The MitraClip system (MCS; Abbott Vascular, Santa Clara, CA) is a percutaneously delivered device aimed at reducing severe mitral valve regurgitation (MR) by approximating the mitral valve leaflets. The device is introduced through the femoral vein and advanced into the left atrium through a transseptal puncture. With echocardiographic guidance, the MitraClip is permanently placed in a fashion that approximates the anterior and posterior leaflets as seen in the surgical technique by Alfieri and De Bonis, although it should be noted that this technique includes mitral annuloplasty as an essential component. After being in development for more than a decade, the MCS was approved for commercial use in Europe in 2008 and is recommended by the European Society of Cardiology for use in patients with symptomatic severe MR who are determined to be inoperable or at high surgical risk by a heart team and who have a life expectancy >1 year (recommendation Class IIb, Level of Evidence C). The MitraClip is currently approved for use in >40 countries with >8000 patients having been treated with this device, most of whom are at high surgical risk.

On March 20, 2013, the Food and Drug Administration’s (FDA’s) Circulatory System Devices Panel met to discuss the premarket approval (PMA) application for the MCS. The scientific data presented to support the PMA were based on the pivotal randomized, controlled Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II trial, along with data from 2 registries: 1 derived from a subgroup analysis of the EVEREST II data and 1 derived from continued-access registries.

Evolution of EVEREST Trial Data to Support the PMA

The first US MCS clinical trial, EVEREST I, was a single-arm feasibility registry of 55 patients. This trial completed its 5-year follow-up with reassuring results. The pivotal EVEREST II trial, initiated in August 2005, was a randomized, controlled trial comparing the MCS (n=184) with mitral valve surgery (n=95) in a 2:1 ratio. The study aimed to establish superior safety and noninferior efficacy of the MCS compared with mitral valve surgery. The primary safety end point was a nonhierarchical composite of 12 major adverse events at 30 days. The study met the superiority safety end point, with differences between groups driven mainly by a greater need for blood transfusions in the surgical arm (45% versus 13%; P<0.001). There were no differences in death, stroke, myocardial infarction, or infection rates. For efficacy, the sponsor designed the end point to be noninferior with a 31% margin, meaning that the clinical success of MCS is no worse than that of surgery at 12 months if the rate of the primary efficacy end point with MCS is not more than 31 percentage points from that of surgery. These margins, agreed on by the FDA, are very broad, especially when considering that all patients in this cohort were operable and could have benefited from surgery. The rate of the primary efficacy end point (freedom from death, from surgery for mitral valve dysfunction, and from grade 3+ or 4+ MR at 12 months) was lower in the MCS group compared with the surgery group (55% versus 73%; P=0.007), which indicates that even when liberal definitions for success were used (ie, MR of 2+ at 12 months), the MCS was found to be inferior to surgery for the studied population because the lower bound of the 95% confidence interval for the treatment effect exceeded the prespecified delta.

After acknowledgment by the sponsor that MR reduction by the MCS was not sufficient for patients who are candidates for surgery, the sponsor decided to narrow the proposed indication for use. As expressed in the modified PMA (Table 1), the proposed indication for use of the MCS is in patients with MR classified as being too high risk for surgery. To support this modified indication, a subset of 78 patients meeting prespecified high-risk criteria (Table 2) was prospectively collected from the EVEREST II High-Risk Registry (HRR). Because the number of patients in this cohort was insufficient to support the PMA, a second cohort of 273 high-risk patients intended to meet similar high-risk criteria was collected from the Real World Expanded Multicenter Study of the MitraClip System (REALISM) registry. Data from these 2 registries (EVEREST II HRR and REALISM High-Risk [HR]) were pooled and retrospectively analyzed to support PMA approval.

Controversies in Trial Design and Data Interpretation

The sponsor’s post hoc analysis of the pooled data from the EVEREST II HRR and the REALISM HR was intended to support PMA approval for using MCS in patients at high risk...
for surgery. Dr Patrick McCarthy (Northwestern University) spoke on behalf of the sponsor, describing the need for the MitraClip in patients with MR. According to Dr McCarthy, although surgery is the standard of care in degenerative MR, in functional MR, this is not the case. Many MR patients, mostly those with functional MR, have multiple comorbidities, which elevate their risk of morbidity and mortality to an unacceptable level that outweighs the benefits of surgery. Thus, a definition of too high risk for surgery was established by the sponsor to include this patient population. It was not clear, however, whether the population of patients included in the discussed registries was indeed too high risk for surgery. Both registries used similar criteria for defining these high-risk patients (Table 2). High-risk patients were included in 1 of 2 pathways: patients with a calculated Society of Thoracic Surgeons (STS) score ≥12% or patients with an STS score <12% but deemed by surgeons to be high risk for operation by meeting ≥1 of the prespecified criteria. Because most of the patients were included through the second pathway, cardiothoracic surgeons on the panel suggested that with the use of the aforementioned definitions, at least some of the included patients are in fact operable. Furthermore, <62% of patients were actually seen by cardiothoracic surgeons before the decision was made to include them in the group that was too high risk for surgery. Although the sponsor’s aim was to include high-risk patients (not necessarily inoperable), panel discussions were focused mainly on the operability of the included patients. After deliberation, the panel concluded that a mix of high-risk, operable patients and nonoperable patients was included in the presented data, which argues against the interpretation of data collected for PMA approval according to the indication for use. Panel member Val Jeevanandam (University of Chicago) commented on the presented data by stating that probably 60% of the patients in these cohorts were not completely inoperable.5

The second issue that arose referred to the pooled data garnered from 2 separate registries. The 2 registries were conducted with a 1-year gap between them and with potential differences in operator experience. Such differences may have skewed the outcome results. Moreover, although similar inclusion criteria were used for both registries, major differences were noted between important baseline characteristics (eg, mean ejection fraction, MR etiology and STS predicted risk), which may indicate different risk strata. After discussing these caveats, the panel did not support the pooling of data from these 2 registries. Panel member Dr Warren Laskey (University of New Mexico) stated that these are combined data from 2 separate and inherently different cohorts and thus should not be pooled.5

A third controversy surrounded the use of STS score for mortality prediction. The STS database is the largest cardiac surgical database, and its models for adverse events risk predictions are constantly changing. Since 2008, this model has been able to separately predict the risks associated with mitral valve replacement and mitral valve repair. This separation results in 50% to 100% higher STS scores for mitral valve replacement compared with mitral valve repair when similar risk factors are used.5

Although

Table 1. Indications for Use and the Data to Support Such Indications

<table>
<thead>
<tr>
<th>Sequence of PMA Proposals</th>
<th>Proposed Indication for Use</th>
<th>Support Data</th>
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<tbody>
<tr>
<td>Original proposal</td>
<td>The MitraClip Delivery System is intended for the reconstruction of mitral valve insufficiency through tissue approximation in patients with significant MR.</td>
<td>EVEREST II</td>
</tr>
<tr>
<td>Modified proposal</td>
<td>The MitraClip Delivery System is indicated for the percutaneous reduction of significant symptomatic MR (MR ≥3+) in patients who have been determined by a cardiac surgeon to be too high risk for open mitral valve surgery and in whom existing comorbidities would not preclude the expected benefit from correction of the MR.</td>
<td>EVEREST II HRR and REALISM HR registries</td>
</tr>
<tr>
<td>Panel proposal</td>
<td>The MitraClip Delivery System is indicated for the percutaneous reduction of significant symptomatic MR (MR ≥3+) in patients refractory to optimal medical therapy with at least a 1-year life expectancy and suitable anatomic criteria who have been determined by an experienced mitral valve surgeon or other members of a heart failure/heart team to be at excessive risk for open mitral valve surgery and in whom existing comorbidities would not preclude the expected benefit from correction of the MR.</td>
<td></td>
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Table 2. High-Risk Criteria for EVEREST II HRR and REALISM HR

<table>
<thead>
<tr>
<th>Calculated STS score ≥12% or Surgeon investigator-determined patient risk for mortality ≥12% owing to the presence of at least 1 of the following:</th>
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</thead>
<tbody>
<tr>
<td>Porcelain aorta or mobile ascending aortic atheroma</td>
<td></td>
<td></td>
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<tr>
<td>Postradiation mediastinum</td>
<td></td>
<td></td>
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<tr>
<td>Previous mediastinitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional mitral regurgitation with ejection fraction &lt;40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;75 y with ejection fraction &lt;40%</td>
<td></td>
<td></td>
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<tr>
<td>Prior reoperation with patent grafts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 prior chest surgeries</td>
<td></td>
<td></td>
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<tr>
<td>Hepatic cirrhosis</td>
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<td></td>
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<tr>
<td>≥3 of the following STS high-risk factors</td>
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<td></td>
</tr>
<tr>
<td>Creatinine &gt;2.5 mg/dL</td>
<td></td>
<td></td>
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<tr>
<td>Prior chest surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;75 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction &lt;35%</td>
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</tbody>
</table>

EVEREST indicates Endovascular Valve Edge-to-Edge Repair Study; HRR, High-Risk Registry; MR, mitral regurgitation; and REALISM HR, Real World Expanded Multicenter Study of the MitraClip System High Risk Registry.
Circulation August 20, 2013

this model was not available during EVEREST II enrollment, the FDA deemed the use of a risk score for mitral valve repair (as an entry criterion for a clinical trial) more appropriate than the risk score for mitral valve replacement. Although published data presented by the sponsor suggest that 85% of patients with an STS score >12% undergo mitral valve replacement and not repair, the majority of panel members agreed that the MCS procedure is a percutaneous analog for mitral valve repair and should be used when calculating the STS score as a comparator for MCS. The panel also acknowledged the caveat of the STS model, which does not capture relevant patient risk factors (ie, frailty); thus, other criteria should be taken into consideration when evaluating a patient’s appropriateness for the MCS.

The panel was asked by the FDA to reflect on the ability of post hoc analyses to support PMA approval. In general, PMA is based on valid scientific evidence. In contrast to drug approval, which requires 2 randomized, controlled trials, valid scientific evidence for device approval was defined by the FDA as:

- well-controlled investigations,
- partially controlled studies, studies and objective trials without matched controls,
- reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

Throughout the panel’s deliberation (after ascertaining the significant caveats of post hoc analyses), the majority of panel members agreed that this issue should not prevent PMA support for the intended patient population.

**Clinical End Points Scrutinized**
The criteria used for assessing effectiveness in EVEREST II and the registries that followed were freedom from death, mitral valve reintervention, and MR >2+. As a result of ample data demonstrating the correlation between the residual postoperative MR degree and the outcome of patients undergoing the Alfieri surgical mitral valve repair, the FDA suggested an alternative definition (MR ≤1+ at discharge as opposed to MR ≤2+ at discharge as defined by the sponsor) for EVEREST II. Some panel members argued against the use of <1+ as standard for patients deemed too high risk for surgery. As shown in Figure 1, however, with the use of the FDA’s definition of MR >1+ as a cutoff for lack of effectiveness, a similar outcome was demonstrated when the pooled data from the high-risk registries were compared with data from the MCS-treated patients in EVEREST II. This was counterintuitive because patients in these high-risk cohorts were expected to have poorer outcomes compared with the heterogeneous population of EVEREST II. It was concluded that this lack of difference may reflect the natural history of the disease; some even questioned the benefit provided by the MCS.

In the absence of an appropriate comparator, the sponsor presented inpatient efficacy data of the 2 high-risk cohorts. This included a statistically significant decrease in the left ventricular diastolic and systolic volumes at the 1-year follow-up in both cohorts (change in diastolic volume from 161 to 143 cm³ [P<0.001] and in systolic volume from 87 to 79 cm³ [P<0.001]), a 48% reduction in hospitalization rate, and a decrease in New York Heart Association class (number of patients in New York Heart Association class III/IV decreased from 82% to 17% in 1 year). Panel members acknowledged the limitations associated with interpreting the effectiveness data without a suitable comparator and expressed the need for clinically relevant data such as quality of life and use of medications for heart failure to establish effectiveness.

To support PMA approval, the sponsor refrained from claiming that the MCS is more effective than other therapies, although the sponsor did provide safety profile data from high-risk, nonoperable patients. To establish that the MCS

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Weibull plot of the freedom from death, surgery, or reoperation, and mitral valve regurgitation (MR >1+ for device and control (surgery) of the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II randomized, controlled trial (RCT) and integrated high-surgical-risk cohort. MV indicates mitral valve.
did not increase the rate of mortality, the sponsor compared the pooled data from the high-risk registries with data from the Duke University Medical Center database. From this database, 953 nonsurgically managed MR patients were identified as potential comparators to the first 211 consecutively enrolled patients in the high-risk registries. During the propensity matching, because of major differences in the compared populations, a trimmed Duke cohort (n=527) was established by excluding patients outside the range of mean±1.5 SD for both age and ejection fraction. The results of the matched 211 couples, presented in Figure 2, demonstrate similar rates of freedom from mortality at 1 year.

Even with these adjustments, Dr Vandana Mukhi, the FDA's statistician, described limitations when interpreting the sponsor’s model. First, certain covariates (eg, history of hypertension and smoking, STS score) were not included in the matched model. Second, the makeup of matched subsets for the final propensity match does not represent any well-defined population. Finally, the Duke University data may represent a different therapeutic era than that recorded by the high-risk registries. Thus, according to the FDA, the actual populations being compared are not well defined, and no conclusions can be deduced. Panel members argued that a propensity-matched model for comparison of mortality was problematic. The panel also criticized the use of mortality as the basis for comparison between the groups and noted that the presented data as follows: (1) EVEREST II did not provide reasonable safety and effectiveness data for using the MCS compared with standard surgical techniques in patients who were eligible for both alternatives; (2) the ability of the single-arm, high-risk registries to provide adequate and relevant data is limited by the unclear population studied and the lack of an appropriate control group; and (3) data analyzed with the propensity-matched Duke information are difficult to interpret.

Although the FDA’s request for sufficient efficacy and safety to support PMA approval use was not met and although the data presented by the Sponsor were criticized, some panel members suggested that MCS should be available as a palliative, last-resort therapy for specific patient subsets on the basis of the safety profile of the device. The panel's premise was expressed by a suggestion to modify the indication for use of the PMA (Table 1) to include patients refractory to optimal medical therapy with favorable anatomic features for MCS and expected life span >1 year. It was further recommended that a patient’s inoperability be decided on by a heart team that ideally includes an experienced mitral valve surgeon. Responding to the sponsor’s suggestion to conduct a postapproval study intended to establish the safety and effectiveness of the MCS, the panel argued against using freedom from mitral valve surgery as the primary effectiveness index and proposed using other indexes such as quality-of-life measures and rate of rehospitalization, which are more relevant for this patient population.

The meeting was adjourned. Panel members voted as follows:
1. Concerning the safety of the MCS, the panel unanimously voted in favor (8:0).
2. Concerning the effectiveness of the MCS, the panel voted against (5:4) accepting the effectiveness data presented by the sponsor, especially in light of the inability to define the population that may benefit most from the procedure.
3. The majority of the panel (5:3) voted that the presented benefits outweigh the risks and thus recommended approving the PMA application by Abbott Vascular.

Conclusions
The data presented by the sponsor on the safety and effectiveness of the MCS for high-risk patients were based on retrospective analyses of various data sets with many methodological faults and limited utility. On the other hand, the need for a therapeutic alternative for patients deemed too high risk for surgery who have exhausted all other therapies was considered by many panel members for the final risk/benefit vote. The panel acknowledged that for a novel device to serve an unmet clinical need, the level of evidence may be provided by registry data. Unfortunately, with the limited data presented, the public, physicians, and the FDA are left with major unanswered questions about the right patient population and the amount of effectiveness that can be expected from this device.
The panel recommendation is not binding to the FDA. The FDA is solely responsible for approving a device for marketing on the basis of its efficacy and safety performance in a specific study population. The dilemma for the FDA is whether to defer the approval until the completion and analysis of the Clinical Outcomes Assessment of the MitraClip Therapy Percutaneous Therapy for High Surgical Risk Patients (COAPT) trial or to grant an approval for narrower labeling as a palliative device for high-risk patients who are not candidates for surgery and who failed medical therapy. This dilemma underscores the need for sponsors and clinicians to work with the FDA to obtain useful safety and effectiveness data in an optimal and efficient manner. The data presented to the current panel discussing the MCS were markedly different in terms of quality compared with the data presented to 2 panel meetings addressing the approval of the transcatheter aortic valve. Clearly, data standards need to be improved in the mitral valve arena so that all stakeholders will benefit from new mitral technology. These should follow the standards applied in the PARTNER trials, including appropriate clinical end points (ie, New York Heart Association class and readmission rates). Given the totality of the safety data and the panel’s deliberation and recommendation, such a proposal is reasonable because it will provide US patients with severe MR who are too high risk for surgery access to a palliative technology.

Disclosures

None.

References


Key Words: heart valves ■ mitral valve ■ mitral valve insufficiency
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Sa'ar Minha, Rebecca Torguson and Ron Waksman

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