The EVEREST II Trial: Design and rationale for a randomized study of the evaclip mitraclip system compared with mitral valve surgery for mitral regurgitation

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Background Mitral valve surgery is the standard of care for patients with symptomatic mitral regurgitation (MR) or asymptomatic MR with evidence of left ventricular dysfunction or dilation. Whether an endovascular approach to repair can offer comparable effectiveness with improved safety remains to be determined in randomized trials.

Study Design The EVEREST II Trial is a multicenter, randomized controlled trial to evaluate the benefits and risks of endovascular mitral valve repair using the MitraClip device compared with open mitral valve surgery (control) in patients with moderate or severe MR. Using a 2:1 randomization ratio, the trial is enrolling up to 186 MitraClip-treated subjects and 93 control subjects. Trial end points include a primary efficacy end point: the proportion of patients free from death, surgery for valve dysfunction, and with moderate-severe (3+) or severe (4+) MR at 12 months; the primary safety end point includes the proportion of patients with death, myocardial infarction, reoperation, nonelective cardiovascular surgery, stroke, renal failure, deep wound infection, ventilation >48 hours, gastrointestinal complication, new permanent atrial fibrillation, septicemia, or transfusion of ≥2 U at 30 days or hospital discharge, whichever is longer.

Conclusions This randomized controlled trial is designed to evaluate the performance of endovascular mitral repair in comparison to open mitral valve surgery in patients with significant MR. (Am Heart J 2010;160:23-9.)

Patients with severe symptomatic mitral regurgitation (MR) have a poor prognosis with an annual mortality rate of 5% per year without surgical intervention1,2 and as high as 60% at 5 years when associated with significant heart failure.3,4 Medical management of MR is limited to controlling the symptoms of heart failure because no medical strategy has been shown to improve survival.5 Surgery is recommended for patients with symptomatic severe MR or asymptomatic severe MR with evidence of left ventricular (LV) dysfunction or dilation.6

Surgical options include mitral valve repair or replacement. When feasible, mitral valve (MV) repair is the operation of choice. Mitral valve repair is associated with improved clinical outcomes including improved LV function, lower mortality, and avoidance of chronic anticoagulation (mechanical valves) compared to valve replacement surgery.7 However, valve morphology is of critical importance for the success of valve repair, and when surgical repair is not possible, replacement may be the only alternative.

Reported operative or in-hospital mortality rates for MV surgery range from 1% to 2% for low-risk, young patients undergoing MV repair to as high as 25% for high-risk or elderly patients undergoing valve replacement.8-12 Comorbidities such as LV dysfunction, renal failure, or chronic obstructive pulmonary disease increase the risk of surgery significantly. Morbidity and mortality are significantly higher for reoperations.

Alfieri et al13 developed and pioneered a modified MV repair technique involving suturing of the middle scallops of the anterior and posterior MV leaflets at the origin of the MR jet, resulting in a double-orifice MV.14-16 This approach has been used predominantly for degenerative MR and is usually used in combination with an annuloplasty ring.
repair has been used in selected patients with durable results reported for as long as 12 years. These late results, reported by Maisano and Alfieri, were characterized as clinical proof of the principle of an endovascular approach.\textsuperscript{17-22}

An endovascular approach to MV repair has been developed that approximates the anterior and posterior MV leaflets with a mechanical implant, resulting in a double-orifice MV (MitraClip System, Abbott Vascular-Structural Heart, Menlo Park, CA).\textsuperscript{23} Animal implants of the MitraClip device did not result in the development of MV stenosis or hemolysis and showed the clip to be fully covered with tissue and securely attached to the leaflets at 12 months.\textsuperscript{24} The 12-month results of the first 107 nonrandomized patients treated in clinical trials of the MitraClip device for percutaneous MV repair have shown that the clip device can successfully reduce MR and be performed safely.\textsuperscript{25}

We describe the design of a randomized controlled trial to evaluate the performance of the MitraClip procedure to achieve mitral repair in comparison to MV surgery with cardiopulmonary bypass in patients with moderate-severe (3+) or severe (4+) MR.

\section*{Methods}

\subsection*{Study design and objectives}

EVEREST II is a prospective, multicenter, randomized, nonblinded study of the MitraClip System in the treatment of MV regurgitation (ClinicalTrials.gov #NCT00209274). The primary objective of this study is to evaluate the safety and effectiveness of the MitraClip System as an endovascular approach to the repair of MR compared with conventional MV surgery under cardiopulmonary bypass.

\subsection*{Device and procedure description}

The MitraClip System is a catheter-based device designed to perform endovascular reconstruction of the regurgitant MV while the heart is beating as an alternative to an open surgical approach. It includes a clip device (MitraClip) and a clip delivery system used with a steerable guide catheter that enables placement of the clip on the MV leaflet scallops, resulting in permanent leaflet approximation and a double-orifice MV (Figure 1). The procedure is performed percutaneously via the femoral vein in the cardiac catheterization laboratory with echocardiographic and fluoroscopic guidance under general anesthesia as previously described.\textsuperscript{23} After the procedure, patients receive aspirin 325 mg daily for 6 months and clopidogrel for 30 days.

The potential benefits associated with the use of the MitraClip device are related to reducing the need for open-chest surgery, cardiopulmonary bypass, and cardiac arrest. The potential risks associated with the use of the MitraClip for the treatment of MR include the risks associated with cardiac catheterization, including transseptal catheterization,\textsuperscript{26} the risk associated with general anesthesia, and risks uniquely associated with the use of the MitraClip device, such as device embolization.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure_1}
\caption{The MitraClip device. The device is covered with polyester fabric to facilitate tissue ingrowth. The gripping element helps with leaflet fixation. The clip delivery system exits through a guide catheter.}
\end{figure}

\section*{Patient population}

Eligible patients include those with symptomatic or asymptomatic moderate to severe (3+) or severe (4+) MR who are candidates for MV surgery and cardiopulmonary bypass (Table I). The inclusion criteria reflect the current indications for MV surgery for the treatment of significant MR.\textsuperscript{6}

\subsection*{Subject screening, enrollment, randomization, and follow-up}

All patients are screened for initial study eligibility by the principal investigator at each site (Figure 2). Both transthoracic echocardiographic and transesophageal echocardiographic studies are evaluated to determine patient eligibility. The echocardiographic core laboratory and the sponsor provide echocardiographic assistance and screening training to all sites to ensure standardization of assessment of MR.

The trial is being conducted at a maximum of 47 sites in the United States and Canada and will enroll up to 279 patients. The expected number of patients in the device arm is 186 (172 evaluable) and in the control arm is 93 (86 evaluable). Randomization will be administered in random blocks of 4 to 6. Sites use an interactive voice response system to complete the randomization assignment for each patient enrolled.

The study site principal investigator is required to consult with the study site cardiac surgeon to confirm that the potential subject is a candidate for MV surgery before randomization. Subjects are randomized in a 2:1 ratio to the MitraClip procedure (device arm) or MV surgery (control arm). After randomization, but before either treatment, patients are required to undergo a transesophageal echocardiogram within 3 days of the procedure to exclude the presence of intracardiac mass, thrombus, or vegetation. Patients undergo the assigned treatment with either the MitraClip system or MV surgery with repair at the discretion of the operator and using standard surgical techniques. Clinical,
laboratory, and echocardiographic follow-up occurs predis-
charge and at 30 days, 6 days, 12 days, 18 days, 24 months, and
annually to 5 years.

end points
The primary efficacy end point is freedom from the
composite end point of death from any cause, surgery for
valve dysfunction, and moderate-severe (3+) or severe (4+)
MR at 12 months (Table II).

The primary safety end point is the proportion of patients
with major adverse events (MAE), a composite end point of all
cause death, myocardial infarction, and additional adverse
events listed in Table II at 30 days.

In addition, there a number of prespecified secondary safety
and efficacy end points. Change in LV dimensions at 12 month

Statistical considerations
The primary objective of this prospective, multicenter,
randomized, nonblinded clinical trial is to evaluate the 30-day
safety and the 12-month efficacy of the MitraClip treatment
compared with surgical treatment of MR.

Primary analysis population. The primary safety and
effectiveness analysis will be on the per-protocol (PP) analysis set,
defined as patients randomized to MitraClip with acute procedural
success and patients randomized to control who underwent MV
repair or replacement surgery. A PP approach was chosen for the
criteria put forth by D’Agostino et al.\textsuperscript{26} in formulating an acceptable delta as preserving 50% to 80% of the superiority of the standard of care over placebo. Specifically, assuming that medical therapy (‘placebo’) is 0% effective at 12 months and that the standard of care, surgical therapy (‘active control’), is 90% effective at 12 months, a delta with absolute value 31% preserves 65% of the superiority of the effectiveness of the standard of care for the treatment of MR.\textsuperscript{28}

It is estimated that 80% of patients undergoing surgery in the trial will undergo MV repair and the rest will undergo MV replacement. It is estimated that the incidence of death at 12 months is approximately 3% based on reported in-hospital mortality of 1.5% and 6% in patients undergoing surgical repair and replacement, respectively.\textsuperscript{29} Recurrence of moderate or severe (3+ or 4+) MR at 12 months after MV repair surgery is estimated to be 4%.\textsuperscript{30,31} To reflect the high quality of the MV repair programs at the centers for EVEREST II, a conservative estimate of the reoperation rate is 3%. In the EVEREST II feasibility study, the rate of MR ≤2+ at 30 days excluding the first 2 training cases for each site was 79%. Thus, the estimated freedom from death, moderate to severe or severe MR, and surgery for valve dysfunction for the control arm at 12 months is assumed to be 90%, and in the device arm, assuming some reduction in efficacy between 30 days and 12 months, 72%.

Using the Farrington-Manning\textsuperscript{32} approach, a sample size of 206 PP patients (122 device, 84 control) will yield 80% power to declare noninferiority of the device arm at the .05 significance level. The total required randomized sample size is 279 patients (186 device, 93 control) to account for the PP (at least 73% of ITT for MitraClip) and lost to follow-up (≤5%).

**Primary safety end point.** The MAE rate at 30 days for the Control arm (ITT and PP analysis sets) is estimated to be 25% from the Society for Thoracic Surgeons report of similarly defined in-hospital composite end points.\textsuperscript{33} The MAE rate at 30 days for the device arm (ITT analysis set) is estimated to be 9.7% based on an MAE rate of 4% in subjects with acute procedural success (PP analysis set), an acute procedural success rate of 73%, and an MAE rate of 25% for patients without acute procedural success who undergo surgery to treat MR.

Often, tests of superiority are designed to detect any nonzero difference between treatments. In contrast, EVEREST II is designed and powered with a prespecified superiority safety margin to define a priori the balance between the safety and efficacy margins in the trial. The alternate hypothesis, therefore, requires the device arm MAE rate to be at least 6% lower than the surgical control MAE rate for the PP population to declare the MitraClip device superior to control with respect to safety. Specifically, the safety null and alternative hypotheses are the following:

\[
H_0 : \pi_M - \pi_C \leq -0.06 \quad \text{vs.} \quad H_1 : \pi_M - \pi_C > -0.06
\]

where \(\pi_M\) and \(\pi_C\) are the primary safety end point rates for MitraClip and control, respectively.

With the assumptions above, a sample size of 166 PP patients (98 treatment, 68 control) followed up to 30 days or hospital discharge, whichever is longer, and 1 interim analysis at 100 patients to evaluate conditional power of the safety end point, at a 1-sided significance level of .0013 (O’Brien Fleming boundary),\textsuperscript{34} will yield 80% power to declare superiority of the device arm by at least 6% at a 1-sided .025 level of significance (.0246 at

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<th>Table II. Study end points</th>
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<td><strong>Primary efficacy end point</strong></td>
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<td><strong>Primary safety end point</strong></td>
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<td>- MAE, defined as a combined clinical end point at 30 days of:</td>
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<td>- Death (all cause)</td>
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<td>- Myocardial infarction</td>
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<td>- Reoperation for failed surgical repair or replacement</td>
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<td>- Non elective cardiovascular surgery for adverse events</td>
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<td>- Stroke</td>
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<td>- Renal failure</td>
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<td>- Deep wound infection</td>
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<td>- Ventilation for &gt;48 hours</td>
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<td>- Gastrointestinal complication requiring surgery</td>
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<td>- New onset of permanent atrial fibrillation</td>
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<td>- Septicemia</td>
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<td>- Transfusion of 2 or more units of blood</td>
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primary endpoint to assess device outcomes, while the intention to treat analysis was for assessment of treatment strategy. Acute procedural success is defined as successful placement of the device with resulting MR severity ≤2+ as assessed by the core laboratory upon review of the discharge echo. If attempts to place a clip or multiple clips do not adequately reduce MR, patients will be referred for elective surgical repair or replacement of the MV and will continue to be followed. A PP analysis was chosen as the primary analysis because it is considered a more conservative approach for efficacy because in an intent-to-treat (ITT) analysis: patients randomized to MitraClip who do not have a clip implanted and then receive surgical MV replacement therapy could bias the efficacy rate favorably for the MitraClip arm under ITT. Such patients may bias the clip unfavorably for safety in ITT analysis. Formal hypothesis testing on the primary efficacy and safety end points will also be performed on the ITT analysis set as a secondary analysis.

**Sample size calculation**

**Primary efficacy end point.** The study is powered to show noninferiority of device to control on the primary effectiveness end point by a prespecified noninferiority margin \(\delta\). Specifically, the efficacy null and alternative hypotheses are the following:

\[
H_0 : \pi_M - \pi_C \leq \delta (\delta < 0) \quad \text{vs.} \quad H_1 : \pi_M - \pi_C > \delta
\]

where \(\pi_M\) and \(\pi_C\) are the primary efficacy end point rates for MitraClip and control, respectively. The noninferiority margin \(\delta\) is based on clinical judgment and should be suitably conservative.\textsuperscript{27,28} A margin of \(\delta = -0.31 (-31\%)\) was prespecified in view of the expectation that the MitraClip treatment may have a lower success rate of reducing MR compared to surgery but is likely to have significantly lower procedural risk. Whether the MitraClip procedure is associated with reduced procedural risks will be formally tested according to the primary safety end point. Furthermore, the acceptability of this margin of effectiveness requires that attempted clip treatment does not preclude subsequent valve surgery. This margin also satisfies the
final analysis). The total randomized sample size is 279 patients (186 treatment, 93 control). Sufficient power is present to test a prespecified superiority margin of 2% for the ITT analysis set.

Analysis plan. Formal statistical tests of the primary hypotheses discussed above will be carried out on the ITT and PP analysis sets, with the PP analysis being considered primary. Because the PP analysis set is a subset of randomized patients, treatment imbalance may exist on baseline characteristics. Thus, PP analysis on the primary safety and efficacy end points will adjust for baseline characteristics through propensity score adjustment.35

For each of the primary efficacy end points, the difference between the observed rates will be presented (device minus control) with either its 1-sided 95% lower confidence bound (efficacy end point) or its 1-sided upper 97.5% upper confidence bound (safety). If the efficacy end point’s lower bound is > 0.31, then noninferiority of device to control on efficacy will be claimed to have been met; if the safety upper bound is < -0.06 for PP (-0.02 for ITT), then superiority of device over control on safety will be claimed to have been met for PP (ITT).

The CIs will be unadjusted32 for both analysis sets and, if necessary for PP, also adjusted for propensity score quintile35 using the adjustment method of Koch et al.36 Missing data due to premature withdrawal will be handled by several approaches, including a Kaplan-Meier approach (where patients are censored at last known follow-up or the scheduled end of follow-up, whichever is earlier) and multiple imputation. Results from the various approaches for handling missing data will be compared to assess sensitivity of results to missing data.

Prospective 5-year follow-up is planned in all subjects. At the time of the 12-month end point reporting however, not all patients will have had extended follow-up beyond 12 months. To assess durability of the 2 treatments beyond 12 months, a secondary Bayesian analysis comparing the treatment groups based on their 18-month and 24-month expected outcomes for the PP population of the primary effectiveness end point will be performed and differences reported with credibility intervals.

Data collection

All required data for the trial will be collected on standardized Case Report Forms. All protocol-mandated echocardiograms and electrocardiograms will be sent to an independent core laboratory (University of California, San Francisco). Quantitative assessment of MR will be performed by the core laboratory using previously published techniques.37 Data management and study analyses will be performed by Harvard Clinical Research Institute (Boston, MA).

Data safety monitoring board

An external, independent Data and Safety Monitoring Board, composed of at least 2 clinicians with expertise in interventional cardiology, a cardiac surgeon, and a statistician, will monitor trial progress including any interim analyses of safety and make recommendations regarding study modification or termination.

After the first 100 PP patients have completed 30-day follow-up, an interim statistical analysis assessing the superiority null hypothesis on the 30-day MAE end point will be carried out on the PP analysis set by an independent statistician and presented to the Data and Safety Monitoring Board. The Lan-DeMets alpha-spending function, based on the O’Brien-Fleming philosophy, will be used for the interim analysis, as described above.

The EVEREST II Trial is funded by Abbott Vascular. The academic authors (L.M., P.G., J.M.M., E.F., D.G., T.F.) are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper and its final contents.

Discussion

Mitral valve surgery is the current standard of care for the definitive treatment of significant MR. We report the design of the first randomized controlled clinical trial of an endovascular treatment for MR. The study is designed to determine whether an endovascular procedure can successfully reduce MR and improve safety compared with MV surgery.

The design of trials comparing endovascular to surgical interventions can be challenging. The expected complications from endovascular procedures and surgical procedures are different in type and relative incidence and, therefore, need to be weighed qualitatively as well as quantitatively. An additional challenge is that although MV surgery with repair when anatomically feasible is considered to be the clinical gold standard for therapy, there have not been randomized trials to definitively assess outcomes in long-term follow-up. Therefore, expected outcomes are based on voluntary datasets of in-hospital events, such as the Society for Thoracic Surgeons database or case series from high-volume surgical centers. As a result, there is some uncertainty in estimation of rates on which to base such a trial.

Furthermore, it is critically important that patients are eligible for both procedures as assessed by both surgeons and interventionalists. Ultimately, if in trials the device is clinically successful, in practice, a decision for a course of therapy between these 2 options would be decided by careful consideration among both types of proceduralists and noninvasive cardiologists weighing the complete evidence of risk and benefit.

Some key lessons can be learned from trials comparing percutaneous versus surgical treatments. The overall benefit of a procedure requires weighing of the relative risks and benefits in specific patient populations. A reasonable balance between safety and effectiveness must be documented—an endovascular treatment that may not be superior to but performs within a specified margin of effectiveness may still be an optimal choice for individual patients when safety is superior. Within the example of early angioplasty, despite a less durable result compared with bypass surgery, many patients and clinicians chose the less invasive approach to avoid upfront procedural risks of surgery. The requisite assumption was that these patients who had recurrent stenosis in the target vessel would still be eligible for future revascularization procedures—either percutaneous or surgical. Similarly, in the EVEREST II Trial, it will be
important to assess the safety of repeat procedures such as surgery after MitraClip treatment. If, as has been observed in the EVEREST I feasibility trial, patients can safely and effectively undergo successful open MV repair or replacement after the MitraClip procedure, then even in the presence of some reduction in efficacy, there may be benefit to delaying the need for future surgery. Surgery may be avoided altogether in patients with a successful result. This strategy has also been used for many years using balloon valvuloplasty to perform mitral commissurotomy for MV stenosis.

Studies of a first in class therapy by definition require comparison of 2 very different types of treatment associated with different expected outcomes and complications. In the case of MR, this gold standard is MV surgery. The EVEREST II Trial is a randomized trial designed to compare the results of novel catheter-based MV repair compared with open surgical MV surgery for MR.

References