What is the effectiveness, safety and cost-effectiveness of the MitraClip® transcatheter mitral valve repair system in patients with moderate to severe or severe mitral regurgitation who are at high surgical risk or are non-surgical candidates?

The background, clinical effectiveness and safety sections of this evidence note are adapted from a review of transcatheter implantable devices for mitral valve repair in adults with chronic mitral valve regurgitation. Published in September 2015 this was developed using the HTA Core Model® for Rapid Relative Effectiveness Assessment as part of the European Network for Health Technology Assessment (EUnetHTA) WP5 Joint Action 2 programme. Healthcare Improvement Scotland was a dedicated reviewer to the project. Of the three technologies addressed in the health technology assessment, MitraClip® was identified as the one currently most applicable to NHSScotland (D. Northridge, Consultant Cardiologist, NHS Lothian, Personal Communication, 13 October 2015).

Key points

- No published randomised controlled trials (RCTs) were identified for the comparisons addressed by this assessment. Three RCTs are ongoing.
- Systematic review of non-comparative prospective observational studies suggests that MitraClip® is a feasible and safe option to improve symptoms of mitral regurgitation (MR) in patients with moderate to severe or severe MR who are considered to be at high surgical risk.
- It is not possible, on current evidence, to make direct comparison between the outcomes of medical therapies and MitraClip® implantation in this patient group.
- One small, methodologically limited, comparative study reported a 1-year survival benefit of MitraClip® implantation in 78 patients with MR at high surgical risk (≥12% estimated risk of surgical mortality) when compared with a cohort of 36 patients receiving standard care. The comparator group was identified retrospectively and after the outcomes of the MitraClip® intervention group were known. The study had high risk of bias.
- One United Kingdom (UK) study demonstrated MitraClip® to be cost-effective with an incremental cost-effectiveness ratio (ICER) of £22,000 from a 5-year time horizon onwards. The robustness of the results is compromised owing to the absence of randomised comparative data, small patient numbers and issues surrounding the comparator arm.
- One Canadian study demonstrated MitraClip® to be cost-effective with an ICER of $23,433 Canadian dollars (£11,555). The analysis parameters and cost data are created from a Canadian perspective, which severely limits the generalisability of the study to the UK.
- The cost-effectiveness of MitraClip® is uncertain.
Definitions

Degenerative mitral regurgitation (DMR): primary mitral regurgitation due to structural lesions of the mitral valve apparatus.\(^2\)

Functional mitral regurgitation (FMR): secondary mitral regurgitation resulting from geometrical distortion of the subvalvular apparatus secondary to cardiomyopathy or coronary artery disease.\(^2\)

Literature search

A systematic search of the published literature was carried out between 16–17 May 2015 using the following databases: PubMed, Embase and the Cochrane Library. Results were limited to English language studies, and the time period from 1 January 2005.

An additional search of the secondary clinical effectiveness literature and the cost effectiveness literature was carried out on 29 October 2015.

Concepts used in all searches included: mitral insufficiency, mitral valve regurgitation, MitraClip system, transcatheter edge-to-edge repair and transcatheter mitral valve repair.

Introduction

Mitral regurgitation (MR) is characterised by backward flow of blood from the left ventricle to the left atrium during the contraction phase of the cardiac cycle (systole). Left untreated, moderate to severe MR can result in congestive heart failure (HF) and eventually lead to death.\(^3\)

MR is a complex condition with two very different aetiologies. Chronic MR can be classified into two groups. Degenerative MR (DMR) encompasses all aetiologies in which lesions affect the structures of the mitral valve (MV) apparatus. In DMR the backflow of blood leads the left ventricle to become enlarged and weakened because of the additional workload required to maintain normal forward blood flow.\(^2\)

In functional MR (FMR) the valve, leaflets and chordae are structurally normal and the MR results from geometrical distortion of the subvalvular apparatus as a consequence of left ventricular pathology.\(^2\)

Symptoms of chronic MR and associated HF include palpitation, breathing difficulties, fatigue, lethargy and severe weight loss. These confer a substantial physical, emotional, and social burden to patients. Severe symptoms may prevent patients from performing everyday tasks and simple activities, such as getting out of bed. The inability to perform activities of daily living can lead to loss of independence, distress, and depression. HF can impact upon all aspects of a patient’s quality of life (QoL).\(^4-6\)

The severity of MR is graded from mild to severe (numerically: mild, 1+; severe, 4+) and is usually determined by echocardiography. Severe MR may be symptomatic or asymptomatic.\(^7\)

Current therapeutic options for the treatment of severe chronic DMR, depending on co-morbidities and whether HF is present, include medical management and surgical repair or replacement of the mitral valve. Surgical repair, where feasible, is considered to be the gold standard treatment for severe chronic DMR. There is less clarity on the most effective therapy for FMR and controversy around the most appropriate surgical approach.\(^7\)

In 2009 a National Institute for Health and Care Excellence (NICE) interventional procedure guidance stated that the evidence on the safety and efficacy of percutaneous mitral valve leaflet repair for MR is currently inadequate in quality and quantity. It recommended that the procedure should only be used with special arrangements for clinical governance, consent and research for patients who are well enough for surgical mitral valve leaflet repair to treat their MR, or in the context of research for patients who are not well enough for surgical mitral valve leaflet repair to treat their MR.\(^3\) More recent guidelines from the European Society of Cardiology and the European Association for Cardiothoracic Surgery in 2012 recommended that percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe primary MR who fulfil the echo criteria of eligibility, are judged inoperable or at high surgical risk by a ‘heart team’, and have a life expectancy greater than 1 year. It was also recommended that the percutaneous mitral clip procedure may be considered in patients with symptomatic severe secondary MR despite optimal medical therapy (including cardiac resynchronisation therapy (CRT) if indicated), who fulfil the echo criteria of eligibility, are judged inoperable or at high surgical risk by a
This evidence note focuses on the effectiveness, safety and cost-effectiveness of MitraClip® in patients with moderate to severe or severe DMR or FMR who are at high surgical risk or are non-surgical candidates. Comparators are as outlined in Table 1.

A recently published systematic review identified that evidence for the effectiveness of medical therapies for MR (largely in FMR patients) was published between 1986 and 2008. When examined alongside the evidence on MitraClip® conducted from 2011 onwards the outcome measures used in the two bodies of evidence do not correlate well. For example, studies of medical therapies rarely report changes in MR grade or QoL. The review authors suggest that the incremental effectiveness will only be determined from robust contemporary studies which can facilitate valid comparison between interventions in patients at high surgical risk.

Primary clinical effectiveness outcomes stated in the EUnetHTA review scope included all-cause mortality, cardiovascular mortality, need for cardiac transplantation, New York Heart Association (NYHA) functional status improvement, freedom from NYHA functional class ≥3, 6-minute walk test (6MWT), reduction in rate of hospitalisation, need for surgery and QoL. Improvements in echocardiographic outcomes such as reduction in MR grade to ≤2+ were examined as secondary outcomes. Safety outcomes focused on adverse events, both device-related and procedural.

**Health technology description**

MitraClip® System is a transcatheter mitral valve repair system for reconstruction of the insufficient mitral valve. The cost of the device is £16,500. The procedure is performed using venous access thereby avoiding open heart surgery and cardiopulmonary bypass. General anaesthesia is used to facilitate real time transoesophageal imaging. The implantation of the Mitraclip® onto the valve leaflets forms a double-orifice allowing greater closure and reduced leakiness. In the United States the device is indicated for the percutaneous reduction of significant symptomatic MR (MR ≥3+) due to primary abnormality of the mitral apparatus (DMR) in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing co-morbidities would not preclude the expected benefit from reduction of the MR. In the European Union the indication is broader with the MitraClip® System intended for the reconstruction of the insufficient mitral valve through tissue approximation. The manufacturer of the MitraClip® is Abbott. The cost of the device is £16,500 regardless of the number of clips required. This cost does not include any other consumables required, for example staff and theatre time. At the time of publication this is the only device of this kind on the market.

**Epidemiology**

In Europe MR is the second most common type of heart valve disease requiring surgery, after aortic stenosis.

The prevalence of MR increases with age: clinically meaningful MR (moderate or greater in severity) is estimated in population based studies to be less than 1% in people aged ≤54 years and 9.3% in people aged ≥75 years.

No data on the size of the target population in Scotland were identified. A 2011 statement on commissioning of MitraClip® in the United Kingdom (UK) notes that the epidemiology of MR....

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMR, no HF</td>
<td>standard medical care</td>
</tr>
<tr>
<td>DMR+HF</td>
<td>standard medical care with pharmacological treatment for HF</td>
</tr>
<tr>
<td>FMR</td>
<td>pharmacological treatment (with or without CRT)</td>
</tr>
</tbody>
</table>
is not fully established and identifying the numbers of cases that would be amenable to either percutaneous or surgical mitral valve repair is not yet possible\textsuperscript{11}. Three centres in NHS England are undertaking the procedure within the Commissioning through Evaluation (CtE) programme (https://www.england.nhs.uk/commissioning/spec-services/npc-crg/comm-eval/). Although no procedures have been undertaken in Scotland to date, it is estimated that around 20 eligible patients per year would be identified. (D. Northridge, Consultant Cardiologist, NHS Lothian, Personal Communication, 13 October 2015). An evidence review notes that more than 25,000 MitraClip\textsuperscript{®} procedures have been performed worldwide\textsuperscript{12}.

**Clinical effectiveness**

A well-conducted systematic review assessed the efficacy of MitraClip\textsuperscript{®} in patients with severe DMR or FMR who were at high surgical risk. High surgical risk was defined as estimated perioperative mortality $\geq 12\%$ using either the Society of Thoracic Surgeons (STS) calculator or logistic European System for Cardiac Operative (EuroSCORE) risk evaluation score, or by the presence of factors not covered by the STS or EuroSCORE, assessed in a multidisciplinary team meeting. The literature search covered the period January 2000–March 2013. Twelve studies were included. All were prospective observational studies from tertiary referral centres\textsuperscript{13}. The review encompassed data from one small comparative study. This study was methodologically limited by the retrospective identification of the patients for the comparator group who were selected after the results for the intervention group were known. The endovascular valve edge-to-edge repair study (EVEREST) II High Risk Study (HRS) enrolled 78 patients and compared outcomes with those from a retrospectively identified cohort of 36 patients receiving standard care (of whom 14\% had mitral valve surgery). There was no statistically significant difference between groups in the 30 day procedure-related mortality rate. Survival at 1 year was significantly higher in the MitraClip\textsuperscript{®} group than in the concurrent comparator group (76.4\% versus 55.3\%; $p=0.047$). The study authors note that caution should be taken in interpreting this finding since the comparator group was made up of patients excluded from the prospective part of the study for various reasons including not meeting anatomic criteria\textsuperscript{14}. Only data from the MitraClip\textsuperscript{®} arm of the study were included in the review.

No other comparative studies were identified by extending the review search to May 2015\textsuperscript{1}.

Although the review was well-conducted the study authors indicated that the available literature should be considered low quality due to the non-comparative nature of the evidence base. They also noted that in nine of the 12 included studies patients with DMR and FMR were combined and highlighted that the definitions of high surgical risk varied a great deal between studies.

Key clinical effectiveness findings are outlined in Table 2.

Where it was reported (six studies) 1-year survival ranged from 75\% to 90\%. Compared with baseline there were large reductions in the proportion of patients in NYHA class III/IV at 12 months. Across studies the proportion of patients with MR grade $\leq 2+$ at baseline was between 0\% and 2\%. At 6 and/or 12 months (eight studies) this improved substantially to range from 61\% to 99\%. Based on three studies there were statistically significant improvements in functional status in exercise performance as measured by the 6MWT with up to 6 months of follow up. Two studies measured QoL and reported statistically significant improvements. There was also some evidence of improvements in left ventricular parameters.
Table 2 Clinical effectiveness findings from Munkholm-Larsen systematic review\textsuperscript{13}

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Number of studies reporting this outcome</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year survival</td>
<td>6/12</td>
<td>Range 75%-90%</td>
</tr>
<tr>
<td>Reduction in proportion of patients in NYHA class III/IV at 12 months</td>
<td>5/12</td>
<td>98% to 35%  88% to 27%  94% to 11%  98% to 22%  90% to 26%</td>
</tr>
<tr>
<td>Proportion of patients with MR grade ≤2+ at 6 and/or 12 months (0% to 2% at baseline)</td>
<td>8/12</td>
<td>Range 61%-99%</td>
</tr>
<tr>
<td>6MWT</td>
<td>3/12</td>
<td>194 ± 44m to 300 ± 70m (p &lt; 0.01)\textsuperscript{15}  171 ± 99m to 339 ± 134m (p &lt; 0.001)\textsuperscript{16}  300 ± 108m to 339 ± 120m (p = 0.02)\textsuperscript{17}</td>
</tr>
<tr>
<td>QoL Short Form (SF-36) (score range 0-100, increasing score indicates improvement) Physical component</td>
<td>1/12</td>
<td>31.6 ± 9.1 at baseline  37.0 ± 9.7 at 1 month  36.5 ± 10.6 at 12 months (p = 0.01)</td>
</tr>
<tr>
<td>QoL Minnesota Questionnaire (score range 105-0, decreasing score indicates improvement)</td>
<td>1/12</td>
<td>56.5 ± 21.9 pre-intervention  39.4 ± 20.5 6-month follow-up (p &lt; 0.001)</td>
</tr>
<tr>
<td>Left ventricular ejection factor</td>
<td>6/12</td>
<td>Improved or unchanged from baseline in all 6 studies</td>
</tr>
<tr>
<td>Reduction in left ventricular volume and diameter</td>
<td>6/12</td>
<td>Improvements from baseline in all 6 studies</td>
</tr>
</tbody>
</table>

Ongoing studies

Four ongoing studies relevant to the comparisons in this assessment were identified as outlined in Table 3. Three of these are multicentre randomised controlled trials (RCTs).

Table 3 Ongoing studies with MitraClip\textsuperscript{®} where comparator is non-surgical

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type/comparison</th>
<th>Patient group</th>
<th>Estimated completion date</th>
<th>Follow up - primary outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESHAPE-HF1-FU (NCT02444286)</td>
<td>Cohort study (n=42) MitraClip\textsuperscript{®} + optimal standard of care versus optimal standard of care</td>
<td>Clinically significant FMR Chronic HF NYHA class II–IV</td>
<td>January 2017</td>
<td>24 months</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MITRA-FR (NCT01920698)</td>
<td>Multicentre RCT (n=288) MitraClip\textsuperscript{®} + optimal standard medical therapy versus optimal medical therapy</td>
<td>Severe FMR</td>
<td>October 2017</td>
<td>24 months</td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(NCT02444338)</td>
<td>Multicentre RCT (n=380) MitraClip\textsuperscript{®} + optimal standard of care therapy versus standard of care therapy</td>
<td>Chronic HF Clinically significant FMR (NYHA II–IV)</td>
<td>September 2019</td>
<td>24 months</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COAPT (NCT01626079)</td>
<td>Multicentre RCT (n=430) MitraClip\textsuperscript{®} vs non-surgical management based on standard hospital clinical practice</td>
<td>Symptomatic HF Unsuitable for MV surgery</td>
<td>August 2020</td>
<td>24 months</td>
</tr>
<tr>
<td>United States and Canada</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Safety

Although no comparative safety studies were identified, two large series provided evidence on safety outcomes including rates of major adverse events (MAE) associated with the MitraClip® intervention as summarised in Table 4\textsuperscript{18,19}.

The largest prospective series combined multicentre registry data from the EVEREST II High Risk Registry (HRR) and the Real World Expanded Multi-center Study of the MitraClip® System (REALISM) HR studies. Patients (n=351, DMR=105, FMR=246) with symptomatic MR (MR grades 3+ to 4+) at high surgical risk (≥12%, estimated using the STS calculator or by a surgeon co-investigator according to pre-specified criteria) were followed for up to 12 months\textsuperscript{18}.

The German Transcatheter Mitral Valve Interventions (TRAMI) register (n=1,002) identified and reported outcomes of MitraClip® in a subanalysis of 557 patients who were assessed as at high surgical risk; logEuroSCORE ≥20. Echocardiographic data for 472 of the patients confirmed that 71% had FMR. This registry was retrospective from 2009–2010 and then prospective up to 2013. Median follow up period was 6 months\textsuperscript{19}.

Across the studies mortality ranged from 4.3% (in-hospital) to 22.8% (at 1-year of follow up). Blood transfusion requiring ≥ 2 units was the most frequent major adverse event related to the procedure. The rate of major vascular complications was 2.2% at 6 months and 3.4% at 12 months.

Table 4 Safety outcomes from large series of MitraClip® in patients at high surgical risk

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EVEREST II HRR + REALISM\textsuperscript{18}</th>
<th>TRAMI\textsuperscript{19}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=351 1-year follow up</td>
<td>n=557 Median follow up 6 months</td>
</tr>
<tr>
<td>In-hospital mortality (mean 10 days)</td>
<td>4.3%</td>
<td>24/554</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>4.8%</td>
<td>17/351</td>
</tr>
<tr>
<td>Mortality at post-discharge follow up (mean 75 days)</td>
<td>13.4%</td>
<td>41/307</td>
</tr>
<tr>
<td>12 month mortality</td>
<td>22.8%</td>
<td>80/351</td>
</tr>
<tr>
<td>MAE at 30 days</td>
<td>18.8%</td>
<td>66/351</td>
</tr>
<tr>
<td>(Blood transfusion ≥2 units)</td>
<td>13.4%</td>
<td>47/351</td>
</tr>
<tr>
<td>In-hospital MAE (mean 10 days)</td>
<td>19.4%</td>
<td>108/557</td>
</tr>
<tr>
<td>(Blood transfusion ≥2 units)</td>
<td>13.7%</td>
<td>75/546</td>
</tr>
<tr>
<td>MAE at 12 months</td>
<td>37.6%</td>
<td>132/351</td>
</tr>
<tr>
<td>(Blood transfusion ≥2 units)</td>
<td>22.5%</td>
<td>79/351</td>
</tr>
<tr>
<td>Re-hospitalisation for cardiac, cardiovascular and other reasons</td>
<td>38.6%</td>
<td>103/267</td>
</tr>
<tr>
<td>Major cardiac and cerebrovascular events</td>
<td>13.4%</td>
<td>14/307</td>
</tr>
<tr>
<td>Major vascular complications</td>
<td>2.2%</td>
<td>12/546</td>
</tr>
<tr>
<td>Major vascular complications at 12 months</td>
<td>3.4%</td>
<td>12/351</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0%</td>
<td>0 events</td>
</tr>
<tr>
<td>Stroke at 30 days</td>
<td>2.6%</td>
<td>9/351</td>
</tr>
<tr>
<td>Stroke at 6 months</td>
<td>0.7%</td>
<td>4 events</td>
</tr>
<tr>
<td>Stroke at 12 months</td>
<td>3.4%</td>
<td>12/351</td>
</tr>
<tr>
<td>Stroke due to device or air embolism</td>
<td>0%</td>
<td>0/351</td>
</tr>
<tr>
<td>Device malfunction related death</td>
<td>0%</td>
<td>0/351</td>
</tr>
<tr>
<td>Single leaflet device attachment</td>
<td>2.3%</td>
<td>8/351</td>
</tr>
<tr>
<td>Partial detachment from one of leaflets</td>
<td>2%</td>
<td>N/A</td>
</tr>
<tr>
<td>Second procedure required</td>
<td>1.1%</td>
<td>4/351</td>
</tr>
<tr>
<td>Mitral valve stenosis</td>
<td>0.9%</td>
<td>3/351</td>
</tr>
<tr>
<td>Procedural complications</td>
<td>8.9%</td>
<td>49/550</td>
</tr>
</tbody>
</table>
Thirteen smaller uncontrolled observational studies were identified. Comparison between studies was difficult due to variation in the characteristics of the included patients, the duration of follow-up and in the definitions of outcomes reported. Mortality data, for subgroups at high surgical risk where these can be identified, are summarised in Table 5. Study quality was assessed according to factors such as whether participants were recruited consecutively and entered the study at similar points in the disease. In studies assessed as acceptable quality, in-hospital mortality was around 4%, 30-day mortality ranged from 1.75% to 5.6% and 1-year mortality ranged from 10% to 22.8%. Study authors generally concluded that the MitraClip® procedure could be safely performed.

### Cost effectiveness

In 2013, a UK *de novo* cost-effectiveness model was developed to determine the cost-effectiveness of MitraClip® compared with conventional medical management in patients with severe MR, who were at high surgical risk (≥12% estimated risk of surgical mortality)34. The paper did not specify what treatments were included in medical management. A six state Markov model was used, which comprised of a short-term model feeding in to a long-term model. The short-term model captured intervention related activity; surgery, short-term subsequent MitraClip® procedures, intensive care, non-invasive care, home rehabilitation and death. The long-term model incorporated health states; home care, subsequent MitraClip®-related procedures, adverse events and death. Patients receiving MitraClip® started in the short-term model and patients in the control arm being treated with medical management entered the model in the home care state. The short-term model had a cycle length of 1 day and after 30 days surviving patients transitioned to the long-term model and the home care health state. Hereafter, and based on monthly cycles, the intervention cohort remained there until they moved onto subsequent procedures or death, and the control cohort patients remained in the home state until death. The model was assessed over a variety of time horizons, including 2 years, 5 years, and lifetime. The analysis discounts costs and benefits at a rate of 3.5%.

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### Table 5 Mortality data from uncontrolled observational studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>In-hospital mortality</th>
<th>30-day mortality</th>
<th>1-year mortality</th>
<th>Acceptable study quality*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeo20</td>
<td>142</td>
<td>4.2%</td>
<td>5.6%</td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Toggweiler et al.21</td>
<td>74</td>
<td>4.05%</td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Vandendriessche et al.22</td>
<td>41</td>
<td>12%**</td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>EVEREST II HRR + REALISM18</td>
<td>351</td>
<td>4.8%</td>
<td>22.8%</td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Attizzani et al.23</td>
<td>171</td>
<td>1.75%</td>
<td>12.99%</td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Hellhammer et al.24</td>
<td>80</td>
<td>3.75%</td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Braun et al.25</td>
<td>119</td>
<td>2 events***</td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Alegria-Barrero et al.26</td>
<td>43</td>
<td>10%</td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>TRAMI19</td>
<td>557</td>
<td>4.3%</td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Armoiry et al.27</td>
<td>62</td>
<td>3.2%</td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Bozdag-Turan et al.28</td>
<td>121</td>
<td>23.1%</td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Rudolph et al.29</td>
<td>663</td>
<td>4.22%</td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Hellhammer et al.30</td>
<td>58</td>
<td>1.72%</td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Reichenspurner et al.31</td>
<td>33</td>
<td>9.1%</td>
<td>24.2%</td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Kolman et al.32</td>
<td>20</td>
<td>10%^</td>
<td></td>
<td></td>
<td>N</td>
</tr>
</tbody>
</table>

*assessment using tool adapted from Moga C et al.33

**in-hospital MAE (death, additional major bleeding, need to undergo major cardiac surgery)

***denominator unclear

^mean follow up 231 days
Data for the MitraClip® arm were taken from the single arm prospective high-risk cohort of 78 patients in the EVEREST II HRS, which is described above in the clinical section of the evidence note14. It is worth noting here that the majority of the data for the comparator arm is based upon patients who were excluded from the EVEREST II HRS as they were not physically eligible for MitraClip® treatment. These data were used to model transition probabilities based on treatment related changes in NYHA class from baseline to 30 days, 12 months and 24 months. For the MitraClip® arm, it was assumed that the changes in NYHA were linear over time up to 2 years following the intervention. After 2 years, NYHA class was assumed to remain constant. Data for the medical management arm for 36 patients were taken from the published literature, which were for a cohort of patients receiving medical management with similar MR, risks and co-morbidities who were screened for the EVEREST II HRS cohort but were not enrolled. It was assumed that the baseline NYHA were constant over time. The authors justified this on the basis that due to high mortality rates associated with severe NYHA classifications, there would not be a build-up of patients in that stage over time. Mortality and other treatment-related events had been built into the model based on data from the EVEREST II HRS or the published literature. Drug costs and resource use were taken from the British National Formulary and UK National Services Schedule of Resource Costs. Utility values were elicited from the published literature and decrements applied for specific health states and events as appropriate.

The results presented in the paper estimated an incremental cost effective ratio (ICER) for the 2 year time horizon model of £52,947; this was based on an incremental cost associated with MitraClip® of £25,565 and an additional quality adjusted life year (QALY) of 0.48. The results were also presented for a 5-year time horizon estimating an ICER of £22,000; this was based on an incremental cost associated with MitraClip® of £27,000 and an additional QALY of 1.22. These results showed that between years 2–5 there is not a substantial increase in the incremental costs (£5,000) but a reasonably large increase in the incremental QALYs gained (0.74). The key driver of the incremental costs associated with MitraClip® was the implant costs, which include the device and additional resource use. Probabilistic sensitivity analysis demonstrates that, over a 5-year time horizon and at a willingness to pay threshold of £20,000 and £30,000, the probability that MitraClip® was cost-effective was 37% and 93%, respectively. The paper presented a variety of deterministic sensitivity analyses, however; these were based on the lifetime time horizon of 20 years and were not provided for 2 or 5 years. A variety of sensitivity analyses were conducted by the authors, for example changing the utility decrements, the cost of the procedure and short-term reoperation rate. The sensitivity analysis was conducted on the lifetime time horizon. Based on this, the model was most sensitive to reducing the time horizon to 2 years and also reducing the cost of MitraClip®.

There were a number of limitations surrounding the analysis. Firstly, a key weakness related to the lack of randomised comparative patient level data from a large cohort, with the model relying on aggregated data from one study with small patient numbers. Furthermore, a significant weakness in the paper was that a proportion of the control arm patients may not have been anatomically eligible for MitraClip®. This is to say that, as detailed above, while at baseline the risk scores and patient characteristics of the two cohorts were similar, the patients in the control arm were not physically eligible for MitraClip® treatment, and thus excluded from the EVEREST II HRS. The comparator arm did not provide a relevant and appropriate comparison on which to base the cost-effectiveness.

In addition, data on the number of patients requiring additional MitraClip® devices to be fitted was incomplete and the numbers could have been higher which would reduce the cost-effectiveness of MitraClip® – the EVEREST II HRS reported that 29% of patients needed to receive more than one device during the initial procedure. However, the paper stated that the manufacturer policy was to charge per procedure not per device, so if a patient required more than one device that would not incur any additional cost.

There was a lack of post-12 month data on MitraClip® replacement rates and procedures. The paper commented that they had data from an Italian modelling study and EVEREST II which reported no additional procedure costs. However,
from clinical studies, repeat procedures may be in excess of 3%, which may not have a impact on the cost-effectiveness but if in practice this was likely to be higher than 3% then this may increase the ICER.

In conclusion, the paper was from a UK NHS perspective estimating that over a 5 years or greater time horizon, MitraClip® was a cost effective treatment option for inoperable patients, but is at the upper limits of the conventionally accepted UK willingness to pay thresholds. However, the key weakness was the lack of data from randomised trials and that patients in the control arm were not truly representative of the patients eligible for MitraClip®. In addition, there was a lack of long-term data which introduced some uncertainty surrounding the estimates. That may result in the treatment effect of MitraClip® being overestimated, and inevitably leads to a high level of uncertainty surrounding cost-effectiveness of MitraClip® for patient ineligible for surgery.

In addition to the above study, in 2014, a Canadian de novo cost-effectiveness model was developed to determine the cost effectiveness of MitraClip® compared with standard care in patients with severe MR, who were at high surgical risk (≥12% estimated risk of surgical mortality)35. The model was a Markov model with a 1-month short-term health state where surviving patients graduate to a long-term model, over a lifetime time horizon. Costs and benefits were discounted at 5% - which is not the recommended rate for the UK (3.5%). As with the UK paper described above, the transition probabilities in the model were taken from the EVEREST II HRS. Resource utilisation data were taken from the EVEREST II HRS, and also from the published literature. Utility decrements were included for procedures and adverse events. The authors estimated a base case ICER over a lifetime time horizon of $23,433 Canadian dollars (£11,555) [all conversions based upon exchange rate as of 16 November 2015]; this was based upon an incremental cost of $40,617 (£20,028) and an incremental QALY gain of 1.73. Sensitivity analysis was conducted and the results were only sensitive to increasing the overall survival hazard ratio to the 95% confidence interval upper bound for MitraClip® which increased the ICER to $84,895 (£41,862). Probabilistic sensitivity analysis demonstrated that at a willingness to pay threshold of $50,000 (£24,655) per QALY, MitraClip® was 92% cost-effective over a lifetime time horizon.

This economic analysis is very similar to the UK study described above, and varies in that it was built from a Canadian perspective. With this in mind, the analysis contains many of the same uncertainties as described earlier; small numbers, non-randomised data and the issues surrounding the comparator arm. However, the analysis parameters and cost data were created from a Canadian perspective, which limits the generalisability of the study to the UK.

Conclusion

In FMR or DMR patients at high surgical risk, non-comparative observational studies, with up to 1-year of follow up, indicate that the MitraClip® procedure is associated with improvements in MR, symptoms and patient QoL and is considered by study authors to have a reasonable safety profile. From the current evidence base it is not possible to directly compare outcomes with standard care for this patient group. The Valvular Academic Research Consortium published recommendations for study design and outcomes for transcatheter mitral valve interventions12,36. The group strongly recommends RCTs with collection of comparative end points and suggests that separate analyses of DRM and FMR are required along with longer term data on safety and durability of the device.

In a UK analysis, assuming a 5 year time horizon onwards, MitraClip® is at the upper limits of conventionally accepted UK cost-effective thresholds for patients at high surgical risk (≥12% estimated risk of surgical mortality). However, there are limitations with the model including; small patient numbers, a lack of randomised comparative data and significant issues with the appropriateness of the patients included in the comparator arm.
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References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network http://www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

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References

References continued


References continued


