

Unmet clinical needs in transcatheter mitral valve interventions in 2014

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Introduction

During the last 10 years, transcatheter mitral valve interventions (TCMVI) have emerged as an option to treat inoperable or high-risk patients with mitral regurgitation (MR). During this period of time a number of devices for mitral valve repair have been evaluated, most of which were abandoned at an early stage, whilst others are still in their infancy. Finally, the first attempts at valve replacement were performed over the last few months, further increasing the interest in percutaneous mitral interventions.

General comments

Mitral regurgitation is the second most frequent native valve disease and its prevalence increases with age¹. This explains why patients who have MR are often elderly with comorbidities, which makes their management more difficult. The anatomy and functioning of the mitral valve are much more complex than those of the aortic valve since they result from an interaction between the annulus, the leaflets, the subvalvular annulus and the left ventricle. There are two distinct entities that should be defined and separated for both diagnosis and treatment: primary MR, when the valve abnormality is key and the left ventricle dysfunction is a consequence of valvular disease; and secondary MR, where the valve structure is almost normal and the distortion of the valvular apparatus is due to left

ventricular remodelling caused by either ischaemic heart disease or cardiomyopathy²⁻⁴. Medical treatment has limited indications in primary MR, but should be the first step in patients with secondary MR. Surgery is very effective in primary MR and, in experienced centres, the valve repair rate is over 90% with a freedom from reoperation after 10 years of 90% in properly selected patients³⁻⁵. Still, surgery for secondary MR remains a challenge. Finally, surveys both in Europe and the USA^{6,7} have shown that a sizeable number of patients are denied surgery by their practising physician, despite the presence of severe mitral regurgitation and other symptoms. Thus, there is a potential need for transcatheter mitral intervention.

Current state of percutaneous interventions

In current practice, clinical experience with TCMVI is limited to percutaneous repair and percutaneous treatment after failure of surgical bioprosthesis or ring annuloplasty repair.

PERCUTANEOUS VALVE REPAIR

Three devices currently have the CE mark for percutaneous mitral valve intervention: the MitraClip (Abbott Vascular, Santa Clara, CA, USA); the Coronary Sinus annuloplasty (CARILLON® Mitral Contour System; Cardiac Dimensions, Inc., Kirkland, WA, USA); and artificial chords (NeoChord Inc., Eden Prairie, MN, USA).

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However, current clinical experience is almost exclusively limited to the MitraClip.

The MitraClip procedure has now been performed in over 15,000 patients. The evidence of its efficacy and risks comes from a randomised trial (EVEREST II) comparing MitraClip to surgery in around 300 patients who were surgical candidates, mostly with primary degenerative MR, and showed better early safety for the MitraClip and equivalent functional results. However, there was more residual MR, and subsequently more frequent need for intervention, in the group of patients treated percutaneously⁸. Results on valve function appear to be stable from 30 days up to five years⁹. In parallel, a large number of patients have been included in registries where the majority of patients did not fulfil the inclusion criteria for EVEREST since they were high-risk patients with secondary MR¹⁰⁻¹². While these registries confirm the safety of the procedure in expert hands and improvement in symptoms midterm, the majority of patients still have mild to moderate residual MR.

On the basis of these findings, the 2012 ESC/EACTS guidelines on the management of valvular disease conclude that “the percutaneous MitraClip procedure may be considered in symptomatic patients with severe primary or secondary MR despite optimal medical therapy who fulfil the echo criteria of eligibility, are judged inoperable or at high risk for surgery by a Heart Team and have life expectancy greater than one year” (recommendation class IIb, level of evidence C)³. The 2012 ESC Guidelines on the management of heart failure came to the same conclusions, correctly emphasising that the expected benefit was mostly seen in functional improvement¹³. In 2013, the ACC/AHA guidelines on heart failure stated that the MitraClip may be considered in selected high-risk patients with secondary MR¹⁴. In addition, the 2014 ACC/AHA recommendations on valvular heart disease state that “transcatheter mitral valve repair may be considered in severely symptomatic patients with chronic severe primary MR who have reasonable life expectancy but a prohibitive surgical risk because of severe comorbidities”⁴. Thus, the sets of guidelines we now have are consistent as regards the need for a comprehensive assessment by a Heart Team and the limitation of the use of the MitraClip in highly selected patients at high risk or with contraindications for surgery. However, they differ concerning their recommendations on the type of MR which could be treated by MitraClip. This clearly mandates more clinical research.

In primary MR, surgical experience, mostly from the Milan group¹⁵, suggests that when combined with annuloplasty edge-to-edge repair may well provide long-term benefits. However, surgical experience is very limited when using edge-to-edge repair in isolation. The stability of valve function in EVEREST II is encouraging, but there is still concern about the persistence of moderate MR in a sizeable proportion of patients, which is likely to lead to unsatisfactory later outcomes¹⁶. This impels us to pursue a cautious evaluation of the technique in this group using specific trials. In these patients, the technique is no doubt more challenging, and the anatomic indications should be refined in order to find out what the real anatomic contraindications to the technique are¹⁷. In addition,

it is necessary to precisely evaluate the feasibility of surgical repair if the percutaneous treatment fails either immediately or in the long term¹⁸. Finally, no data exist on rheumatic and post-endocarditic aetiology, where replacement would probably be the preferred technique due to the lack of valve tissue.

In secondary MR many questions remain. The demonstration of a clear and powerful association between presence and severity of secondary MR and prognosis might only suggest that the treatment of MR might improve outcome, but this remains to be proven. Surgical literature failed to show that the treatment of MR in secondary MR has a real impact on the prognosis of patients¹⁹. Both recent sets of guidelines state that “transcatheter mitral valve repair or mitral valve surgery for functional mitral insufficiency is of uncertain benefit”. A first answer to this fundamental question will hopefully be given upon completion of ongoing randomised studies such as COAPT in the US, RESHAPE in Europe and MITRAFR in France where MitraClip therapy is compared to optimal medical management in patients with severe secondary MR and heart failure.

TRANSCATHETER MITRAL VALVE IN A VALVE AND MITRAL VALVE IN A RING

Redo surgery is the treatment of choice following mitral valve bioprosthesis or surgical annuloplasty failure, but it may be associated with high mortality and morbidity in patients with comorbidities. Today, limited experience has been reported with TCMVI in high-risk patients, though procedural success is high in experienced centres and mortalities are rare. Overall, the haemodynamic performance of the valve is satisfactory. Moderate and severe regurgitation were seldom observed. Follow-up is still limited to a few months, but most patients experience functional improvement early on^{20,21}. Questions and challenges remain concerning valve types, valve sizing, risk of left ventricular outflow tract obstructions, haemodynamic function when small prostheses are used, and risk of paravalvular leak, and long-term outcomes are needed to evaluate the durability of these prostheses as well as their thrombogenicity. Today, limited available experience has led to the restriction of TCMVI to high-risk/inoperable patients as evaluated by Heart Teams. If larger series with longer follow-ups prove positive, this new option may also have important clinical implications since it will lower the age threshold for the implantation of bioprostheses.

Finally, very limited experience of MitraClip for severe MR after surgical failure has been reported²². This technique is unlikely to be used in a large number of patients.

How can we move forward?

TCMVI represents an important challenge, but there are several potential ways of improving our knowledge as well as the results of the procedure.

- First, it is important to better characterise the patient population, in particular for secondary MR, by evaluating the prevalence and presentation of the disease using prospective studies with quantitative echocardiography. It is likely that current estimations

overestimate the incidence of severe MR in this context, especially when optimal medical therapy is administered.

- Second, recent guidelines consistently stress the fact that evaluating and treating patients with complex valvular heart disease and severe comorbidities requires a multidisciplinary Heart Team working at a high-volume centre^{3,4}. The model established for TAVI should be relevant to TCMVI, and perhaps even more so. The Heart Team should comprise, in this case, general cardiologists, interventional cardiologists, imaging specialists, cardiac surgeons and also electrophysiologists and heart failure specialists. The first role of the Heart Team is to select the appropriate patient for intervention.

In both types of MR it is relatively easy to consider TCMVI when surgery is contraindicated for anatomic reasons such as sequelae from thoracic radiation therapy, mammary bypass crossing the sternum or massive mitral annular calcification.

The discussion becomes more difficult when the surgical risk is high because of an advanced condition, in order to avoid interventions which are “futile more than utile”. A “too-advanced” cardiac condition is much more frequent in patients with MR than in those with aortic stenosis. It is pointless to expect a durable improvement from mitral repair or replacement in patients with chronic MR along with very severe enlargement of the left ventricle and severely depressed left (and/or right) ventricular ejection fraction where ventricular dysfunction is irreversible²³. At advanced stages of secondary MR, TCMVI should be discussed by the Heart Team as an alternative to left ventricular assist and heart transplantation. Still, it is necessary to use only medical therapy in patients where any correction of the mitral valve is more “futile than utile” for extra-cardiac reasons.

The experience with TCMVI in emergency situations is very limited, but this could be an interesting field of application, at least as a bridge to surgery^{24,25}.

At the other end of the clinical spectrum, in the distant future, the application of percutaneous techniques could be contemplated at an early stage - i.e., in asymptomatic patients - in order to delay the advent of left ventricular dysfunction and, subsequently, surgery. The prerequisites to such an “early intervention” are the demonstration of safety and durability of TCMVI, and whether performance of the percutaneous technique will “burn the bridges” to surgery and, more precisely, durable repair in primary MR¹⁸.

Last but not least, combined tricuspid intervention is indicated in patients with severe tricuspid regurgitation undergoing left-sided valve surgery in order to improve long-term outcomes. It should also be considered in patients with moderate, primary TR undergoing left-sided valve surgery as well as in those with severe tricuspid annulus enlargement^{3,4,26}. The absence of a percutaneous treatment for tricuspid disease is an important current limiting factor, which hopefully will be overcome in the future.

- Third, improvement in techniques will occur as regards devices and imaging.

A variety of new devices has been introduced. In the field of percutaneous repair, we see this in direct annuloplasty and chordal

implants²⁷. As shown by surgical results, it is expected that we will be able to combine the techniques in order to provide durable repair. More than 15 devices for percutaneous mitral valve replacement, specific to the native mitral valve, are under evaluation and the first-in-human implants have been performed. Multiple technical challenges are still to be overcome²⁸. At the present time it is not possible to define the respective futures of repair vs. replacement in the field of TCMVI but it is likely that they could be complementary.

Imaging plays a key role as well in patient selection, guidance of the procedure and evaluation of the results.

- Fourth, evaluation will be essential, and should follow in many respects what is done in the field of TAVI by defining the methodology of the evaluation of new devices and studying long-term follow-up using a combination of randomised studies and comprehensive dynamic registries.

Conclusions

The challenge of TCMVI is even greater than that of TAVI. However, the evolution of the epidemiology of MR with an increasing number of elderly patients with comorbidities, thereby at high risk or even contraindicated for surgery, leads us to think that there is a potential role for TCMVI. Thanks to ongoing technological advancements in the technique itself, as well as careful evaluation, it could be expected to become a valuable addition to mitral valve surgery, with the final goal being to have more patients with MR effectively treated either by less and less invasive surgery or percutaneous techniques.

To quote Martyn Thomas, “percutaneous treatment for mitral valve disease will be a long journey, but we are already on the road”.

Conflict of interest statement

A. Vahanian is a consultant/Advisory Board member for Valtech and Abbott. D. Himbert is a Consultant and Proctor Physician for Edwards Lifesciences. B. Iung has received consultant fees from Abbott, Boehringer Ingelheim and Valtech as well as speaker’s fees from Edwards Lifesciences.

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