relevant and important valve-associated factors such as size, design and the precise manner of deterioration were rarely analysed and are of vital importance.

Other limitations include limited follow-up (<1 year in many studies), small sample sizes, a lack of randomisation and the inclusion of many retrospective observational studies. The lack of clear reported selection criteria in many included studies as well as a wide variation of inclusion criteria among studies are other limitations.

This gives rise to the obvious negatives of selection and allocation bias. As mentioned earlier, lack of data relating to degenerated prosthesis type; implanted bioprosthesis type, for example, stented, stentless and rapid deployment; the type of implanted TAVR (self-expanded versus balloon-expandable) and TAVR approach route renders meaningful scientific hard conclusions difficult to make. Randomised control trials with longer follow-ups and large multi-centre registries are essential to better analyse and define the differences in survival between these two procedures.

The overall broad conclusion of these large meta-analyses is that ViV-TAVR demonstrates better short-term mortality compared with redo-SAVR, but mid-term mortality is similar. Higher rates of severe patient prosthesis mismatch, high transvalvular gradients and post-procedural aortic regurgitation are associated with ViV-TAVR. Given the likely selection/allocation bias in the included studies and limitations mentioned earlier, authors universally advocate an adequately powered multi-centre randomised control trial with sufficiently long follow-up.

In a recent retrospective, propensity score-matched, multi-centre UK study, 911 patients were studied between 2005 and 2021. 125 pairs for analysis were created with a mean age of 75 years. In-hospital mortality was 7.2% for redo-AVR versus 0% for ViV-TAVR ($p = 0.002$). Intensive care unit and hospital length of stay and post-operative complications were significantly reduced with ViV- TAVR, but rates of moderate aortic regurgitation at discharge and elevated post-procedural gradients were increased [25]. Median follow-up was 4.2 years for redo-AVR and 3.1 years for ViV-TAVR, and no difference in mid-term survival was found in discharged patients. **Table 1** summarising the publications comparing ViV-TAVR with redo-SAVR.

1.3 Bioprosthetic valve failure

1.3.1 Pre-disposing factors

Minimising the chances of bioprosthetic valve failure is critical, and modifiable factors should be addressed to the maximum if possible, to avoid/retard structural valve degeneration. Patient characteristics, comorbidities, the type and size of implanted valve contribute to valve failure. Ochi et al. identified multiple risk factors for structural valve degeneration. Presence of patient prosthesis mismatch, sub-coronary implantation technique, absence of anti-calcification preparation, concomitant coronary artery bypass graft surgery, small valve sizes, high post-implantation gradients and renal disease were all implicated.

Meta-analysis identified younger age, increased body surface area, smoking and patient prosthesis mismatch as significant drivers of structural valve degeneration [26].

1.3.2 Patient-prosthesis mismatch

Discussion relating to patient prosthesis mismatch is complex and extensive and is not the focus of this chapter. However, review of the literature suggests that patient prosthesis mismatch is likely a critical factor contributing to structural valve degeneration [27]. Patient prosthesis mismatch can be and must be mitigated at the time of initial SAVR by implanting an appropriately sized valve, selecting the optimum valve design profile and/or surgical intervention to facilitate the implantation of an appropriately sized valve. Patients at high risk of significant patient prosthesis mismatch ideally should be identified pre-operatively, with the application of a targeted

Study	(n)	Outcomes	Conclusions
Pompeu et al. [18] 2021 Meta-analysis 12 studies	16,207	ViV-TAVR was associated with lower rates of 30-day mortality, permanent pacemaker implantation, major bleeding and shorter hospital stay. ViV-TAVR was associated with higher rates of myocardial infarction, and severe patient prosthesis mismatch. No difference in mortality was seen at 1 year.	ViV-TAVR is a valuable option in the treatment of degenerated aortic bioprosthesis, especially in patients with high operative risk due to a lower incidence of peri-operative complications and better early survival compared with redo-SAVR ViV-TAVR is associated with higher rates of myocardial infarction and severe patient-prosthesis mismatch.
Thandra et al. [19] 2021 Meta-analysis 9 studies	2891	30-day mortality rate was significantly lower in ViV-TAVR group. No significant difference in mid-term and 1-year mortality between ViV-TAVR and redo- SAVR ViV-TAVR group had lower 30-day bleeding rate and length of stay. ViV-TAVR had higher post-operative gradients.	ViV-TAVR should be preferred over redo- SAVR particularly in those at intermediate-high surgical risk.
Saleem et al. [20] 2021 Meta-analysis 11 studies	8326	30-day all-cause mortality cardiovascular mortality and major bleeding rate were significantly lower in ViV-TAVR group. No difference in stroke rate, myocardial infarction and permanent pacemaker rate. No differences for all-cause mortality, cardiovascular mortality and stroke rate at 6 month-5 year follow up. ViV-TAVR had higher risk of patient-prosthesis mismatch and greater transvalvular pressure gradients post-implantation.	ViV-TAVR compared to redo-SAVR is associated with significant improvement in short-term mortality and major bleeding. For mid to long-term follow up, the outcomes were similar for both groups.
Hirji et al. [21] Multicentre US National database propensity-score matched analysis	6815	ViV-TAVR showed lower 30-day morbidity, and major bleeding. ViV-TAVR displayed shorter length of stay.	ViV-TAVR appears to confer an advantage over redo-SAVR in terms of 30-day mortality, morbidity, and bleeding complications in high-risk patients. Further studies are warranted to benchmark in low- and intermediate-risk patients and to adequately assess longer-term efficacy.
Raschpichler et al. [22]	8881	Short-term mortality was 2.8% in ViV-TAVR group compared to 5.0% redo-SAVR group (P = 0.02).	Better short-term mortality after ViV-TAVR compared with redo-SAVR. Mid-term mortality was similar between groups.

Study	(n)	Outcomes	Conclusions
2022 Meta-analysis 15 studies		Midterm mortality did not differ between groups. Rate of acute kidney injury was lower following ViV-TAVR. Prosthetic aortic valve regurgitation and severe patient-prothesis mismatch occurred more frequently after ViV-TAVR. No significant differences between groups with respect to stroke, myocardial infarction and pacemaker implantation	An adequately powered multi-center randomized clinical trial with sufficiently long follow-up in patients with low-to-intermediate surgical risk is warranted.
Formica et al. [23] 2023 Meta-analysis 12 studies	3547	Redo-SAVR group showed higher 30-day all-cause mortality. No mortality difference was observed between 30 days and 1 year. From 1 to 5 years redo-SAVR showed a survival benefit over ViV-TAVR.	ViV-TAVR shows significantly lower mortality within 30 days. This advantage disappeared between 30 days and 1 year and reversed in favour of redo-SAVR 1 year after the intervention.
Bruno et al. [24] Meta-analysis 11 studies 2022	8570	30-day all-cause and cardiovascular mortality were significantly lower in ViV-TAVR group. After a mean follow-up of 717 (180–1825) days, there was no mortality difference between the two groups. Risk of stroke, myocardial infraction, major vascular complications, and permanent pacemaker implantation at 30 days did not differ between groups. Major bleedings and new-onset atrial fibrillation were significantly lower in ViV-TAVR group.	In high- and intermediate-risk patients ViV-TAVR shows reduced short-term mortality, compared with redo-SAVR. No differences were found in all-cause and cardiovascular mortality at midterm follow-up.
Gatta et al. [25] 2023 Multi-centre retrospective propensity-score matched analysis	250	Mean age 75.2 years. In-hospital mortality was 7.2% (n = 9) for redo-SAVR vs 0 for ViV-TAVR, (p = 0.002). Redo SAVR patients suffered more post-operative complications: including IABP support, early re-operation, arrhythmias, respiratory and neurological complications and multi-organ failure. ViV-TAVR group had a shorter intensive care unit and	In elderly patients ViV-TAVR provides better early outcomes compared to redo-SAVR. However, there was no difference in mid-term survival between groups in patients successfully discharged from hospital.

Study	(n)	Outcomes	Conclusions
		hospital stay. Moderate aortic regurgitation at discharge and higher post-procedural gradients were more common after ViV-TAVR. Survival probabilities in patients who were successfully discharged from hospital were similar after ViV-TAVR and redo-AVR over the 6-year follow-up period.	

Table 1.
Publications comparing ViV-TAVR with Redo-SAVR.

preventative strategy to reduce the occurrence and severity of patient prosthesis mismatch. This is particularly important in younger patients and in those with depressed left ventricular function. Patient prosthesis mismatch is defined as occurring when the effective orifice area of the implanted prosthetic valve is inadequate for the patient's body surface area and activity. Patient prosthesis mismatch is defined by indexed effective orifice area/body surface area and is graded in severity as follows: none (>0.85 cm^2/m^2), moderate (0.85–0.65 cm^2/m^2), and severe (≤ 0.65 cm^2/m^2). The incidence of moderate to severe patient prosthesis mismatch following SAVR has been reported as high as 65% [28], and patient prosthesis mismatch post-SAVR is more common than no patient prosthesis mismatch [29, 30]. Increasing patient prosthesis mismatch grade is associated with a stepwise increase in long-term all-cause mortality [30]. The seriousness and clinical relevance of moderate patient prosthesis mismatch is unclear, controversial and still debated. Some studies propose that only severe patient prosthesis mismatch translates into clinically relevant harmful effects, with others proposing that even moderate severity is clinically damaging [28–31]. Severe patient prosthesis mismatch following SAVR has been shown to be associated with an increased risk of redo-SAVR by some [28] and not others [29, 30], but significantly raised readmission rates and decreased survival are clearly demonstrated [28–31].

1.3.3 Valve selection and surgical aortic root enlargement

Selection of bioprosthesis and accurate sizing is critical in the initial treatment of aortic valve disease. The largest valve that can be safely implanted is the general principle to be followed, and internal orifice diameter is of the primary importance. This should be identified and appreciated and differs between valve models and manufacturers for the same labelled valve size. The minimal prosthetic valve effective orifice area required to avoid patient prosthesis mismatch should be calculated and then a prosthetic valve model and size that fits into the patient's aortic annulus/root selected, which meets the minimum effective orifice area calculated.

A small aortic annulus may necessitate aortic root enlargement or root replacement during SAVR. During TAVR, the initial valve that provides the largest effective orifice area and the best haemodynamics is chosen. One advantage of TAVR planning is the detailed CT aortography and annulus assessment performed pre-intervention, thus facilitating optimum prosthesis selection. Aortic root intervention during SAVR should be guided by effective orifice area index and considered when falling below ≤ 0.85 cm^2/m^2, particularly in young patients. However, aortic root enlargement is performed in 10% or less of patients receiving SAVR [32].

Several surgical techniques exist to augment aortic root diameter. Detailed discussion of them is not the focus of this chapter, but more awareness of and emphasis on the principle of their use at primary aortic valve intervention. Nicks and Manouguian procedures enlarge the aortic annulus using a posterior extension of the aortotomy. The Nicks extends through the non-coronary sinus and the Manouguian through the left/non-coronary commissure with extension onto the anterior mitral leaflet [33, 34]. Closure is usually then enabled with the use of an aortic patch technique. A Konno procedure is very rarely performed in adults and involves anterior annular augmentation extending onto the right ventricle [35]. Other less common enlargement techniques are also available but are rarely used in everyday practice. Aortic root replacement during SAVR reduces rates of patient prosthesis mismatch and is safe with no added risk, but whether it improves long-term outcomes remains unproven [36, 37].

Of note, TAVR has been associated with reduced risk of patient prosthesis mismatch compared to SAVR, especially in patients with small aortic annuli, particularly in patients receiving a valve size ≤23 mm [38, 39]. SAVR with sutureless prosthesis has also shown excellent haemodynamics and similar rates of patient prosthesis mismatch to TAVR [40]. These findings and their exact future clinical relevance require further exploration and clarification. They re-highlight that valve genre/species selection as well as size, too, need careful consideration by all members of the structural heart team including the surgeon. This represents yet another critical factor when planning primary aortic valve intervention, particularly in the young and those with small aortic roots.

1.4 Technical issues associated with valve-in-valve TAVR

1.4.1 Elevated post-implantation gradients

Valve-in-Valve International Data (VIVID) Registry shows elevated post-procedural gradients and severe patient prosthesis mismatch to occur in 26.8% [41]. It is more common with balloon expandable devices compared to self-expanding devices and in surgical valves ≤21 mm. These figures apply to when the bioprosthetic valve ring fracture technique is not utilised [41]. It is suggested that only severe patient prosthesis mismatch post-ViV-TAVR may affect mortality [42]. However, it is wise to aim for as low post-procedural gradients as possible, to enhance valve durability and patient performance, particularly in patients having extended life expectancy.

Patient prosthesis mismatch is not infrequent following SAVR in patients with small anatomies and is highly relevant during the planning of reintervention for structural valve deterioration. Surgical 19 mm bioprostheses are of particular concern and display high physiological mean gradients (10–25 mmHg) [43].

ViV-TAVR is associated with haemodynamic deterioration with gradient increase ≥10 mmHg between discharge and 30-day follow-up in the STS/ACC TVT registry [44]. Understandably, patients at the greatest risk for severe patient prosthesis mismatch following ViV-TAVR were those arriving with structural valve deterioration following previous SAVR complicated by severe patient prosthesis mismatch [41, 45]. Severe patient prosthesis mismatch prior to ViV-TAVR displays higher 30-day and 1-year mortality [46]. Such clear findings again re-highlight the absolute importance of appropriate, far-sighted primary aortic valve intervention. The critical importance and complexity of post-ViV-TAVR patient prosthesis mismatch is reflected by the creation of a patient prosthesis mismatch predictive calculator by the VIVID registry [47].

Patient prosthesis mismatch following ViV-TAVR is complex and multi-factorial, and numerous contributing factors have been proposed: (A) pre-procedural—baseline patient prosthesis mismatch, stented bioprosthesis, small bioprosthesis and stenotic failure; (B) procedural—intra-annular transcatheter heart valve, deep implantation and non-fractureable valve and (C) post-procedural—structural valve deterioration, leaflets thrombosis and transcatheter heart valve-associated prosthesis-patient mismatch.

1.4.2 Positioning of valve during valve-in-valve TAVR

The choice of a supra-annular valve and a high position of implant have shown success in reducing the risk of high post-procedure gradients [48]. Better leaflet

function and haemodynamic results may be achieved using transcatheter heart valve with supra-annular valve position. Experimental in-vitro study has shown that in failed surgical 19 mm stented bioprostheses, a supra-annular implantation of a transcatheter heart valve lowers post-procedural gradients and augments effective orifice area [48]. A clinical study has shown high implantation depth inside failed bioprostheses to be a strong independent predictor of lower post-procedural gradients in both self-expanding and balloon-expandable transcatheter valves [49]. The situation is complex with variations that need to be appreciated between prosthesis types. Self-expanding valves display lower post-ViV-TAVR gradients than balloon-expandable valves especially in pre-existing severe patient prosthesis mismatch [50].

In TAVR, deep implantation strongly predicts patient prosthesis mismatch, with recommended cut-offs for high positioning for CoreValve/Evolut and SAPIEN 3 being 5 mm and 20%, respectively [51, 52]. Conversely, the optimal height for deployment for ViV-TAVR prostheses remains undefined. Elevated risk of aortic regurgitation and valve embolization are concerns surrounding higher valve implantation depth, concerns that affect different prostheses to varying degrees [53, 54].

1.4.3 Bioprosthetic valve fracture

Bioprosthetic valve fracture is proposed as another technique to ameliorate or prevent high post-procedural gradients [55]. The aim is to increase the true internal orifice diameter of the transcatheter heart valve to facilitate either a (A) larger transcatheter heart valve or (B) better expanded transcatheter heart valve to be implanted, increase effective orifice area and enhance haemodynamic function.

Importantly, not all stented valves allow fracture. For example, experimental testing reveals Abbott Trifecta and Medtronic Hancock II valves cannot be fractured [56, 57]. It follows that sutureless and stentless valves are also not suitable for fracture but can be remodelled using an over-expansion technique [58].

Bioprosthetic valve fracture is performed using high-pressure, non-compliant balloons, such as the Atlas Gold (BARD Peripheral Vascular, Tempe, Arizona, USA) and TRUE balloon (BARD Peripheral Vascular). A 60 mL syringe plus an indeflator assembly connected with a high-pressure three-way stopcock is used; under rapid ventricular pacing, the syringe is quickly emptied to inflate the balloon, then switched to cranking the indeflator to achieve high-pressure inflation [59].

Bioprosthetic valve fracture can be performed prior to, or after ViV-TAVR, but the majority is performed after. The timing of bioprosthetic valve fracture, before or after ViV-TAVR, represents an important question [60, 61]. A larger-sized prosthesis can be used with bioprosthetic valve fracture before transcatheter heart valve implant, whereas further expansion of the transcatheter heart valve itself can be performed if bioprosthetic valve fracture is performed afterwards. Prior bioprosthetic valve fracture allows the implantation of a self-expanding valve reducing sizing mismatch and allows confirmation of successful fracture prior to implantation [58–61]. However, it can induce haemodynamic instability from severe acute aortic regurgitation, necessitating post-dilation in order to improve haemodynamics. Correct sizing of the balloon, a balloon slightly smaller than the constrained segment of the self-expanding transcatheter heart valve, and positioning the balloon shoulder lower, more ventricular than the leaflet anchor position, can largely avoid this state of affairs [56].

Bioprosthetic valve fracture after ViV-TAVR is likely to allow greater transcatheter heart valve expansion and reduces the risk of haemodynamic instability from acute severe aortic regurgitation. However, possible bioprosthetic valve fracture leaflet

injury and unknown long-term effects on transcatheter heart valve durability are concerns. Other potential complications associated with bioprosthetic valve fracture include: transcatheter heart valve migration, annular rupture, debris embolization, coronary artery obstruction, leaflet tearing and accelerated degeneration with decreased transcatheter heart valve longevity [55, 56].

The minimum inflation pressures necessary for valve ring fracture differ according to the original surgical heart valve type. For surgical heart valve with metal ribbon ring (i.e. Magna and Magna Ease), the fracture threshold (18–24 atm) is greater than the surgical heart valve with a polymer ring (i.e. Biocor Epic, Mosaic, Mitroflow; 8–12 atm). In experimental settings, and most clinical cases, balloons sized 1 mm larger than the labelled valve size were used, although in clinical settings, smaller balloons have been used successfully. Balloons larger than the surgical heart valve internal orifice diameter are also able to fracture the valve, especially if a transcatheter heart valve is already implanted [62]. Recently, ex-vivo bench testing has shown that bioprosthetic valve fracture performed after transcatheter heart valve implantation improves residual gradients [63], but potential early and accelerated degeneration effects on the transcatheter heart valve remain unknown. Bioprosthetic valve fracture is a valid technique to be considered in avoiding and/or ameliorating high post-procedural gradients after a ViV-TAVR, but significant attention needs to be placed on balloon sizing and positioning to achieve optimal results. Improved expansion of the transcatheter heart valve leads to increased circularity of the transcatheter heart valve and therefore increased internal orifice diameter. An important mechanism thought to improve valve haemodynamic performance during higher implant, bioprosthetic valve fracture and post-implant dilatation during ViV-TAVR is the reduction of pinwheeling (**Figure 1**). Improved expansion of the transcatheter heart valve leads to increased circularity of the transcatheter heart valve and therefore increased internal orifice diameter. **Table 2** summarising the bench

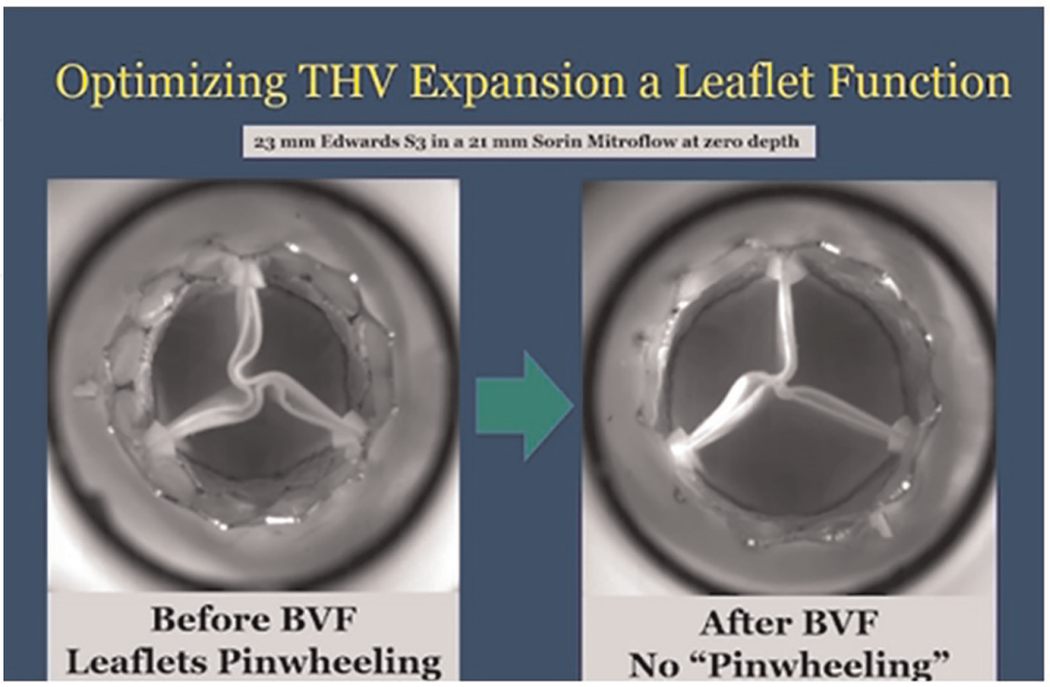


Figure 1.
Reduction of pin-wheeling effect after biological value fracture.

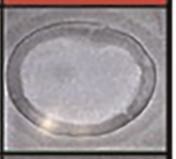
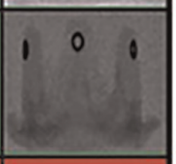
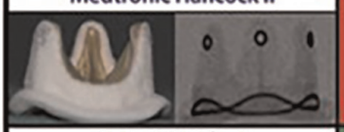
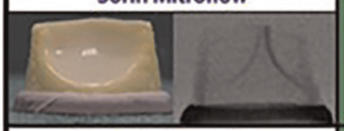
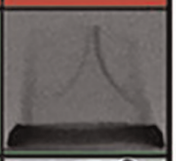
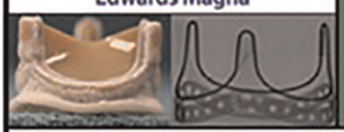
Manufacturer/ Brand	Valve Size	Bard TRU Balloon Fracture/Pressure	Bard Atlas Gold Balloon Fracture/Pressure	Appearance After Fracture
St. Jude Trifecta 	19 mm 21 mm	NO NO	NO NO	
St. Jude Biocor Epic 	21 mm	YES / 8 ATM	YES / 8 ATM	
Medtronic Mosaic 	19 mm 21 mm	YES / 10 ATM YES / 10 ATM	YES / 10 ATM YES / 10 ATM	
Medtronic Hancock II 	21 mm	NO	NO	
Sorin Mitroflow 	19 mm 21 mm	YES / 12 ATM YES / 12 ATM	YES / 12 ATM YES / 12 ATM	
Edwards MagnaEase 	19 mm 21 mm	YES / 18 ATM YES / 18 ATM	YES / 18 ATM YES / 18 ATM	
Edwards Magna 	19 mm 21 mm	YES / 24 ATM YES / 24 ATM	YES / 24 ATM YES / 24 ATM	
1. Balloons sized 1 mm larger than valve size. 2. Medtronic Mosaic and Sorin Mitroflow have no metal in ring therefore appearance after fracture unchanged.				

Table 2.
Summary of bench testing of high pressure balloon inflation to fracture the valve frame of commercial US surgical tissue valves (ATM 1/4 atmospheres; TRU 1/4 Tru dilation) [56].

testing of high-pressure balloon inflation to cause bioprosthetic valve fracture of several commercially available valves [56].

1.4.4 Coronary occlusion

TAVR is associated with a coronary obstruction incidence of 1% [64], and during ViV-TAVR, the incidence rises to 4% [65]. This complication is very serious, associated with a more than 15 times increase in 30-day mortality (~48% vs. 3%) [66]. The primary responsible mechanism is thought due to the displacement of native valve leaflets towards the coronary ostia. The obstruction may be partial or complete, and obstruction of the left coronary artery is more common (72%) than obstruction of

both ostia (20%) or the right coronary artery alone (8%). In a third of cases, coronary obstruction has delayed onset, occurring in mainly self-expanding devices due to their continued expansion after deployment. Delayed coronary occlusion is defined as obstruction that occurs after the patient leaves the operating room. It occurs in almost two-thirds of patients within 7 days but in a third of patients beyond 60 days. Proposed mechanisms include continuous transcatheter heart valve expansion, aortic root haematoma and coronary dissection and endothelization of native or surgical bioprosthetic leaflets or thrombus embolization with delayed obstruction [67].

1.4.5 Risk factors for coronary occlusion and difficult coronary re-access

Several anatomical and valve-related risk factors have been identified for this dreaded complication. These include a low coronary ostium height and small sinus of Valsalva size. In addition, the original valve type is important, with ViV-TAVR in stented bioprostheses with leaflets mounted externally and stentless surgical bioprostheses associated with a greater incidence of coronary occlusion, compared with valves with internally mounted leaflets [68].

Other risk factors include those with small anatomies, especially narrow sinuses of Valsalva and narrow sinotubular junctions, who are likely to have received a small surgical valve.

The virtual transcatheter valve-to-coronary ostium distance predicts coronary occlusion, with a shorter distance increasing the risk. An optimal cut-off level of 4 mm has been proposed [69].

Using the VIVID registry, an anatomical classification of the aortic root and valve leaflet was designed to assess the risk of coronary obstruction [70]. Three types of patients were identified: Type I with aortic valve leaflets below the coronary ostium, Type II with leaflets above the ostium in the presence of wide (IIa) or effaced sinuses (IIb) and Type III leaflets above or very close to the sinotubular junction with wide sinotubular junction/sinuses (IIIa), with effaced sinuses (IIIb) and with narrow sinotubular junction (IIIc). According to this algorithm, some procedural strategy should be considered in case of a virtual transcatheter valve-to-coronary ostium distance <4 mm as in Types IIb, IIIb and IIIc [71].

After ViV-TAVR the leaflets of the original surgical prosthesis tilt up, creating a virtual cylinder. The height of this virtual cylinder is labelled and referred to as the neoskirt [72–74]. This forms a "barrier" to future coronary access and must be appreciated carefully during ViV-TAVR planning. The size of the sinotubular junction, the location of coronary ostia in relation to the neoskirt, the type of previous surgical prosthesis as well as the present THV all influence coronary re-access, adding to the complexity of ViV-TAVR planning [58].

1.4.6 Interventions for the prevention of coronary occlusion during ViV-TAVR

1.4.6.1 Coronary stenting

In ViV-TAVR procedures with a high risk of coronary occlusion, coronary artery stenting is valuable. It is imperative that the guide wire used to access the coronary ostia does not interfere with transcatheter heart valve implantation. Low threshold for stent deployment has been recommended in high-risk candidates even in the presence of immediate adequate coronary flow, due to the not infrequent incidence of delayed coronary occlusion [75]. Numerous sophisticated coronary stenting techniques have

now evolved and are beyond the scope of this chapter [76–79]. Unfortunately, even these techniques may be associated with several complications such as the inability to withdraw the stent, mechanical stent deformation caused by bioprosthesis and inability to re-access the coronary arteries in the future. In addition, no data regarding the long-term patency of these stents are available [80].

Tarantini et al. have proposed an algorithm based on the anatomy of the aortic root and its relations with different transcatheter heart valves to predict the risk of acute coronary occlusion and feasibility of future coronary access after ViV-TAVR [72]. Using CT and coronary angiography analysis, they identified a risk plane below which the passage of a coronary catheter will be impossible after the second transcatheter heart valve and identified various situations based on a patient's anatomy and the first valve implant type, which could guide safe implantation.

1.4.6.2 Basilica procedure

Another technique developed to prevent coronary obstruction is the Bioprosthetic Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction (BASILICA) procedure [81, 82]. Valve leaflets are lacerated via an electrified guidewire, thereby facilitating blood flow to the coronary artery. Excellent success rates and low mortality in high-risk patients for coronary obstruction is demonstrated during TAVR [81, 82], but results for ViV-TAVR are awaited.

1.4.7 Valve choice and implantation

The type of transcatheter heart valve is extremely relevant, and the use of a recapturable self-expanding transcatheter heart valve can be beneficial. Clinical and angiographic assessment of coronary flow after deployment can be performed prior to complete release or retrieval of transcatheter heart valve performed in the setting of coronary occlusion to restore flow. Certain newer transcatheter heart valve devices possess clipping mechanisms enabling grasping of surgical leaflets, thus preventing coronary obstruction [83]. Intentional implantation of a smaller transcatheter heart valve or under expansion of a balloon-expandable transcatheter heart valve reduces the lateral movement of surgical valve posts and leaflets, thereby decreasing chances of coronary obstruction, as does, low-depth transcatheter heart valve implantation compared to high-depth implantation, although the risk of elevated post-procedural gradients may be increased with the latter.

1.5 Valve thrombosis

Sub-clinical leaflet thrombosis is a worry that continues to surround TAVR and ViV-TAVR. The potential need for anti-coagulation is important to patient choice and lifestyle. It is defined as the presence of reduced leaflet motion associated with CT proven hypoattenuating lesions and is associated with a greater risk of transient ischemic attacks [84]. The effects on patient outcome and long-term valve performance remain unclear [85, 86]. A variety of causes are responsible for leaflet thickening and impaired leaflet motion, including leaflet thrombosis, infection and leaflet degeneration [16]. Both TAVR and SAVR are affected by a reduction in leaflet motion, and the incidence is reported as 4% and 13%, respectively [84]. Currently, no robust randomised evidence exists guiding antiplatelet versus anti-coagulation use after ViV-TAVR.

The appropriate treatment of sub-clinical leaflet thrombosis is unclear with evidence showing that it may regress spontaneously. Up to 25% of patients on antiplatelet therapy display this phenomenon, with oral anticoagulants showing efficacy in both its prevention and regression with associated improvement in valve gradients [86–88].

Whether sub-clinical leaflet thrombosis translates into an increased number of thromboembolic neurological events is unclear, but it appears to be associated with elevated valve gradients [89]. ViV-TAVR patients are likely to be at a high risk of leaflet thrombosis due to lesser haemodynamic performance and suboptimal blood flow patterns associated with low implant depth and turbulent blood flow patterns between new transcatheter heart valve leaflets and degenerated valve leaflets [90, 91]. Valve design affects propensity towards leaflet thrombosis, with certain valve types more prone than others [88]. For this reason, a more stringent anti-coagulation regimen has been recommended following ViV-TAVR particularly in patients with elevated thrombotic risk [92]. The issue of possible anti-coagulation for ViV-TAVR is hugely important especially in patents with extended life expectancy and remains unresolved. It is likely that the need for anti-coagulation will be a patient specific, bespoke decision based on anatomical and patient-related risk-factors.

1.6 Cerebral embolism

Transient ischaemic attacks and cerebrovascular accidents are a dreaded complication of any aortic valve intervention, and cerebrovascular accident remains an independent risk factor for death after TAVR [93]. Embolisation is the primary aetiopathogenic mechanism, although the pathogenesis is well known to be multifactorial. The rate of silent embolic lesions following TAVR approaches 80%, and anything that can be done to mitigate this phenomenon is welcome. Despite this, fortunately the incidence of new, persistent clinical neurological injury is only 3–6% [94, 95]. Cerebrovascular accident rates continue to decline after TAVR, but attention is still focussed on strategies to reduce this further [86]. Luckily, the incidence of major stroke following ViV-TAVR has been reported at less than 2% [41], and recent meta-analysis shows no discernible difference in 30-day stroke rate and mortality among ViV-TAVR, TAVR and redo-SAVR [96].

The main proposed factors influencing cerebrovascular accident/transient ischaemic attack risk include atrial fibrillation, acute and sub-acute thromboembolism stemming from the transcatheter heart valve, aortic debris and device instrumentation [81]. Cerebral embolic protection devices are evolving and have been mainly studied during TAVR on native valves. They have shown efficacy in reducing cerebral emboli load, without any effect on short-term cerebrovascular accident or 30-day mortality rates or hospital length of stay [97]. Despite these findings, consideration of the use of cerebral embolic protection devices during ViV-TAVR planning is important, especially where significant instrumentation or technical difficulties are anticipated.

1.7 ViV-TAVR in the young

The patient with aortic stenosis and a long life expectancy that exceeds the durability of a bioprosthesis must be managed very carefully by the heart team, as “optimal” first intervention is paramount. Future negative and positive effects of any bioprosthesis must be anticipated and the anatomy of the aortic root appreciated fully

at first intervention. The heart-team approach is an integral part of valvular discussions in patients with severe aortic stenosis and will likely gain increasing importance in the future. A distinct shift of focus towards lifetime management is now occurring after the approval of low-risk TAVR.

Treatment options in younger patients is attracting considerable debate. For those that elect to undergo SAVR, the options for structural valve deterioration are ViV-TAVR or redo-SAVR. For those that undergo TAVR, the options for structural valve deterioration include TAVR explant with SAVR or TAVR-in-TAVR. Of huge importance, many patients with longer life expectancy or early valve failure may need a third valve intervention. A multitude of anatomical scenarios are likely to now be encountered and have to be adjusted for. In patients who are candidates for TAVR-first, transcatheter heart valve with a short frame and large open stent frame cells may be better within the context of large aortic roots and high coronary ostia, in patients with favourable anatomy for future TAVR-in-TAVR implantation [72, 98]. Whereas in patients with low coronary ostia and small aortic roots, TAVR-in-TAVR will be more problematic and therefore SAVR-first with bioprosthesis with as large an orifice as possible plus/minus aortic root enlargement may be better, followed by future ViV-TAVR [99].

1.7.1 SAVR-first strategy

As discussed in detail earlier, ViV-TAVR is associated with better short-term outcomes than redo-SAVR [100]. However, the long-term durability for ViV-TAVR is still unclear. Encouragingly, at mid-term follow-up, <10% of patients display clinically significant structural valve deterioration [101, 102]. Coronary obstruction, difficult re-access to coronaries, severe patient prosthesis mismatch and unclear need for anti-coagulation are residual ongoing concerns surrounding ViV-TAVR. The serious complication of coronary obstruction requires advanced techniques for coronary protection such as chimney stenting or BASILICA, both of which are not simple and increase procedural risk [103, 104]. Rates of paravalvular leak are low but significantly higher than redo-SAVR [19]. Intriguingly, after ViV-TAVR failure, the potential for repeat ViV therapy may be possible, if aortic root diameter allows [105].

1.7.2 Summary of factors favouring SAVR-first policy in young, low-risk patients

Young, low-risk patients often have high anatomical risks such as bicuspid aortic valves, severe annular calcification and low coronary heights. The long-term patient impact of increased permanent pacemaker use and paravalvular regurgitation, along with long-term transcatheter heart valve durability, remain unknown.

Leaflet thickening and coronary re-access remain significant concerns surrounding TAVR.

Valve choice in this group for SAVR also becomes important for the life-time management of aortic valve disease. The largest SAVR valve should be implanted, ideally not less than 23 mm with root enlargement if required. Implanting surgical valves which are prone to fracture for future optimisation of ViV-TAVR is also relevant for this sub-group of patients. The Edwards Inspiris Resilia valve has built-intechnology which enables easy expansion of the valve annulus, and other new generation “TAVR ready” surgical valves will no doubt follow from other manufactures.

1.7.3 Redo SAVR

Being more invasive, it is not surprising that short-term outcomes following redo-SAVR appear inferior to ViV-TAVR [102], but longer-term, major cardiovascular outcomes appear the same [102]. As discussed earlier, no randomised prospective data directly comparing the two techniques are available and are greatly needed. Redo-SAVR is much more invasive than ViV-TAVR but is considered by many as the more complete intervention. In well-selected patients, excellent outcomes with excellent freedom from intervention at 10 years is achieved [106–108], with less incidence of severe patient prosthesis mismatch, leaflet thrombosis and paravalvular leak [19]. Another perceived advantage is that redo-SAVR "resets" the clock and again facilitates the possibility of ViV-TAVR as a potential third intervention if needed.

1.7.4 TAVR-first strategy

1.7.4.1 TAVR explant and SAVR

As summarised above, the TAVR-first strategy in young patients has raised concerns from a wide group of people as doubts remain relating to permanent pacemaker rate, paravalvular leak rate, long-term durability of the TAVR valves and possible need for anti-coagulation [109]. These doubts are more striking when the excellent long-term durability, outcomes and robustness of the anatomical SAVR are used for comparison. TAVR explantation rates are increasing. Most cases have been performed due to unsuitability for the ViV-TAVR procedure and often need extensive surgery and are associated with mortality as high as 15% [110–112]. Sometimes, longer-term TAVR explants require extensive aortic endarterectomy and/or aortic root or ascending aortic replacement. Surgical explantation of SE TAVR valves is more complex and high risk than balloon-expandable TAVR valves. The self-expanding stent can be incorporated into the aortic root and require more extensive surgical procedures. Therefore, TAVR explant mortality rates have been elevated [110]. Surgical expertise is limited in this unique type of surgery and with time is likely to increase and may lead to improved mortality rates during surgical re-intervention for primary TAVR [111].

As mentioned earlier, another perceived advantage of this strategy is SAVR as the second intervention in anatomically suitable patients allows the third potential intervention if needed to be ViV-TAVR in a surgical valve.

1.7.5 TAVR-in-TAVR

TAVR-in-TAVR appears safe, but longer-term data and larger series are needed [113]. Concerns remain about durability and higher rates of paravalvular leak and valve thrombosis and the need for anti-coagulation [84]. In addition, it is believed that many patients will not be suitable for TAVR-in-TAVR because of anatomical constraints centred around the risk of coronary obstruction and coronary re-access [98]. The options for coronary protection are more limited with TAVR-in-TAVR and are a major concern if this strategy is to be employed widely in a large number of younger patients. Recent development of "balloon-assisted BASILICA" shows promise, but it is complex and requires more investigation and refinement [114].

One positive finding is that because of its greater ability to overexpand the transcatheter heart valve, a greater internal orifice diameter is achieved following

TAVR-in-TAVR than ViV-TAVR in a surgical valve, leading to less incidence of high gradients [113].

2. Conclusions

Redo-SAVR traditionally was the only treatment modality for failed bioprostheses. Many elderly patients are not good candidates for a second operation or do not desire to go through a redo-sternotomy. The arrival of transcatheter technology has transformed the landscape of therapy for aortic valve disease and structural valve deterioration. More than a decade after the first reported ViV-TAVR case, this procedure is now consistently performed worldwide in most patients with failed bioprosthetic valves. ViV-TAVR is safe and effective and now a credible, approved alternative treatment option for failed surgical bioprosthetic valves in patients deemed at a prohibitive risk for redo surgery. It is clear that ViV-TAVR is more complex than TAVR in native valves, with a greater risk of peri- and postprocedural complications. A super specialised, multi-disciplinary team with high-volume practice, precision pre-intervention planning, using multimodality imaging is required for optimum results.

With the increasing use of TAVR in younger patients and the increasing use/choice of bioprostheses for SAVR in younger patients, a future with a not inconsiderable population with failed bioprostheses is expected. A downward risk-drift for ViV-TAVR use is also anticipated. Therefore, the real future challenge is identifying what is the best lifetime treatment strategy for aortic valve disease for the individual, as primary intervention is of pre-dominant importance in dictating the individual's subsequent treatment course.

Further, improving ViV-TAVR outcomes is likely to centre around ameliorating and mitigating elevated postprocedural gradients, coronary obstruction risk and leaflet thrombosis. However, efforts focused upon (A) improving bioprosthesis durability/longevity and (B) optimising operative strategies for redo-SAVR are equally important and should be maintained. Providing a good solution for the failed SAVR and investigation into providing an acceptable technical answer for the failed TAVR and also for a potential third valve after a failed ViV-TAVR also merit consideration as part of the lifetime management of aortic valve disease.

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