Chapter 29: Current controversies, active trials, and future directions

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Introduction

In the last decade, the advent of transcatheter aortic valve replacement (TAVR) for severe aortic stenosis (AS) has greatly disrupted the paradigm that structural heart disease should be treated with open, surgical procedures. Recent trials have supported the use of TAVR devices or surgery in both high and intermediate risk patients. Trials are currently underway in patients with low surgical risk and it is plausible that TAVR may even become the predominant treatment modality for AS. For lower risk younger patients an emerging caveat may be the ability to implant a suitably sized first TAVR that could accommodate a repeat valve-in-valve without over concern about patient-prosthetic-mismatch.
With the success in treating the aortic valve, a great deal of interest has shifted to approaching the treatment of the mitral regurgitation (MR) through transcatheter approaches. In the U.S., the only FDA-approved device is the MitraClip® (Abbott Vascular). This device mimics the surgical Alfieri stitch in which the anterior and posterior mitral valve leaflets are connected to create a double orifice mitral valve.

With the success of MitraClip®, many new devices approaching the mitral valve are in various stages of development. However, caution must be advised as percutaneous mitral valve repair may not follow the same rapid growth of TAVR secondary to fundamental differences in treating mitral valve pathologies compared to the more straightforward process in AS.

Current controversies

Compared to AS, there are several factors that make treating MR significantly more challenging. First, there is an absence of calcium in most patients with mitral regurgitation, making anchoring of devices more challenging. Disease anatomy and pathology also differ greatly from patient to patient. Left ventricular outflow tract obstruction must also be considered with any mitral valve replacement device given the relationship of the anterior leaflet and the ventricular septum. Finally, the subvalvular apparatus of the mitral valve is intimately involved in both mitral valve function but also with left ventricular function.

Currently, the approaches to the mitral valve among the devices in development include transapical, trans-septal, and via the coronary sinus. The direct approach and proximity of the mitral valve to the apex are key advantages with transapical access, especially in devices utilizing chordal repair techniques. There is also substantial experience with this approach from TAVR. Unfortunately, as we have learned with TAVR, the invasiveness of this approach may prove to be a limitation, especially in those patients with a low ejection fraction or severe chronic obstructive pulmonary disease.
The second approach is trans-septal. This is the approach used by MitraClip®, and it is significantly less invasive than transapical access. The lack of a thoracotomy can greatly reduce morbidity and avoidance of apical access can spare left ventricular function. Additionally, the antegrade approach is beneficial with some devices. A challenge to this approach is the long, circuitous route for device positioning and

deployment. Also, devices may require a large atrial septostomy necessitating closure in those patients with a left-to-right shunt, adding to the overall cost of the procedure. A third approach for transcatheter mitral valve repair is via the coronary sinus. Although devices using this approach have been tested in humans over the past decade, the significant variability in the positioning of the coronary sinus to the posterior mitral valve annulus has led to unreliable amelioration of MR. Newer devices and careful preoperative planning with computed tomography are enhancing the results of this class of devices.

In addition to the mitral valve repair devices that are either available or in clinical trials, there has been the introduction of transcatheter mitral valve replacement devices. An advantage of the transcatheter replacement devices is that in the over 95% of cases, there is complete resolution of mitral regurgitation. Early results with mitral valve replacement devices have shown excellent efficacy with reduction of MR, but the mortality remains higher than with transcatheter mitral valve repair techniques.
Currently, there are a plethora of transcatheter mitral valve repair and replacement devices under development, and it is far from clear who the winners will be. This is in part because many different strategies are being employed including direct and indirect annuloplasty, chordal repair, coaptation enhancers, and left ventricular cinching devices, to mention a few. Due to this 'innovation overload', it will be challenging, yet important, to identify the advantages and disadvantages of these promising technologies.

While most of the new transcatheter mitral valve technologies are concentrating on high-risk patients, the future will most likely include those considered low risk. An important factor for consideration is whether subsequent surgical repair will be possible; many of the leaflet capturing devices currently under development will likely make this very difficult. Moreover, novel mitral valve repair techniques for primary degenerative MR should reach the efficacy of current surgical therapy with a >95% success rate.

Active trials

The MitraClip® gained CE mark approval in 2008 and FDA approval for primary MR in late 2013. To date, over 40,000 MitraClip® procedures have been performed, the majority overseas. Most clinical evidence with MitraClip® in the EVEREST trials [1] was in treating degenerative disease, however most patients treated in European registries have been those with secondary mitral regurgitation. To better evaluate the efficacy of MitraClip® in this population, two large randomized studies are currently underway, the COAPT [2] and RESHAPE-HF [3] trials. Since MitraClip® is only approved for primary MR in the United States, a positive result in the COAPT study could lead to expanded indications.

The Carillon Mitral Contour System® is an indirect annuloplasty device currently undergoing clinical testing. The device is implanted via the coronary sinus, which runs near the mitral valve annulus. The two ends of the device are cinched together to help reduce the annulus of patients with secondary MR. Several small trials have already been completed (AMADEUS, TITAN, and TITAN II) with encouraging results, and a pivotal trial [4] is currently enrolling 400 patients which will compare the Carillon® device to optimal medical therapy.

Two devices are also under development to perform a direct annuloplasty (like a mitral valve ring used in open surgical repair). With the Mitralign device, arterial access is obtained, then via the left ventricle pledgets are deployed in the posterior mitral valve annulus then plicated together to shrink the annulus. This is done at several locations to create the desired reduction in posterior annulus size. CE mark approval has been obtained, and there were encouraging improvements in left ventricular dimensions and 6-minute walk tests. There were no improvements in quality of life or NYHA functional classification, so the company has chosen to pivot to treating the tricuspid valve; no pivotal trial is currently planned.

Unlike the Mitralign device, the Cardioband is delivered trans-septally. With this device, a band with multiple anchoring points is secured to the posterior mitral valve annulus. Once secured, the device is cinched to reduce the annular size and reduce MR. Cardioband obtained CE mark approval in 2015 in a study of 30 patients which showed improved MR and 6-minute walk tests. The company was acquired by Edwards Lifesciences and their pivotal trial will soon commence in late 2017.
While the previous devices are percutaneous and used to treat secondary MR, the Neochord is a device to treat primary MR. Access is obtained transapically via a small thoracotomy. The device then captures flail leaflets and secures them to the apex of the heart using PTFE chords. Feasibility studies have been completed, and a pivotal trial [5] is currently enrolling to compare NeoChord to mitral valve surgery in 585 patients. The Harpoon device is a comparable device for transapical chordal repair in degenerative mitral valve disease. Trials in the U.S. will start in 2017 or 2018.

In addition to the above pivotal trials, numerous companies are in earlier stages of development (bench work, animal studies, and feasibility studies). Several transcatheter mitral valve replacement devices are also currently undergoing clinical testing, which will be discussed elsewhere.

Future directions

The treatment of MR is at a major crossroads in the U.S. A variety of devices for a multitude of disease processes have been introduced within the past 2-3 years and many more are to follow soon. While transcatheter mitral valve replacement will be performed in those considered high-risk, some mitral valve repair technologies are going to intermediate risk patients. It appears that patient selection by a dedicated heart team will be paramount. Understanding the pathophysiology of primary and functional MR remains critical. As there will likely be several devices and approaches on the market, picking the right approach for the right patient will be essential, and should be made in a heart team environment.

References:

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