The MitraClip System: A Systematic Review of Indications, Procedural Requirements, and Guidelines

Dorothee HL Bail1,2  Klaus Doebler1

1 Competence-Center Quality Assurance, Medical Service of Statutory, Healthcare Insurance, Tuebingen and Stuttgart, Germany
2 Asklepios Stadtklinik Bad Tölz, Bad Tölz, Germany


Abstract

Background  Transcatheter interventions (TIs) are new treatment options for patients with severe mitral valve regurgitation (MR) who cannot undergo open mitral valve surgery (oMVS). Despite the lack of scientific evidence demonstrating the benefit of these procedures, there has been a steady increase in their use. The aim of this study was to evaluate whether there are any indication criteria, process, and structural requirements, or scientific society and institutional guidelines for the use of the MitraClip System (Abbott Vascular-Structural Heart, Menlo Park, California, United States).

Method  A systematic literature search was conducted using the common medical and scientific databases. Of a total of 1,395 publications, 42 publications met the inclusion criteria and were included for the evaluation.

Results  Despite a general lack of high-quality evidence and of consensus recommendations from scientific societies or institutions, an assessment of indication criteria and process and structural requirements for the use of the MitraClip System, including noncontrolled studies, was possible. The majority of studies agree that an interdisciplinary heart team including a cardiothoracic surgeon, an interventional cardiologist, and an echocardiographic specialist should actively participate in clinical decision making, and in the procedure itself. Participation in a scientific-based registry is strongly recommended.

Conclusions  The MitraClip System is a promising procedure, but evidence-based indication criteria, structural, and process requirements for its use are lacking. Further results from prospective, randomized controlled trials are needed to determine patients, potential adverse events, device durability, and long-term follow-up. MitraClip should be used in only a small number of centers with procedure-specific, high-quality surgical and interventional experience, and training.

Keywords  ► MitraClip  ► mitral regurgitation  ► mitral valve repair  ► transcatheter interventions

Introduction

Mitral valve regurgitation (MR) is the second most common valve disease in Europe.1 The classification and recommendations for intervention in MR are defined in the Clinical Practice Guidelines of the European Society of Cardiology (ESC) and the American College of Cardiology and American Heart Association (ACC/AHA) Task Force.2,3 Surgical mitral valve repair (MVR) is generally considered the “gold standard” treatment for MR; however, randomized studies documenting the
outcomes and long-term follow-up of patients are still lacking.3–6 As a significant number of patients (49%)7 with severe MR are not treated because of age, reduced left ventricular function, comorbidities, or other contraindications to open mitral valve surgery (oMVS),7 less invasive percutaneous MVR procedures have been developed. The MitraClip System (Abbott Vascular-Structural Heart, Menlo Park, California, United States) is the only approved system in Europe for beating-heart endovascular transcatheter MVR. In this technique, both mitral valve leaflets are attached with one or more clips, resulting in a so-called “double-orifice mitral valve”. Despite the lack of scientific evidence of proven benefit of the MitraClip procedure, a steady increase in its use has been seen in Germany and Europe. According to Federal Statistical Office registered data (provided on request), 51 endovascular MVR procedures were performed in 2008, whereas in 2010, 809 procedures were performed, corresponding to an increase of 1,500%. The age distribution (<75 years) seems to suggest that the procedure was not restricted to only elderly and high-risk patients.

Aims of the Study

The aims of this study were to perform a systematic literature review to evaluate (1) whether there are any indication criteria, process and structural requirements, or scientific society and institutional guidelines for the use of the MitraClip System, and (2) to establish whether there is an evidence base demonstrating clinical benefit of the MitraClip System.

Method

A systematic literature search was performed and analyzed with evidence criteria in the following databases: PubMed/ Medline, Cochrane Library, and Health Technology Assessment of the German Institute of Medical Documentation and Information. In addition, a general topic-based search was performed using the Google search engine, and a manual search for publications was performed. The search was limited by the following criteria: meta-analyses, controlled clinical trial, humans, randomized controlled trial (RCT), comparative study, review, systematic review, practice guidelines, guidelines, and 10-year period.

Results

A total of 1,395 search results were obtained, and after checking for duplicates and relevance a total of 223 publications remained for evaluation. Of the 1,395 publications, 42 were included to answer the questions. In March 2013, the German Cardiac Society (DGK) together with the German Society of Thoracic and Cardiac- and Vascular Surgery (DGTGH) published a consensus statement and requirements for the treatment of mitral regurgitation and transcatheter treatment with the MitraClip System.8,9 No further consensus statements or requirements/guidelines from relevant European and international scientific societies or health-care institutions were found. Because of the lack of evidence and controlled studies, the presented results with respect to indications, for the procedure, and structural and process requirements, are also based on data extracted from noncontrolled (NC) studies. The publications included in the review and analysis are presented in Table 1.

Scientific Evidence Base for the Use of the MitraClip System

In the only RCT, the EVEREST II study (Endovascular Valve Edge-to-Edge Repair Study), the MitraClip (MitraClip group) was compared with conventional oMVS (oMVS group) for the first time in 279 patients.10 The EVEREST II study, funded by Abbott Vascular, is a multicenter, prospective, single-arm study to evaluate the feasibility, safety, and effectiveness of the MitraClip System with a 30-day, 6-month, 12-month, and 5-year clinical follow-up (Clinicaltrials.gov number NCT00209339). The primary end point for effectiveness at 12 months was absence of death, reoperation due to mitral valve dysfunction, or MR >+2. Procedural success was between 80 and 100%, and reduction of MR to <+2 at 30 days was 77% in the MitraClip group versus 100% in the oMVS group. This was consistent with the success rates seen in the NC studies, which showed a reduction in MR to 60 to 100% of the patients. The need for a second oMVS procedure in EVEREST II was 5.7% in the MitraClip group versus 0% in the oMVS-group at 30 days, and 20 versus 4% at 12 months. The NC studies also showed reoperation rates between 6 and 22.7%. After 2 years, the reoperation rates were 22 and 4% for the MitraClip group and oMVS group, respectively. New York Heart Association (NYHA) class and quality of life were improved within the first 30 days, but there was no difference after 12 months between the two groups in the RCT. The NC studies showed an improvement in NYHA class in 60 to 100% of the patients after 12 months. The major adverse event (MAE) rate was significantly lower at 30 days in the MitraClip group compared with oMVS group. NC studies showed MAE rates between 3 and 26% in patients treated with MitraClip, and therefore, the superiority of the clipping procedure with respect to MAE remains to be proven. With respect to mortality at 30 days (1%) and at 12-month and 24-month follow-up (7%), there was no difference between the two groups in the RCT. NC studies showed mortality rates between 0 and 15% at 30 days and between 7 and 24% at 12 months after the MitraClip procedure. The MitraClip procedure is less invasive than oMVS. To date, no data about cost effectiveness are available, although it has been suggested that costs might be reduced using transcatheter interventions (TIs) such as MitraClip because of shorter hospital stays and a reduction in hospital admissions.11

Measures for Quality Assurance

Despite the lack of evidence, poor quality of the majority of the publications, and lack of international guidelines, indication criteria, and structural and procedural standards could be extracted from the current literature. The extracted requirements are shown in Tables 2–4.

Thoracic and Cardiovascular Surgeon Vol. 62 No. 1/2014

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.
Table 1 Studies included in the analysis

<table>
<thead>
<tr>
<th></th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Divchev D, Kische S, Paranskaya L, et al. In-hospital outcome of patients with severe mitral valve regurgitation classified as inoperable and treated with the MitraClip® device. J Interv Cardiol 2012;25:180–189.&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>15</td>
<td>Holmes DR, Jr., Mack MJ. ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement: developed in collaboration with the American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Failure Society of America, Mended Hearts, Society of Cardiovascular Anesthesiologists, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. Thorac Cardiovasc Surg 2012;144(3): e29–e84&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td>20</td>
<td>NHC. Transcatheter mitral valve repair for severe mitral valve regurgitation. National Health Committee, New Zealand; 2011:1–81&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Discerning the significance of the MitraClip System compared with oMVS. There were also no significant differences with respect to MAE and mortality rate. The high reoperation rate after the MitraClip procedure of 20% at 12 months, missing data on long-term follow-up and outcomes, and inadequate reporting of the number and nature of MAEs also cannot be ignored.

Recommendations Concerning Indication Criteria
There are no clear, scientifically based, indication criteria for the use of the MitraClip System. The literature suggests that there may be a benefit for “inoperable” or “high-risk” patients with severe MR (3+ or 4+) with clear indication for oMVS (similar to the definition of inoperability and high risk in high-surgical-risk patients: do we hit the target? JACC Cardiovasc Interv 2012;5:105–111).
transcatheter aortic valve implantation [TAVI] procedures). There is, however, agreement within the literature that indications for the use of the MitraClip System should be adapted to the guidelines of the ESC and ACC/AHA for the treatment of MR.

There are ongoing discussions about suitable etiologies of MR indicating the use of MitraClip for treatment. Functional MR (FMR) is currently the main indication for the MitraClip System; in FMR, there are no structural alterations of the mitral leaflets so optimal clip placement is anatomically possible. The decision for treatment should be taken according to similar guidelines established for the TAVI procedure, namely, in a multidisciplinary heart team which includes an interventional cardiologist, a cardiac surgeon, and an echocardiography specialist.

**Table 2** Indication criteria and contraindications for the use of the MitraClip system

<table>
<thead>
<tr>
<th>Certain indications (patients benefit from treatment)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic/asymptomatic MR 3+ to 4+ with reduced LVEF Functional MR</td>
<td>8–12,19,29,31,36,39,40,47,48</td>
</tr>
<tr>
<td>Multimorbid, high-risk patient, contraindication for oMVS: log EuroScore &gt; 20% and/or STS-Score &gt; 10%</td>
<td>11,13,14,19,21,24,26,31,35,42,43,48,49</td>
</tr>
<tr>
<td>AHA/ASC/ESC criteria for oMVS fulfilled</td>
<td>10–12,20,21,38,40,43,47,50</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>13,14,20,26,40,45</td>
</tr>
<tr>
<td>Echocardiographic criteria for treatment with MitraClip system fulfilled</td>
<td>8,9,19,32,33</td>
</tr>
<tr>
<td>Chest radiation/porcelain aorta</td>
<td>8,9,16,26,45,51</td>
</tr>
</tbody>
</table>

**Possible indications**

| Symptomatic or asymptomatic MR 3+ to 4+ with normal LVEF and above described risk factors Degenerative MVR (DMI) | 11,13,14,19,21,24,31,35,42,43,48,49 |
| Ultrasound ratio after failed oMVS | 8,9,19 |
| Younger patients (< 75 y) as a bridge to cardiac surgery or for whom life-long anticoagulant medications would be unacceptable (women before childbearing or pregnant) | 8,9,19 |

**Contraindications**

| Mitral valve area < 4.0 cm² Severe annular and leaflet calcification Active endocarditis Transient ischemic attack or stroke 6 mo previously Myocardial infarction < 3 mo previously Intracardiac thrombus mass Degenerated from rheumatic disease Clip placement not possible due to anatomical characteristics Flail leaflet LVESD von > 60 mm LVEF < 20% MI 2+ coronary artery disease with the need of revascularization | 8,9,12,18,21,44,48,50 |

Abbreviations: AHA, American Heart Association; ESC, European Society of Cardiology; LVEF, left ventricular ejection fraction; left ventricular enddiastolic diameter; MI, myocardial infarction; MR, mitral regurgitation; oMVS, open mitral valve surgery.

**Recommendations for Structural, Procedural, and Documentation Standards**

This literature does not provide the scientific evidence base for the structural, procedural, or documentation standards that should be adopted for MitraClip use. Before MitraClip treatment, medications need to be optimized and, if applicable, cardiac resynchronization therapy should be performed. The presence of a catheter laboratory and/or a hybrid operation room, and transesophageal echocardiography (TEE), are minimal requirements. Many authors recommend three-dimensional TEE, a specialized echocardiography laboratory, and an echocardiographic specialist with specialist expertise in the MitraClip System and/or expertise in MVR.

The MitraClip procedure should be performed only in an interdisciplinary heart team in hospitals with departments of cardiac surgery and cardio-anesthesia that possess technical equipment for treatment of intraprocedural complications using extracorporeal circulation (ECC). A special focus is placed on the demand for an interventional cardiologist with specialist expertise in transseptal puncture. A further recommendation is the inclusion of the patients treated with the MitraClip System in a scientific registry and controlled clinical studies, the German aortic valve registry could serve as a model for this.

**Further Areas of Research**

Before any further expansion of the use of the MitraClip procedure further data about indications and long-term results are needed to enable valid comparison with “gold-standard” oMVS. In the early postoperative course, the MAE...
rate is an essential criterion, in particular bleeding, although neurological and renal complications should also be evaluated. Furthermore, critical points for evaluation are reoperation and reintervention rates in the early postoperative period, and during long-term follow-up. A clear definition of high-risk patients is missing, although the TAVI definitions might provide a framework for future guidelines. So far, no superiority in cost effectiveness has been shown for the MitraClip System.

Perspectives
Currently, there do appear to be hazards associated with MitraClip therapy. However, the MitraClip procedure has the potential to be a valid treatment option for selected patients with severe MR. In particular, based on current evidence, high-risk symptomatic, or otherwise inoperable patients with severe MR seem to be the best candidates for the MitraClip System, whenever echocardiographic criteria of eligibility are met. From the current results, no conclusions can be drawn on what the routine indications are for the MitraClip System. It is also of concern that there is no obligation or statutory regulation on necessity for multidisciplinary care, with involvement of a cardiac surgeon and cardiac anesthesiologist. The MitraClip device should be used only in a small number of centers, with specialized surgical and interventional experience and training. It is believed that other innovative interventional procedures are already in use for treatment of MR, rules and recommendations need to be applicable and available at an early stage of implementation.

Conclusions
Analogous to the widely used TAVI procedures, treatment with the MitraClip System should be restricted to patients in which oMVS is contraindicated, or where there is very high perioperative risk (such as Society of Thoracic Surgeons score > 10 or EuroScore > 20, age > 75 years) in selected cases. Specific risk scores and models should be developed for the implementation of novel products for transcatheter interventions.

The majority of studies are in agreement that a “heart team” approach, in which a cardiac surgeon, an interventional cardiologist and an echocardiographic specialist actively participate in the procedure. Participation in a national scientific-based registry is strongly recommended. Further results from prospective, RCTs are needed to determine device durability and the ideal candidates for the procedure.

Reference


4 Carabello BA. The current therapy for mitral regurgitation. J Am Coll Cardiol 2008;52(5):319–326


7 Mirabel M, Jung B, Baron G, et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? Eur Heart J 2007;28(11):1358–1365


11 NHC. Transcatheter mitral valve repair for severe mitral valve regurgitation. New Zealand: National Health Committee; 2011:1–8


22 Feldman T, Cilingiroglu M. Percutaneous leaflet repair and annuloplsty for mitral regurgitation. J Am Coll Cardiol 2011;57(5):529–537


41 Turi ZG, Rosenbloom M. An option for the high-comorbidity patient with mitral regurgitation. J Am Coll Cardiol 2012;59(2):140–142
46 Vahanian A, Jung B. ‘Edge to edge’ percutaneous mitral valve repair in mitral regurgitation: it can be done but should it be done? Eur Heart J 2010;31(11):1301–1304