Adding a clasp to the toolbox for transcatheter mitral valve repair

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Moderate to severe mitral regurgitation (MR) has a high incidence of up to 9.3% in the elderly population and is associated with significant morbidity. (1,2) Due to high surgical risk and limited evidence, a considerable proportion of patients has been denied treatment beyond medical therapy, leading to the emergence of new transcatheter treatment methods. (3) Most of the available transcatheter mitral repair devices mimic surgical procedures, such as leaflet approximation, direct annuloplasty or valve replacement. The MitraClip® (Abbott Vascular, Chicago, USA) - first implanted in 2003, and since then used in > 100.000 patients – is a well-established treatment option with data from randomized clinical trials in the setting of both primary and secondary MR. Published data indicate similar long-term prognosis but less effective reductions of MR in patients with primary MR. Among patients with secondary MR, one trial failed to show benefit in terms of mortality and rehospitalization compared with medical therapy, whereas a larger trial with longer follow-up reported a large treatment effect in terms of rehospitalization and all-cause mortality. (4,5) Despite growing clinical experience and evidence, the MitraClip system itself has undergone only minor device iterations until recently (Figure). In the meantime, a shift towards transcatheter treatment of more complex anatomies has been observed, emphasizing the need for a more versatile and individualized approach.

The PASCAL transcatheter mitral valve repair system (Edwards Lifesciences, Irvine, USA) aims to overcome some of the technical limitations of previous transcatheter mitral repair systems by enabling independent leaflet grasping and featuring a wider and larger implant with an integrated central spacer to address larger coaptation gaps and to reduce tension of the leaflet tissue. Initial reports from compassionate-use case series in 23 patients showed encouraging results in terms of procedural and technical success as well as functional improvement. (6) The early feasibility CLASP study was designed as a multicenter, prospective, single-arm study investigating the safety and efficacy of the PASCAL in patients with symptomatic moderate to

severe MR of both primary and secondary etiology. The 30-day outcomes have been previously reported for 62 patients and reported favorable results in terms of safety and feasibility. Procedural success was reportedly high with a MR reduction ≤ 2+ in 98% of patients accompanied by improvement in functional status with 85% of patients being in NYHA functional class I or II. There was a significant improvement in 6-minute walk distance (36m, $p<0.0018$) and KCCQ (17 points, $p<0.0001$). All-cause mortality amounted to 1.6% and no stroke was observed. (7) Based on these results, commercial approval of the PASCAL device was granted in Europe for the treatment of primary and secondary MR in 2019.

In this issue of the *Journal*, Webb et al. (reference) present the 30-day follow-up of an extended population (109 patients) in addition to the 1-year outcome of the previously reported 62 patients. Patients have been treated at 14 sites worldwide and echocardiographic results were monitored by a core laboratory. Successful implantation defined as at least one device being implanted and the delivery system retrieved, was achieved in 95% of patients with a single-leaflet device attachment requiring conversion to open-heart surgery in one case (0.9%). Nearly half of the patients (47%) received more than one implant and the mean number of implants per patient was 1.4. The primary composite endpoint at 30 days (cardiovascular mortality, stroke, new dialysis, severe bleeding and re-intervention) occurred in 8.3%, including one death, one stroke and eight cases of bleeding. All events but one case of bleeding occurred in the secondary MR population – an observation that was confirmed at the 1-year follow-up with a survival rate of 89% and 96% and a freedom from heart failure hospitalization of 80% and 100% for the secondary and primary MR population, respectively. Echocardiographic follow-up at 30 days showed successful reduction to MR ≤ 2+ in 96% of patients, a proportion that increased to 100% at 1 year (presumably explained by the death of patients with suboptimal result). In addition, a significant decrease in left ventricular end-diastolic diameter as a marker for reverse remodeling was observed in both groups and sustained at 1 year. Assessment of functional

improvement revealed improvement in both primary and secondary MR patients in terms of NYHA functional class (89% of patients in NYHA class I/II), 6-minute walk distance (improvement of 21 m), KCCQ (improvement of 13 points) and EQ5D (improvement of 7 points) score at 1 year. In summary, the presented data confirm the feasibility, safety and efficacy of the novel PASCAL system for the treatment of both primary and secondary MR.

It is tempting to put the results of the PASCAL device in perspective to similar studies performed with the MitraClip device and its recent iterations keeping in mind the limitations of uncontrolled, non-randomized comparisons. Compared to the new-generation MitraClip XTR system (8), similar reductions of MR were observed at 30 days (MR ≤ 1+ in 77% and MR ≤ 2+ in 93% of the patients treated with the MitraClip XTR vs. 80% and 96% with PASCAL). Despite the larger size of the PASCAL implant, the proportion of patients receiving multiple devices remained comparable (43% with XTR versus 47% with PASCAL). Correspondingly, the mean transvalvular gradient was slightly higher with PASCAL (3.9 ± 1.7 mmHg vs. 3.3 ± 1.5 mmHg). While SLDA occurred rarely in the CLASP study (0.9%), it was noted in 4% with the XTR system, particularly during the early experience. In few patients (2%), leaflet damage requiring surgical treatment were observed. The site reported 30-day data from the Global EXPAND study collected in more than 400 patients showed a SLDA rate of 3.6% and a rate of non-elective cardiovascular surgery for device-related complications in 1.4%. (9) This signal led to the recommendation to restrict the use of the XTR device to specific challenging anatomical settings. The fourth generation MitraClip system (Gen 4) approved by the US Federal Drug Administration, but not yet available in Europe, may address this issue by providing a larger XTR implant with improved distribution of the tension exerted on the valve leaflets.

As already the case for transcatheter aortic valve implantation, there is certainly enough space for multiple devices with different characteristics in the toolbox of transcatheter mitral valve

repair. In the near future, head-to-head comparisons between these systems will be of interest. The CLASP DII/F study comparing the PASCAL and the MitraClip system is already underway and further studies with the latest iteration of the MitraClip (Gen 4) may provide insightful information. In addition to the use in the treatment of MR, the PASCAL system may potentially occupy space in the transcatheter treatment of tricuspid regurgitation (TR) since its design may be beneficial in the setting of thinner leaflets and larger coaptation gaps. Early clinical reports (10) have recently led to CE mark for the use of PASCAL in TR.

The choice between different devices and sizes will further broaden the spectrum of anatomical settings amenable to leaflet approximation enabling a more individualized approach adapted to the multiplicity of mitral valve pathologies.

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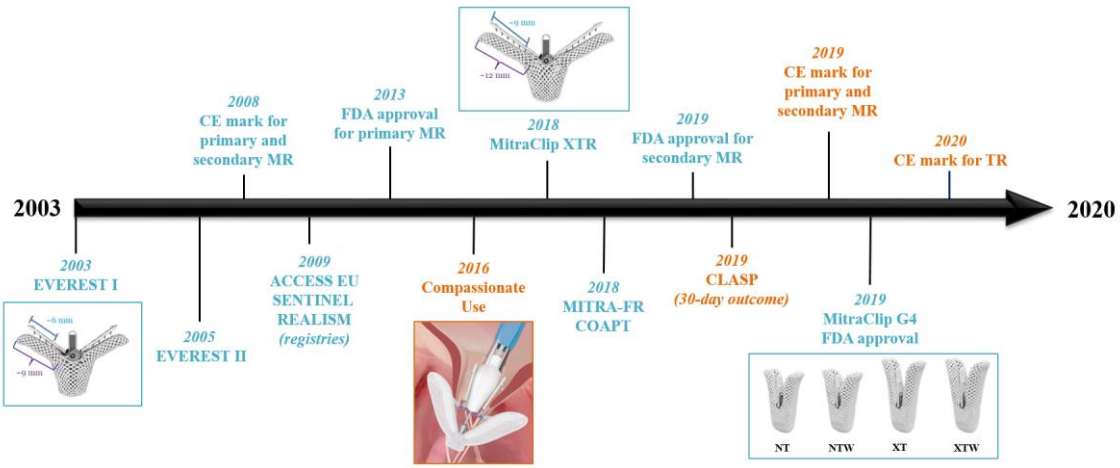

Figure: Development of transcatheter mitral valve repair devices for leaflet approximation. *MitraClip® (blue), PASCAL transcatheter mitral valve repair system (orange).*