Editorial

Transcatheter Mitral Valve Replacement: slow and steady progress

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In contrast to the exponential growth of transcatheter therapies performed for the treatment of aortic valve stenosis, transcatheter treatment of mitral valve regurgitation (MR) has moved relatively slowly from concept to clinical reality. Whereas it is anticipated that there will be >125,000 transcatheter aortic valve replacement (TAVR) procedures performed globally in 2018 (1), the total number of transcatheter mitral valve interventions performed for MR since the first transcatheter mitral repair 15 years ago remains well short of 100,000. This relates in part to the relative lack of randomised data to support reimbursement for these procedures, and to uncertainties regarding the value of correcting secondary MR in the setting of severe left ventricular dysfunction (2). It also relates to the technical challenge of engineering devices that conform to the complex anatomy of the mitral valve apparatus (3).

To date, the most successful transcatheter therapy for MR has been the MitraClip (Abbott Vascular, Santa Clara, California, USA), a means of approximating and clipping together the mitral leaflets to create a double-orifice valve (4). The procedure is an adaptation of a surgical technique of edge-to-edge leaflet suturing, which is typically combined with a surgical ring annuloplasty (5). MitraClip has the advantage of being extremely well tolerated, even in patients with severe left ventricular dysfunction and multiple non-cardiac co-morbidities (6). However, with few exceptions, large series have shown that residual mitral regurgitation is common even in experienced hands, with rates of residual grade 3+ or 4+ MR of 10–20% (7-9). An additional 25–35% have moderately severe (grade 2+) MR at 12-month follow-up echocardiography. The importance of residual MR in determining survival and the need for repeat hospitalisation was highlighted recently in an analysis from the Society of Thoracic Surgery/American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) Registry of 1,867 patients with severe, symptomatic MR treated by MitraClip implantation (10). The median age of the group was 82 years, 55.8% were men, and 85.9% had degenerative MR. Acute procedural success was achieved in 91.8%. The 1-year mortality for the population was 25.8%, and the rate of heart failure hospitalisation at one-year was 20.2%. By multivariate analysis, grade 0 or 1+ residual MR had a considerably lower 1-year mortality, and combined endpoint of death and heart failure hospitalisation, than that of grade 2+ residual MR (hazard ratio 0.65, P=0.0004) (10).

These observations support the need for strategies to better control the extent of residual MR post-intervention. Transcatheter mitral valve replacement (TMVR) is one such strategy. Multiple devices have been developed, and several have been evaluated in the clinical arena, predominantly via a small, left lateral thoracotomy and transapical delivery (11). Two studies have now reported the outcomes of moderate sized cohorts of patients with short to intermediate-term follow-up (12,13). The larger of these two studies, published in the *Journal of the American College of Cardiology* in January this year by Bapat and colleagues (13), enrolled

50 patients between May 2015 and July 2017. The patients were deemed to be at high or extreme risk for open valve surgery with a STS predicted risk of mortality score of 6.4%±5.5%. The mean age of the group was 72.6 years, 58% were men, and 84% had secondary or mixed pathology MR. The device used in this system (Intrepid valve, Medtronic Cardiovascular, Santa Rosa, California, USA) was a self-expanding, nitinol valve delivered through a 35-F access catheter introduced from the left ventricular apex. The valve has two frames, an outer frame that wedges the device in the annulus and sub-annular space, and a circular inner frame that houses a trileaflet, bovine pericardial valve (13). Valve implantation was successful in 48 of the 50 patients. One procedure was abandoned because of access site bleeding. Circulatory support using an intra-aortic balloon pump or extracorporeal membrane oxygenation was required in 7 patients. There were 4 procedural deaths, 3 due to uncontrolled apical access bleeding and one due to refractory heart failure associated with a malpositioned device. There were 3 deaths between 1 and 4 months post-operatively due to sudden cardiac arrest. At 30-day follow-up echocardiography in those with successful implants showed that MR was absent or mild in all patients (n=42). There was no left ventricular outflow tract (LVOT) obstruction. However, there was an increase in left ventricular end-systolic diameter (LVESD) (51±9 *vs.* 48±10 mm at baseline, P=0.0007), and a decrease in left ventricular ejection fraction (LVEF) (36.2%±10.2% *vs.* 43.6%±2.1% at baseline, P<0.0001). In spite of this, there was significant improvement in functional class and quality of life measures (13).

The study highlights several issues that currently limit the widespread application of this technology to patients with severe MR. First, transapical access carries a significant risk of catastrophic bleeding in this population. The hazards of placing large calibre delivery sheaths in the left ventricle apex became evident in the initial TAVR experience, in which a clear difference in outcome between transapical and transfemoral access was observed (14). Myocardial thinning due to previous infarction or non-ischaemic injury results in a greater loss of muscle integrity in the MR population than in aortic stenosis patients, and the need for early anticoagulation in patients with MR-related atrial arrhythmias further increases the risk of peri-procedural hemorrhage. Although measures such as the use of an epicardial pad might reduce access site bleeding after transapical access with some devices (12), femoral venous, transeptal access is clearly the preferred option. A second design consideration is the need for prostheses to be retrievable. Maldeployment does occur with all of the TMVR devices, and can be associated with hemodynamic collapse due to torrential MR or LVOT obstruction. Suboptimal device placement can also result in paravalvular regurgitation and refractory hemolysis. An ability to retrieve the device in this situation, and to reposition it, minimizes the need for bail-out open valve surgery, and reduces the procedural mortality. While the risk of LVOT obstruction can be minimised with pre-operative 3D echocardiography and CT planning, and was not seen in the study of Bapat and colleagues, it imposes a considerable limitation on the number of patients who are anatomically suitable for the procedure. Devices with a lower intra-ventricular footprint are clearly needed.

In addition to optimizing device design, considerable work still needs to be done to identify the patients who will most benefit from this procedure, and those who could be harmed. The study of Bapat and colleagues (13), like others (12), suggests a decline in left ventricular performance after transapical TMVR. While a reduction in LVEF does not on its own reflect a fall in myocardial contractility (15), the increase in LVESD is of concern. A similar decline in LVEF was observed after transcatheter mitral repair by MitraClip implantation in the STS/ACC TVT Registry (10), but surprisingly, was less evident after surgical valve repair or replacement in the recent Cardiothoracic Surgery Trials Network (CSTN) trial (16). Whether myocardial injury associated with apical access, or other alterations to left ventricular architecture, are responsible for the apparent change in LV function after TMVR remains to be determined.

Future directions

Several ongoing clinical trials should help answer some of the remaining questions. The COAPT trial (NCT01626079) has completed enrolment and will report its preliminary results later this year. The trial randomly assigned 610 patients with severe, symptomatic secondary MR to MitraClip therapy or to guideline-directed optimal medical therapy. Outcomes of this and other similar trials, such as RESHAPE-HF2 (NCT024443338), should help determine whether the benefits of reducing MR in patients with impaired left ventricular function are confined to reducing symptoms and the need for heart failure hospitalization, or whether there is also a survival advantage. The demonstration of a significant benefit of transcatheter

mitral valve repair over medical therapy should promote interest in combinations of MitraClip with transcatheter mitral annuloplasty to minimise the degree of residual MR and to further improve clinical outcomes. Devices such as the Valtech Cardioband (Edwards Lifesciences, Irvine, California, USA), Millipede (Boston Scientific, Minneapolis, Minnesota, USA) and Carillon Mitral Contour System (Cardiac Dimensions, Kirkland, Washington, USA) would provide annuloplasty support for leaflet technologies, or could potentially work as stand-alone systems.

Based on the outcomes of the Intrepid feasibility trial (13), Medtronic has initiated the Apollo trial (NCT03242642), a randomized controlled comparison of Intrepid TMVR *vs.* surgical valve repair or replacement for severe secondary MR in surgically eligible candidates. Surgically ineligible patients will be treated by TMVR in a non-randomized registry. The trial will enroll 1,380 patients and will follow participants for up to 5 years. A similar randomized, controlled, pivotal trial of the Tendyne mitral valve system (12) is also planned. In the meantime, work is progressing towards reliable, trans-septally delivered TMVR devices. Small numbers of patients have been treated using this approach with some success. Preliminary data have been reported for CardiaQ (Edwards Lifesciences, Irvine, California, USA), Caisson (LivaNova, London, UK), and for Edwards M3 (Edwards Lifesciences, Irvine, California, USA). Others, including Edwards CardioValve (Edwards Lifesciences, Irvine, California, USA) and Cephea (Cephea Valve Technologies, Santa Clara, California, USA) are scheduled to begin clinical trials this year. It is likely that use of these systems will eliminate some risks, such as apical access bleeding, but will introduce other procedural concerns. The systems are likely to require larger calibre venous access than required for MitraClip or valve-in-valve mitral interventions (17), and will leave a larger defect in the atrial septum. This increases the potential for retroperitoneal bleeding, pelvic vein thrombosis, and paradoxical thromboembolism. Whether transeptal TMVR is superior to transcatheter mitral valve repair remains to be determined. Although surgical repair for primary, or degenerative, MR is clearly preferable to replacement (18), the same has not been clearly demonstrated for secondary MR (2,16). Ultimately, what might matter most in the long-term for patients with secondary MR is the completeness of correction of the mitral regurgitation, rather than the means by which this is achieved. Those systems that can achieve excellent control of MR, with the lowest procedural risk, and the least likelihood of causing further myocardial injury will be the preferred systems. The journey to identifying this optimal system has only just begun.

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Footnote

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