Mitral regurgitation (MR) is the second most frequent valvular disease among referred patients in Europe [1]. Indications for surgery are well defined in the guidelines for organic MR, but their application is unsatisfactory in practice [2,3]. Conversely, current uncertainties arising from risk–benefit analysis explain why indications for surgery are more restrictive and less well defined for functional or ischaemic MR [4]. The availability of less invasive interventions is therefore the subject of growing interest and initial results obtained using different percutaneous approaches have recently been reported.

**Edge-to-edge technique**

The percutaneous edge-to-edge technique reproduces the surgical technique described by Dr Alfieri, which consists of a suture of the mid part of both mitral leaflets to create a double mitral orifice. The surgical technique has been used mainly in organic MR but cases have also been performed in patients with functional MR [5].

The percutaneous edge-to-edge technique uses a transseptal approach to insert a device, which aims to secure both leaflets. The technique currently used involves the MitraClip (Abbott Inc.), in which a metallic clip is positioned at the free edge of the valve and then closed to grasp both leaflets. The procedure is technically demanding, not only because of the required expertise for transseptal catheterization, but also because of the difficulties in catching the appropriate part of the leaflets under transoesophageal echocardiography.

The MitraClip has been used in more than 2000 patients in the USA and in Europe, where CE marking has been obtained this year. The most relevant evaluation of the MitraClip is the Endovascular Valve Edge-to-Edge REpair Study (EVEREST) II randomized trial, which was presented at the American College of Cardiology Meeting in 2010 but has not yet been published. In this trial, 279 patients with severe MR were randomized in 37 centres to MitraClip (n = 184) or surgical valve repair or replacement (n = 95). Mean age was 66 years and 73% of the patients had organic MR. Procedural success was achieved in 74% of patients.
Coronary sinus annuloplasty

The other percutaneous approach used to treat MR consists of inserting a retractable device into the coronary sinus to shrink the mitral annulus. The procedure reproduces the principle of surgical valve repair in functional MR, which consists of a remodelling annuloplasty using an undersized prosthetic ring. The rationale is the vicinity between the coronary sinus and the mitral annulus, but there are also limitations. Firstly, there is some distance between the coronary sinus and the mitral annulus. Secondly, the coronary sinus corresponds only to approximately half of the circumference of mitral annulus so that the annuloplasty is not circumferential, unlike with prosthetic rings. Finally, the circumflex artery often crosses the coronary sinus and may be compromised by the retracting device.

At the present time, three devices have been tested in humans:
- the MONARC™ device (Edwards Lifesciences Inc.) consists of a proximal and a distal stent connected by a bridge that retracts progressively during the months following implantation [9];
- the CARILLON™ Mitral Contour System (Cardiac Dimensions Inc.) device comprises a proximal and a distal nitinol self-expandable anchor. The bridge connecting the two anchors is positioned by manual traction under echocardiographic and fluoroscopic control [10];
- the Viacor PTMA© (PTMA Viacor Inc.) system is based on a different approach and uses the implantation of several nitinol rods through a multilumen catheter, enabling the stiffness of the coronary sinus to be adjusted according to the reduction of MR [11].

Potential impact of percutaneous techniques in the treatment of mitral regurgitation

Although experience with percutaneous treatment of MR is limited, there is evidence that different technical approaches are feasible. Procedural success rates are high and severe procedure-related complications are rare. It is likely that these figures will improve with growing experience and technical refinements.

Feasibility does not, however, imply efficacy, and it is too early to ascertain the clinical utility of these techniques. The decrease in MR severity is the most consistent finding and it is obviously the first goal when treating MR. The quantitation of MR should combine different criteria including quantitative measurements; their application to the MitraClip raises problems since no quantitative measurement is validated for a double-orifice. Results should be evaluated with longer follow-up since surgical experience has shown a higher rate of late deterioration when the double-orifice technique was not associated with annular remodelling [12]. Another pitfall in the interpretation of MR severity in studies using the MitraClip is that they mix patients with organic MR with those with functional MR, although prognosis differs according to thresholds of MR severity. In addition, functional MR severity is subject to changes over time, particularly according to loading conditions and/or treatment. The effect on NYHA class is a relevant endpoint but its assessment may be subjective.

Defining indications for percutaneous techniques in the treatment of MR will require separate analyses of organic and functional/ischaemic MR.

Intention-to-treat analysis showed a 30-day major adverse event rate of 15% in the MitraClip group and 48% in the surgical group ($p < 0.0001$ for superiority). The superiority of the MitraClip can be partially explained by lower rates of atrial fibrillation and, mainly, blood transfusions. The 12-month clinical success rate was 67% in the MitraClip group and 74% in the surgical group ($p = 0.0005$ for non-inferiority). According to per-protocol analyses, i.e. considering patients who actually had an effective procedure, the 1-year residual rate of MR grade greater than 2/4 was 2% in the MitraClip group and 3% in the surgical group. Respective 1-year rates of New York Heart Association (NYHA) class I or II were 98 vs. 88% and quality of life improved in both groups.

At present, published MitraClip experience is limited to an observational series from the EVEREST registry involving 107 patients and two series from Germany and Italy comprising, respectively, 51 and 31 patients [6–8]. These series differ particularly with regard to the aetiologies of MR, since the European series included a majority of patients with functional/ischaemic MR, whereas they accounted for only 21% of cases in the EVEREST registry. Patients from the European series also had a higher risk profile. Despite these differences, these three series consistently showed high procedural success rates, with a successful implantation of the clip in greater or equal to 90% of patients and a final MR less or equal to two in at least three of four patients.

Published experience in functional/ischaemic MR concerns 72 patients treated with the MONARC™ device, 48 with the CARILLON™ device and 27 with the Viacor PTMA© device. Implantation success rates vary between 48 and 82%, but included MR reduction in one series. Thirty-day death rates are low, between 0 and 2%. The two main complications are tamponade due to coronary sinus perforation, in 3–6% of cases, and myocardial infarction in up to 6% of cases. Complication rates are low for early feasibility trials but they illustrate the specific risks of this approach. Compression of the circumflex artery by the device, although seldom leading to myocardial infarction, is frequently observed when using a computed tomography scan during follow-up, in 30% of patients with the MONARC™ device, resulting in coronary stenosis greater than 50% in 8% [9].

Efficacy has been evaluated in only small non-randomized series using surrogate endpoints. There was a decrease of at least one grade of MR in 50% of patients at 1 year with the MONARC™ device and in 22% of patients at 6 months with the Viacor PTMA© device. Within the first year, the effective regurgitant orifice area decreased by approximately 30% and the regurgitant volume by 20–25%. The response was heterogeneous and certain patients experienced more marked reductions of MR. Series analysing functional results within the first year reported an improvement in NYHA class and/or 6-minute walk test [9,10].

The use of the MitraClip in organic MR should be compared with the results of valve repair, which is frequently feasible in the cases of valve prolapse selected in the EVEREST registry. Given the low operative risk and the good immediate and late results of valve repair for valve prolapse, it is unlikely that the MitraClip will replace surgery. The rates of patients who still have at least moderate MR after the MitraClip procedure raise questions regarding long-term benefit. Nevertheless, percutaneous techniques are attractive in patients with degenerative MR who are at high surgical risk because of advanced age, comorbidities, mitral annular calcification or prior aortic valve replacement.

As regards functional/ischaemic MR, the situation is more difficult since, unlike in organic MR, surgery is not a reference treatment. Surgery carries a higher risk than in organic MR, has not been shown to decrease mortality, and its effect on symptoms varies across studies, in particular because of the impact of confounding factors. It remains that the availability of low-risk interventions may be of potential interest in these patients, who present an important population since ischaemic MR has been shown to occur in as many as 50% of patients after myocardial infarction and to have a negative prognostic impact [13].

An accurate evaluation of existing techniques is needed even more now that other procedures using transcatheter approaches are under investigation, to be used individually or in combination: annuloplasty using radiofrequency, chordal cutting, insertion of artificial chordae, etc. The only application of an implantable prosthesis in mitral position today is its use for valve-in-valve procedures in a degenerated bioprosthesis [14]. Transcatheter implantation of mitral prosthesis in a native valve is under consideration but raises difficult problems, in particular the question of how to stabilize the prosthesis in the mitral ring.

In conclusion, it is now likely that percutaneous treatments will play a part in the treatment of MR. Beyond early feasibility studies, randomized trials are needed to control for confounders, particularly in functional MR, since experience with surgery has shown limitations of observational series in this setting. Continuous evaluation through large series and registries is also mandatory to assess safety, not only because of the need to assess larger numbers of patients but also because application of the techniques will be expanded beyond a limited number of expert centres. Large series will also contribute to the identification of patients who are likely to derive a particular benefit from the procedure on the basis of objective and reproducible endpoints.

Conflicts of interest statement

Bernard Iung received speaker’s fee from Edwards Lifesciences and a consulting fee from Abbott.

Alec Vahanian is consultant for Edwards Lifesciences.

References