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Review article

The evolution of aortic valve therapies - the surgeon's perspective

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Abstract During the past 10 years there has been a significant shift in how aortic valve disease is managed. The development of catheter-based therapies, specifically trans-aortic valve replacement (TAVR), has offered treatment options for patients in whom surgery (SAVR) was previously their only option. The global growth in the utilization of TAVR has been tremendous and embraced with much enthusiasm. However, such growth has not been without significant controversies and costs. The used of Heart Teams to help guide the evaluation and management of patients with aortic valve disease has been an important step in trying to match the specific therapy options with the unique patient characteristics – however, it is important to recognize that catheter-based therapies are still relatively new, in constant evolution, and potentially influenced by substantial conflicts of interest. While the role of TAVR in high or prohibitive risk patients is established, the evolving role in low and intermediate risk patients is unclear and potentially controversial given some of the concerns that the short-term benefits when compared to traditional surgical therapies might not result in durable long-term outcomes and freedom from major events and reinterventions. The literature on this topic is extensive and the goal of this review is to hopefully raise some of the concerns regarding the perceived benefits of TAVR over SAVR especially in the context of whether this extremely expensive therapy should be considered the new global standard of care.

Kew words aortic stenosis, aortic valve disorder, heart surgery, Heart Team, structural heart therapies, transcatheter therapies

Introduction

The development of catheter-based therapies – and in particular, transaortic valve replacement (TAVR) – has revolutionized the management options for patients who present with symptomatic aortic stenosis. While the appeal of TAVR cannot be understated when compared to the invasiveness of the traditional open-heart aortic valve replacement surgery (SAVR), the global explosion in the utilization of TAVR must be taken with caution. There is no doubt that TAVR can offer a reasonable option for patients in whom surgery is considered high or extreme risk, but with the simultaneous advances in surgical techniques, anesthesia, myocardial protection, and overall peri-operative care, the decision-making options for patients continues to change. Nevertheless, with more options for patients, the challenge is to also recognize that patients are getting older, frailer, and are presenting with more advanced cardiac disease and co-morbidities. Furthermore, with the growing use of TAVR in higher risk patients, there is the natural extension into lower risk and younger patients – especially those who are expected to have many years, if not decade, of potential quality of life ahead – for which it is critical that options reflect the current data that considers both the short and long-term experiences. The goal of this review is to highlight some of the controversies and difficulties in the management of aortic valve disease. The topics presented, by definition are under constant study and by no means complete, but hopefully this review will help establish a baseline understanding of the complex concerns that must be considered when treating patients with newer technologies. Despite the desire for less-invasive options, it is important to remember that less-invasive does not always translate into better, safer, cheap, or more effective – either in the short or long-term. Furthermore, we also need to recognize that the economic considerations of being able to help as many patients as possible in times of limited financial resources is a topic that must be acknowledged.

It is critical as the use of TAVR over SAVR continues to expand to lower risk patients and different pathologies (such as bicuspid valves, patients with concomitant coronary disease or aortic aneurysms) in an era of "shared-decision making" (in which patients have a greater role and, hopefully, responsibility in directing their care) that it is recognized that there are often different solutions to different problems and it is rare that there is a single approach that can be applied to everyone all of the time[1].

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Background

Aortic stenosis is the most comment type of cardiac valvular disease. Hemodynamically significant stenosis, as determined by catheter or echocardiographic pressure gradients measured across the valve, are found in up to 2% of the patients greater than 65 years old, 3% in 75 years old patients, and 4% in those old than 85 years old. Symptomatic bicuspid aortic valve disease – either stenosis or insufficiency – is also a substantial problem. It is estimated that over 100,000 people in the United States are given a diagnosis of severe aortic stenosis each year. Historically, open-heart surgery (SAVR) was the only definitive options for those presenting with symptomatic severe and critical aortic stenosis. It is clearly established that the risks of surgery increase substantially with patients age and comorbidities. Despite the success of SAVR, there are concerns that elderly, frailer, or sicker (i.e. multiple advanced comorbidities or advanced organ dysfunction) might have difficult post-operative recoveries that limit their potential ability to benefit both short and long-term from valve replacement. It has been this mindset that has often resulted in many patients who "could have" benefited from surgery never referred for an appropriate evaluation.

The early symptoms of severe or critical stenosis is associated with shortness of breath, early fatigue, or exercise intolerance. However, the later symptoms include heart failure, chest pain, and syncope. Once advanced symptoms develop, their prognosis is worse than some cancers, including colon and breast. Without intervention, advanced symptomatic aortic stenosis is associated with a less than 50% two-year survival.

Treatment Options

The survival difference between symptomatic aortic stenosis patients treated medically compared to those treated with surgery is significant. In fact, in the absence of significant contraindications, it is felt to be inappropriate and maybe even an ethical to withhold therapy in patients who are symptomatic. Given the poor prognosis of untreated critical aortic stenosis with a less than 20% survival at two years when compared to the greater than 85% 4-to-5-year survival in patients who undergo surgery it is easy to appreciate the need for appropriate and timely referral and intervention. However, not all patients are suitable for surgery and over the years there have been several risk-assessment tools that have been developed to aid in clinical decision making with regards to how to manage these patients. The most commonly used risk-assessment tool is the predicted risk for mortality calculator that is based upon objective outcomes data submitted to Society of Thoracic Surgeons database[,]. The limitations of this risk calculator are well known and that is why other variables that consider a formal assessment of the impact of comorbidities, patient frailty, and organ system dysfunction, combined with the technical or anatomical aspects of the procedure that may increase perioperative risks are used to stratify patients into low, intermediate, high, and prohibitive (or extreme) risk. These evaluations are then used by patients to participate in shared decision-making management options as advised by a Heart Team of specialists. In the past, with the emphasis on surgery, the major decision-making was focused on mechanical or biologic (tissue) valved with each having various advantages and disadvantages. The development of TAVR has dramatically changed the options available to patients who traditionally were considered prohibitive risk,. Recently, based upon evolving data from highly-selective randomized trials, TAVR is now being offered low risk populations. However, despite the appeal of TAVR over SAVR, there are still many questions and concerns that should to be considered with regards to durability, paravalvular leaks, need for permanent pacemakers, and the overall impact on reported real-world short and long-term morbidity and mortality. Despite the growing literature and significant of industry-driven support promoting the excitement over transcatheter therapies, there are still concerns that surgery might still be the preferred approach for certain patients. Furthermore, the significant costs associated with these based therapies cannot be ignored in the context of limited resources and the underlying question of whether something that is more expensive and less invasive is inherently "better"

The early randomized trials that focused on high or extreme risk patients indicated a survival advantage. These outcomes resulted in a significant amount of enthusiasm for TAVR being an option for patients who otherwise would have died from their valve disease. Following regulatory approval of TAVR, studies in intermediate and lower risk patients quickly followed. The criteria for intermediate risk were determined using a predicted risk of mortality, other significant baseline characteristics (i.e frailty) comorbidities were considered in the decision-making. These selection variables – such as what defines "frail" – used to define an intermediate risk patient were often subjective and the source of much debate. Again, despite the desire to avoid open-heart surgery, the data in the intermediate risk patient population showed similar risks for disabling stroke and all-cause mortality of around 13-14% at two years. These results suggested that TAVR was "non-inferior" to SAVR, and despite the non-inferiority of the results, these findings have often been used to suggest that TAVR may be preferred by the patients and are even potentially *better* with both short- and long-term when compared to conventional surgery. While SAVR was associated with a recovery time that impacted patient reported quality of life assessments, by about six months, the self-reported assessments of quality of life were similar regardless of the treatment . Furthermore, the short- and long-term stroke and mortality risks were similar in low, intermediate, and higher risk patients – a concept that supports the idea of "non-inferiority" but not superiority. Understandably, there has been significant interest to help define which patient factors and comorbidities might be better suited for one therapy over the other. A review of multiple studies that included over 9500 intermediate risk patients there was no significant advantage of one therapy over another at one year. Similar results

were seen in reviews of studies that focused on low-risk patients. In fact, looking at the 2-year mortality and procedure-related risk for stroke in almost 3500 patients, there was no benefit of TAVR over SAVR - again demonstrating the idea of non-inferior outcomes. Importantly, the data demonstrated a potential 2-year survival advantage for patients undergoing SAVR compared to TAVR. This survival benefit was also seen in a meta-analysis of 14 studies that included almost 4200 intermediate risk. In this review, by 3 years, there appeared to be a significant survival benefit for intermediate risk patients undergoing SAVR when compared TAVR.

Despite some of the growing concerns regarding the long-term outcomes in patients undergoing TAVR, there have been several randomized multi-center studies specifically looking at the role in low risk patients []. The 1-year outcome data has also demonstrated non-inferiority – and maybe even a small survival advantage in those undergoing TAVR. However, these trials have been heavily criticized based upon their scientific and statistical methods and highly-selective patient selection. In the PARTNER-3 trial, there was concern that, despite enrolling low risk patients only, some of the comorbidities and surgical procedures required for these patients implied an inherently much higher risk profile []. In addition, many patients were excluded based upon anatomical considerations with patient selection potentially playing a substantial role in outcomes favoring TAVR. Other low risk trials validated some of the short-term outcome experiences that contributed to regulatory approval with low-risk patients. A major consideration is that low risk is not synonymous with younger. As such, given the evolving data suggesting intermediate- and long-term survival differences, there remains considerable concerns about offering TAVR to patients who have a predicted life expectancy beyond several years. Unfortunately, this has not slowed the considerable interest in TAVR over SAVR in a patient population that still, based upon best available evidence, might still benefit from a surgical approach. Of course, the reality is that many patients present with a bias that "surgery" is bad and "less-invasive therapies" are better (even if they do not understand the difference between each) and might still chose an option based upon incomplete understanding of the short and long-term consequences of their decision-making. In other words, does "shared-decision making" truly reflect "informed consent"?

The concerns of the low-risk TAVR trials have prompted investigators to review some of the real-world outcomes. For example, registry data from Israel examining very low risk and low risk patients showed a 10 and 15% two-year mortality rate, respectively. These outcomes were substantially worse than similar two-year survival rates reported in modern surgical studies where the mortality rates were almost half of those reported in similar TAVR patients. It is unclear if patients are aware of the substantial risks of these procedures when they are making decisions or are being consented.

Without a doubt, there is still much to learn regarding the risks, benefits, and how to decide which therapy might be best for which patient when treating aortic stenosis. But, what is clear, is that regardless of the which therapy, both TAVR and SAVR have been shown to be safe and effective despite the many challenges and unanswered questions.

Unanswered Questions

The list of unanswered questions regarding the management of aortic stenosis is extensive and extends beyond the scope of this review. Even a partial list, such as below, only illustrates the complexity of valve disease and patient selection. Even the tools used to guide therapies – such as Heart Teams (similar to cancer tumor boards in which each patient is reviewed individually with recommendations based upon their clinical characteristics and pathologies in the setting of local experiences and best available data) and "shared decision making" (a term used to describe the role a patient has in deciding how they want to be treated after weighing the pros/cons of the options as presented to them) – are evolving.

Below is only a small list of topics that must be considered in the management of valve disease:

- Endocarditis
  - Early vs late surgical vs medical management
  - Oral vs intravenous antibiotic therapies
  - Native vs prosthetic valve
  - Therapies for TAVR infections
  - Re-operative options in the setting of substance abuse
  - Indications for left-sided vs right-sided valves
- Aortic insufficiency
  - Timing of surgery
  - Role of TAVR
- Bicuspid valve disease
- Evolving repair technologies
- Impact of previous cardiac surgery
- Special, but common, patient populations
  - Chronic or End-stage renal disease – i.e. dialysis
  - Morbid obesity
  - Small/large aortic roots
  - Complex co-morbidities (i.e. active cancers)
  - "Younger" patients
  - Women of child-bearing age
- Interventions in asymptomatic patients
- Impact of and options for concomitant cardiac pathologies
  - Atrial fibrillation
  - Obstructive coronary artery disease
  - Other valvular pathologies
    - Mitral, tricuspid
  - Ascending aortic aneurysms
- Prosthetic tissue and structural options
  - Bovine vs porcine vs mechanical
  - Anti-calcification treatments
  - Internally vs externally wrapped valves []
  - Stented vs non-stented
  - Role of "sutureless" or rapidly deployed surgical valves
- Role of anticoagulation / anti-platelet agents
  - Impact on short-term risk for stroke
  - Risk for tissue or valve degeneration/thickening

Even with the growing list of topics that complicate the decision-making process in how to treat patients with

aortic valve disease, there are several major areas that are of special and growing interest and concern.

Pacemaker Rates

As showed in almost every major review and study on TAVR, the procedure is associated with a significantly higher rate of need for a permanent pacemaker compared to SAVR. While arrythmias and conduction problems are not uncommon after SAVR, there are concerns that needing a pacemaker after TAVR is neither trivial nor benign. Some large-scale studies suggest a four-fold increase in the need for permanent pacemaker after TAVR. The long-term consequences of needing a pacemaker are still unclear, especially since the natural history and management of post-TAVR/SAVR conduction problems is complex, there is evidence that the need for a pacemaker is associated with worse long-term survival[]. Also troublesome is the emphasis (and potential benefit) on early discharge and the fact that some significant conduction abnormalities (like complete heart block) might not present until after the patient is discharged is still unclear.

Stroke and Neurologic Complications

Patients have the belief that TAVR is associated with fewer strokes - and this belief is often used to guide their decision to undergo TAVR over SAVR. However, this has not been objectively demonstrated in the high-profile randomized trials. In addition, there are concerns that the neurologic events in TAVR patients might not present until after the patient has been discharged. For example, in one study reviewing a Medicare database consisting of over 44,000 patients - an 86% greater risk of ischemic stroke and a six-fold increase risk of hemorrhagic stroke after TAVR was seen when compared to SAVR with many of the events occurring in subsequent readmissions to the hospital within the first year. The 90-day readmission rate for neurologic events after TAVR was considerably higher than many cardiac and non-cardiac procedures, including other procedures often associated with increased risks for neurologic complications such as left ventricular assist device placement, surgical aortic valve replacement, and coronary artery bypass procedures. Especially in the context of the rigorously reviewed trial data, the real-world experiences with post-TAVR and post-SAVR neurologic events requires further objective review.

To offset the procedural related stroke risks, there has been a substantial increase in the development and use of temporary cerebral protection devices during TAVR. While, in concept, these devices sound appealing, they are associated with considerable cost. Furthermore, definitive data demonstrating a clinical improvement and reduction in neurologic events is still lacking[]. It is easy to understand why this is an area of tremendous research and development[].

Paravalvular Leaks

In SAVR, the valvular and paravalvular calcified leaflets and surround material is physically removed – but, in TAVR inserts and expands against the existing valve. This major difference between the two procedures can explain why TAVR is associated with a much higher rate of paravalvular leaks – especially in patients with bicuspid or complex valvular/paravalvular/subvalvular calcifications. The long-term impact of paravalvular leaks is incompletely understood. However, those patients with at least moderate leaks have a much worse survival at 2 years than those with mild or less leaks. The PARTNER 2 study, as previously discussed above, demonstrated a 34% risk of mortality in patients with moderate to severe paravalvular leaks, when compared to the 13-14% risk in those with none, trace, or mild leaks. While there is much discussion regarding options for the management of leaks, such as delayed expansions or 'plugging' technologies, such interventions are also not without risks or technical challenges.

Indications for Treatment

The American and European Society guidelines for intervention on aortic valve disease has also been evolving to reflect the developments in therapy options []. This is an important point since there is still an indication for SAVR is asymptomatic patients with critical aortic stenosis. Furthermore, there is growing evidence that adverse, and potentially irreversible, structural changes in the myocardium occur prior to developing symptoms. Patients with very advanced disease can have minimal symptoms and tools such as cardiac magnetic resonance imaging, strain-rate, and stress-echocardiography are being used more frequently to help direct management decisions.

Coronary Artery Interventions

Many of the patients who present will also have underlying obstructive coronary artery disease. Separating the symptoms related to their valvular disease from their coronary disease can be difficult with carefully consideration given to the severity and clinical implications of each problem and whether they need to be managed separating or at the same time. While the appeal of TAVR is that both valvular and coronary pathologies can be addressed often with catheter-based therapies, definitive guidelines directing one option over another is lacking. Furthermore, many of the early studies comparing SAVR to TAVR specifically excluded concomitant coronary procedures or those patients with significant obstructive disease – even though, especially in the surgical arms of the trials, a significant percentage of patients underwent some degree of surgical revascularization . Furthermore, some of the criticisms of the more recent low risk trials is that the surgical patients were at much higher risk profile because many of them underwent concomitant coronary revascularization at the time of their SAVR – hence implying that the two groups were not similar enough to suggest one

therapy (SAVR or TAVR) was better, worse, or even non-inferior to the other. Of growing concern is that structural frames of biologic valves also raises concerns of difficult coronary access in patients with previous valve replacements (both surgical and TAVR). While some procedures are being developed to try and overcome these concerns, such evolving interventions are also not without potential significant risk and can be very technically challenging. These topics further emphasize the importance of complete revascularization at the time of valve therapies. It must be also acknowledged that many SAVR-TAVR studies specifically excluded patients with significant coronary artery disease with current guidelines still tending to favor surgery by recognizing the limitations of the data[7]. In addition, preliminary results suggest that patients who undergo coronary stenting prior to TAVR may have worse outcomes and increased need for re-interventions due to major adverse cardiac and cerebrovascular events[7].

Repeat Interventions

One aspect aortic valve disease that is the most supportive of TAVR is patients that have had previous valve intervention, either surgical or trans-catheter, who develop symptomatic structural valve degeneration. Over the years, patients underwent SAVR with a biologic valve, despite guidelines and a documented survival advantage advocating the use of a mechanical valve, under the hope of avoiding anticoagulation that their next "valve" would be a trans-catheter valve[7]. The appeal of this approach is undeniable and logical; however, the practical applications are still under considerable study. Conflicting data exists regarding the best approach for the management of a failing biologic valve. Even though the risks of repeat surgery can be substantial, many experienced centers can offer re-operative surgery with a risk profile similar to first-time valve replacement – and placement of a TAVR inside a failing biologic valve is also not without short and long-term risks. . Furthermore, there are concerns surrounding a reduction in the effective orifice areas and the development of patient-prosthesis mismatch after placement of a TAVR inside of a failing SAVR or TAVR valve. An area of growing excitement is the role of valve "fracking" – a technique in which an existing bioprosthetic valve annular ring is "cracked" (or fracked) with a valvuloplasty balloon with the goal of enlarging the annular to thereby allow for implantation of a larger TAVR valve and reduce the risk of developing patient-prosthesis mismatch. While technically interesting and feasible, the clinical benefits – especially with current generation of biologic surgical valves – is unclear with little long-term data supporting this approach

Choice of Valves

Historically, the choice of surgical valves consisted of biologic (tissue) valves and mechanical valves. Mechanical valves required life-long anticoagulation and this was often unappealing to patients even after data suggested a potential survival advantage of mechanical valves in appropriately selected patients. Biologic valves did not require long-term anticoagulation, but were associated with structural degeneration and the need for repeat interventions – often at significant risk as outlined above with younger patients experiencing valve degeneration much earlier than older patients. Many different types of tissue valves are currently available –porcine, bovine, homographs, stentless, sutureless, etc – and each has substantial literature supporting the advantages and disadvantages of each valve type. Much of the decision-making regarding the initial valve choice is extensively discussed with the development of "valve-in-valve" TAVR for failing tissue valve. Since the concept (as mentioned above) of "valve-in-a-valve" has altered the natural history of patients with biologic valves, there is growing enthusiasm for use in younger patients. As discussed above, concepts regarding strut design and annular cracking (or fracking) to increase the annular size to allow for larger replacement valves under intense study. Similarly, the choice of transcatheter valve design – annular, supra-annular, self- vs balloon-expanding – is also the source extensive clinical research and discussion.

Durability and Cost

No discussion on TAVR vs SAVR would be complete without recognizing the substantial costs associated with each therapy. Even though the costs and expenses vary depending on the specific structure and reimbursement models of a health-care system, there is conflicting evidence regarding the short- and long-term costs of each therapy. TAVR valves are more expensive than SAVR – but patients can go home earlier, require less hospital-based care, and require less rehabilitation resources. However, considering the needs for pacemakers, stroke management, and concomitant coronary disease, the data on costs, short and long-term overall is difficult to assess[7]. This concern is even more apparent in countries with limited resources and budgets that cannot justify the substantially more expensive valves – especially when other costs (such as in-patient and post-discharge rehabilitation) are potentially much less compared to countries, such as The United States.

Conclusions

The topics that can be debated when comparing SAVR to TAVR is endless – and well beyond the scope of this review. However, the topics addressed above can serve as a foundation to illustrate some of the evolving concerns regarding the widespread growth of both therapies. It is important to remember that patient preferences – i.e. shared decision-making – can and should play a role in which therapy is offered, but providers must be objective and transparent with patients and their families so that "a best" decision can be make. Fortunately, the evolution of SAVR and TAVR has resulted in excellent options for patients – many of whom had none in the past – with the growing role of multi-disciplinary Heart Teams helping to guide patients. Never-

theless, with the current trend towards less-invasive therapies – be it catheter-based or small incisions – it is imperative to rely on high quality, unbiased, objective data and guidelines because small and less-invasive does not always translate into better or safer (regardless of how such terms are defined).

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Sažetak

Evolucija lečenja aortne stenoze – pogled hirurga

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Tokom poslednjih 10 godina došlo je do značajnog pomaka u načinu lečenja bolesti aortne valvule. Razvoj terapija zasnovanih na kateterima, posebno zamene trans-aortnog zaliska (TAVR), ponudio je mogućnosti lečenja za pacijente kod kojih je operacija (SAVR) ranije bila jedina opcija. Globalni rast upotrebe TAVR-a bio je izuzetan i prihvaćen sa puno entuzijazma. Međutim, takav rast nije prošao bez značajnih kontroverzi i troškova. Korišćenje "Tima za srce" za pomoć u proceni i lečenju pacijenata sa bolestima aortnog zaliska predstavlja važan korak u pokušaju da se specifične opcije terapije usklade sa jedinstvenim karakteristikama pacijenta - međutim, važno je prepoznati da su terapije zasnovane na kateterima još uvek relativno nova, u stalnoj evoluciji i potencijalno pod uticajem značajnih sukoba interesa. Iako je utvrđena uloga TAVR-a kod pacijenata sa visokim ili neprihvatljivim hirurškim rizikom, uloga kod pacijenata sa niskim i srednjim rizikom je nejasna i potencijalno kontroverzna s obzirom na neke nedoumice da kratkoročne koristi u poređenju sa tradicionalnim hirurškim terapijama možda neće rezultirati trajnim dugoročnim ishodom i odsustvom teških neželjenih događaja i ponovnih intervencija. Literatura o ovoj temi je opsežna i cilj ovog pregleda je da pokrene neke od dilema u vezi sa prednostima TAVR-a u odnosu na SAVR, posebno u kontekstu da li bi ovu izuzetno skupu terapiju trebalo smatrati novim globalnim standardom nege.

Ključne reči: aortna stenoza, poremećaj aortnog valvule, operacija srca, "tim za srce", strukturne terapije srca, transkateterske terapije