



Review

Percutaneous treatment of mitral valve regurgitation: Where do we stand?

Alessandra Sala, Ottavio Alfieri *

Department of Cardiovascular and Thoracic Surgery, San Raffaele University Hospital, Milan, Italy



ARTICLE INFO

Article history:

Received 26 September 2018

Accepted 1 October 2018

ABSTRACT

Surgery has been the standard of care for mitral valve diseases to date. In the last fifteen years, due to increased aging of the population, with a great number of patients being high-risk for surgical treatment, transcatheter treatments for mitral valve disease have greatly developed. Further development and expansion of transcatheter treatments are expected. However, some limitations remain, such as efficacy and durability, which impact the widespread use of these devices.

© 2018 Elsevier B.V. All rights reserved.

In the last fifteen years transcatheter treatments for mitral valve disease (MV) have greatly developed, gradually growing and slowly becoming a realistic option for an important number of patients, particularly patients considered at high risk for surgical treatment. It is quite appropriate in this historical time point to focus on percutaneous transcatheter mitral valve treatments, because these procedures are constantly and consistently expanding. This was recently underlined by the German Heart Report 2017, showing the large and progressive increase in adoption of percutaneous MV repair [1]. Nevertheless, the progress concerning mitral valve devices has taken a slower path compared to transcatheter aortic valve replacement (TAVI) treatment. Many features play a relevant role in determining the slower development of percutaneous approaches for the mitral valve. First and foremost, the mitral valve apparatus is a complex anatomical and functional structure, made up of several components: MV annulus, MV leaflets, sub valvular apparatus with chordae and papillary muscles. Furthermore, the interplay of the various components with the left ventricle and left atrium is essential for a correct valve functioning [2]. Moreover, different mechanisms and etiologies determining mitral regurgitation (MR), associated with the heterogenic pathophysiology, have further contributed to the great challenges of developing percutaneous MV treatment.

A large proportion of patients with MR are affected by degenerative MV disease. In such a subset, surgical repair represents the optimal treatment, with superb results that are extremely difficult to reproduce with the currently available percutaneous devices. Furthermore, within the spectrum of functional MR, surgical indication is still a matter of debate. The most recent European Guidelines recommend surgical or percutaneous treatment for severe functional MR only in severely

symptomatic patients, refractory to optimal medical management (IIB C) [3]. Certainly, the unsatisfactory results obtained with surgical treatment of functional MR [4,5] have rendered this clinical scenario particularly appealing for percutaneous treatment.

Additionally, concomitant factors associated to mitral valve disease, such as tricuspid valve insufficiency or atrial fibrillation, which contribute to procedural outcome, cannot be addressed during percutaneous mitral valve repair [6,7].

1. Expectations

Surgery has been the standard of care for mitral valve diseases to date. However, there are nowadays great expectations on the expansion of transcatheter mitral valve repair/replacement due to population characteristics and population projections.

The high prevalence of valvular heart disease, together with its increase with aging, as shown by Nkomo and colleagues [8], indicate a high and increasing burden of such condition. MV disease is greatly increasing among the general population, with MR being the predominant valve disease. Approximately 10% of individuals aged ≥ 75 years of age have significant MR, which is associated with decreased survival. Patients are therefore elderly, with increased frailty, number of comorbidities and disabilities, placing them at higher surgical risk and increasing the likelihood of being deemed inoperable [9].

D'Arcy et al. have recently evaluated valve disease in the European population [10]. They found a significant increase in prevalence of valvular heart disease with age, with mitral regurgitation being very relevant and quite underdiagnosed. Furthermore, based on population projections and natural history of MV disease, they estimated that the prevalence of clinically significant valvular heart disease will double before 2050. The current findings and future expectations further validate the need of less invasive approaches to treat a progressively increasing proportion of the population.

* Corresponding author at: Department of Cardiovascular and Thoracic Surgery, San Raffaele University Hospital, Via Olgettina 60, 20132 Milan, Italy.
E-mail address: alfieri.ottavio@hsr.it (O. Alfieri).

Moreover, more liberal indications can be expected, together with possible future changes in the Guidelines, as a result of randomized controlled trials recently performed, especially in the area of functional MR and heart failure. As a matter of fact, while results of MITRA-FR [11] recently published by Obadia and colleagues are not convincing, those of the COAPT Study [12], are likely to more strongly influence treatment of patients within this subgroup.

The latter study demonstrated that percutaneous treatment with MitraClip device (Abbott) of functional MR in patients with heart failure reduces both hospitalizations and mortality.

The former brought to light another crucial aspect: timing of intervention. Patients are frequently deemed high-risk surgical patients due to severe left ventricular impairment related to delay in referral. Hence, surgical and percutaneous treatments result in lower than expected outcomes and survival; late referral to such procedures is detrimental, with suboptimal results and minimal patient benefit.

The importance of medical management, clinical framing, and patient selection are nowadays fundamental, and treatment earlier in the course of the disease, may have an impact on the natural history of the condition. Therefore, it is important for both surgeons and interventional cardiologists to be also good clinicians, in order to gain sufficient experience in patient evaluation and timing of treatment.

Further expansion of percutaneous MV treatment in the future is linked to improvement and increased availability of new and better devices. While in open surgery more aspects contributing to MV disease can be addressed concomitantly, with transcatheter therapies only one single aspect can be treated and solved. Therefore, the next challenging step is addressing different components (annulus and leaflets) simultaneously, increasing the likelihood and possibilities of successful repair. With the great amount of tools and techniques, the majority of prototypes still in the developmental phase, it will be possible to tailor the right device or strategy to the right patient and clinical setting.

2. Current limitations

One of the main limitations in patients undergoing percutaneous transcatheter treatment of MR is the challenge to find good candidates for these therapies. This holds true for patients screened for treatment with the MitraClip system, with annuloplasty devices and for transcatheter mitral valve replacement, with rejection rates being as high as 60% [13].

Rejection may be due to futility in too advanced disease, complexity of the procedure and anatomical constraints. Therefore, too many patients are excluded due to both anatomic and functional criteria.

Another relevant limitation are the suboptimal results obtained. Feasibility and safety of such treatments have been largely described in a variety of studies and case-reports [14]. Results concerning efficacy and durability are not entirely satisfactory.

Among the various transcatheter therapies the largest clinical experience is with the MitraClip device. Various registries have demonstrated technical success rate as high as 94%, with significant reduction in MR grade (mean 3.3 to 1.6), associated to in-hospital mortality of 2.5% in high-risk patients [15]. However, results tend to be less impressive in the immediate post-procedure control compared to surgical MV repair.

The EVEREST II trial suggested that in patients with secondary MR and initially successful MitraClip therapy, results were maintained at 4-years follow up, making MitraClip treatment comparable to surgery in terms of late efficacy [14]. However, De Bonis and colleagues showed that among a selection of patients with optimal initial results, the recurrence of significant MR at 4 years was not uncommon [16]. Freedom from MR $\geq 3+$ at 4 years was $75 \pm 7.6\%$ in the MitraClip group vs $94 \pm 3.3\%$ in the surgical group ($p = 0.04$), and freedom from MR > 2 was 37 ± 7.2 vs $82 \pm 5.2\%$ respectively ($p = 0.0001$). Therefore, these devices provide lower durability in time compared to surgery.

These limitations greatly emphasize the need for improving current devices.

Within the decision making process the role of the Heart Team is essential in order to treat the patient as an individual rather than the pathology per se, according to the concept of “patient-tailored treatment” [17]. In this era of booming technology, the collaboration between industry and academic institutions is of utmost importance in order to bring further advancements in the field of percutaneous treatment of MV disease.

Currently, results obtained are suboptimal, partially due to difficulty in identifying the optimal candidates and partially due to the complex nature and natural history of MR.

The need of less invasive treatments for mitral regurgitation is required and, based on population projections, will be exponentially demanded [10]. Hopefully, adjustments and improvements of currently available devices will allow treatment of a larger proportion of patients with increased effectiveness, achieving results closer to those obtained with open heart surgery.

When more data from randomized controlled trials will prove increased efficacy and durability of treatment with such devices, also patients at intermediate and low surgical risk may be considered for transcatheter therapy. Indeed, if results will be equivalent to open heart surgery, by definition less invasive approaches will be preferable.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

- [1] T. Munzel, T. Jansen, E. Schulz, R.S. Von Bardeleben, A first dedicated heart valve unit, *Eur. Heart J.* 39 (2018) 2612–2613.
- [2] J.L. Zamorano, A. González-gómez, P. Lancellotti, Mitral valve anatomy: implications for transcatheter mitral valve interventions, *EuroIntervention* 10 (2014) 106–111.
- [3] H. Baumgartner, V. Falk, J.J. Bax, M. De Bonis, C. Hamm, P.J. Holm, B. Lung, P. Lancellotti, E. Lansac, 2017 ESC/EACTS guidelines for the management of valvular heart disease, *Eur. Heart J.* 38 (2017) 2739–2791.
- [4] S. Maltais, H.V. Schaff, R.C. Daly, R.M. Suri, J.A. Dearani, T.M. Sundt, M. Enriquez-sarano, Mitral regurgitation surgery in patients with ischemic cardiomyopathy and ischemic mitral regurgitation: factors that influence survival, *J. Thorac. Cardiovasc. Surg.* 142 (2011) 995–1001.
- [5] D.D. Glower, R. Tuttle, L. Shaw, R. Orozco, J.S. Rankin, Patient survival characteristics after routine mitral valve repair for ischemic mitral regurgitation, *J. Thorac. Cardiovasc. Surg.* 129 (2005) 860–868.
- [6] M. De Bonis, E. Lapenna, A. Pozzoli, T. Nisi, A. Giacomini, M. Calabrese, G. La Canna, F. Pappalardo, A. Miceli, M. Glauber, F. Barili, O. Alfieri, Mitral valve repair without repair of moderate tricuspid regurgitation, *Ann. Thorac. Surg.* 100 (2015) 2206–2212.
- [7] A. Zientara, M. Genoni, K. Graves, D. Odavic, H. Löblein, A. Häussler, O. Dzemali, Tricuspid valve repair for the poor right ventricle: tricuspid valve repair in patients with mild-to-moderate tricuspid regurgitation undergoing mitral valve repair improves in-hospital outcome, *Thorac. Cardiovasc. Surg.* 65 (2017) 612–616.
- [8] V.T. Nkomo, J.M. Gardin, T.N. Skelton, J.S. Gottdiener, C.G. Scott, M. Enriquez-Sarano, Burden of valvular heart diseases: a population-based study, *Lancet* 368 (2006) 1005–1011.
- [9] R. Pfister, S. Baldus, Atrioventricular valve disease: challenges and achievements in percutaneous treatment, *Clin. Res. Cardiol.* 107 (2018) 88–93.
- [10] J.L. D'Arcy, S. Coffey, M.A. Loudon, A. Kennedy, J. Pearson-stuttard, J. Birks, E. Frangou, A.J. Farmer, D. Mant, J. Wilson, S.G. Myerson, B.D. Prendergast, Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study, *Eur. Heart J.* 37 (2016) 3515–3522.
- [11] J. Obadia, D. Messika-Zeitoun, G. Leurent, B. Lung, G. Bonnet, A. Piriou, T. Lefevre, J. Trochu, B. Cormier, X. Armoiry, F. Boutitie, D.M. Boulch, C. Barnel, Percutaneous repair or medical treatment for secondary mitral regurgitation, *N. Engl. J. Med.* (2018) 1–10.
- [12] G. Stone, J. Lindenfeld, W. Abraham, S. Kar, D.S. Lim, J. Mishell, B. Whisenant, P.A. Grayburn, M. Rinaldi, S.R. Kapadia, V. Rajagopal, I. Sarembock, A. Brieke, S. Marx, D.J. Cohen, N. Weissman, M.J. Mack, Transcatheter mitral-valve repair in patients with heart failure, *N. Engl. J. Med.* (2018) 1–12.
- [13] M. Urena, A. Vahanian, L. Søndergaard, Patient selection for transcatheter mitral valve implantation: why is it so hard to find patients? *EuroIntervention* 14 (2018) 83–90.
- [14] T. Feldman, S. Kar, S. Elmariah, S.C. Smart, A. Trento, R.J. Siegel, P. Apruzzese, P. Fail, M.J. Rinaldi, R.W. Smalling, J.B. Hermiller, D. Heimansohn, W.A. Gray, P.A. Grayburn, M.J. Mack, D.S. Lim, G. Ailawadi, H.C. Herrmann, M.A. Acker, F.E. Silvestry, E. Foster,

- Randomized comparison of percutaneous repair and surgery for mitral regurgitation, *J. Am. Coll. Cardiol.* 66 (2015) 2844–2854.
- [15] R.J. Siegel, S. Biner, A.M. Rafique, M. Rinaldi, S. Lim, P. Fail, J. Hermiller, R. Smalling, P.L. Whitlow, H.C. Herrmann, E. Foster, T. Feldman, The acute hemodynamic effects of MitraClip therapy, *J. Am. Coll. Cardiol.* 57 (2011) 1658–1665.
- [16] M. De Bonis, E. Lapenna, N. Buzzatti, G. La Canna, P. Denti, F. Pappalardo, D. Schiavi, A. Pozzoli, M. Cioni, G. Di Giannuario, O. Alfieri, Optimal results immediately after MitraClip therapy or surgical edge-to-edge repair for functional mitral regurgitation: are they really stable at 4 years? *Eur. J. Cardiothorac. Surg.* 50 (2016) 488–494.
- [17] M. Taramasso, N. Buzzatti, G. La Canna, A. Colombo, O. Alfieri, F. Maisano, Interventional vs surgical mitral valve therapy. Which technique for which patient? *Herz* 38 (2013) 460–466.