Chapter 23: The evidence base for transcatheter mitral valve repair (TMVr)

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EVEREST Trials

The EVEREST I trial was a prospective single arm study that recruited patients between September 2005 and November 2008 at 37 different study sites in North America(1,2). The objective was to evaluate the feasibility, safety, and efficacy of the Mitral Clip system (Evalve Inc., now Abbott Vascular). Patients with 3 to 4+ functional or degenerative MR, left ventricular ejection fraction (LVEF) > 25%, and a left ventricular end-systolic diameter (LVESD) ≤ 55 mm were enrolled. Asymptomatic patients were required to have at least one of the following (a) an LVEF of 25% - 60%, (b) LVESD of 40 mm - 55 mm, (c) new atrial fibrillation (Afib), or (d) pulmonary hypertension (PH). Anatomically, the primary regurgitant jet had to originate from malcoaptation of the middle scallops of the anterior and posterior leaflets. All patients had to be candidates for mitral valve surgery. The trial enrolled 107 patients.

The procedure was successful in 74% of patients; of those, the composite primary efficacy endpoint of freedom from death, mitral valve surgery, or MR >2+ at 12 months was reached in 50 of 76 (66%) patients. Ten (9%) had a major adverse event, including 1 nonprocedural death. Furthermore, 10 (9%) patients experienced partial clip detachment. At discharge, 64% of patients had ≤1+ MR. During 3.2 years of mean follow-up, 32 patients (30%) had mitral valve surgery; repair was successful in 84% of the patients in whom it had been planned. Freedom from death was 95.9% and 90.1% at 1 and 3 years respectively (2).

The EVEREST II, which randomized patients with functional or degenerative (grade 3+ or 4+) mitral regurgitation to either percutaneous repair or surgical treatment (repair or replacement) of the mitral valve, followed (3-5). While the two randomized groups were otherwise similar, there were more patients with a history of heart failure in the percutaneous group compared to the surgery group (91% vs. 78%). The primary composite efficacy end point was freedom from death, surgery for mitral valve dysfunction, and from grade 3+ or 4+ mitral regurgitation at 12 months. By the end of follow-up at 4 years, 39.8% of patients in the percutaneous repair group, vs. 53.4% in the surgery group, were free of the combined endpoint ($p=0.07$)(4). The difference was largely driven by mitral valve re-operation (20% for the percutaneous group vs 2 % for the surgery group at 1 year)(5). The primary safety end point was a composite of major adverse events within 30 days that included death, reoperation for failed mitral-valve surgery, myocardial infarction, non-elective cardiovascular surgery for adverse events, stroke, mechanical ventilation for more than 48 hours, gastrointestinal complication requiring surgery, renal failure, deep wound infection, new-onset permanent atrial fibrillation, septicemia, and transfusion of 2 units or more of blood. This was seen in 15% of patients in the percutaneous group vs. 48% of patients in the surgery group ($p<0.001$)(5). Both groups had similar improvements in secondary endpoints including left ventricular size, NYHA functional class, and quality-of-life measures.

At 5 years, the rate of the composite endpoint of freedom from death, surgery, or 3+ or 4+ MR in the as-treated population was 44.2% in the percutaneous arm versus 64.3% in the surgical arm (p=0.01)(6). Similar to previous findings, the difference was driven by higher rates of recurrence of 3+ to 4+ MR in the percutaneous repair arm. Importantly, there were no differences in long-term mortality.

A subgroup analysis was performed in the EVEREST II and REALISM registries of high-risk study patients(7). In the 351 patients with an estimated surgical mortality ≥12% by the STS risk score, procedural success was 96%, and the 30-day mortality was 4.8%, lower than the predicted STS mortality had they undergone surgery. The 12-month survival was 77.2%, freedom from mitral valve surgery 97.8%, and 83.6% of survivors had an MR grade of ≤2+. Left ventricular end-diastolic volume improved from 161 ml to 143 ml and end-systolic volume improved from 87 ml to 79 ml. NYHA functional class I/II was seen in 83% of patients at 12 months, compared to 18% of patients at enrollment. Finally, the annual rate of hospitalization for congestive heart failure decreased from 0.79 to 0.41 (p = 0.034).

The MitraClip thus proved safe and effective in patients at high risk of adverse events and mortality with surgery. While the mid- and long-term need for reintervention was higher in patients randomized to MitraClip vs. surgery, the reduction in short-term adverse events and improvements in symptoms with the MitraClip device makes it a useful new therapy.

The EVEREST trials were not without their limitations. The EVEREST II trial was randomized but patients and their physicians were not blinded, though the endpoint adjudicators were. Multiple etiologies of MR were included, which may have limited the ability to draw conclusions on the utility of the MitraClip system for specific MR etiologies. Importantly, there is a suggestion that in cases in which MR recurs after percutaneous repair and requires surgery, the chances of a successful repair rather than a replacement are decreased. In addition, outcomes were not analyzed in a center-specific fashion, even though outcomes of mitral valve surgery are known to vary widely across centers.

The MitraClip device was approved based on these trials for treatment of patients with significant symptomatic degenerative MR (MR≥3+). These patients have to be determined to be of prohibitive surgical risk by a heart team that includes an experienced mitral valve surgeon and a cardiologist experienced in mitral valve disease. Finally, those patients must also not have comorbidities so significant as to preclude the benefits of correction of the MR.

The COAPT trial

In an effort to both strengthen and add labeling claims regarding safety and clinical benefits of the MitraClip System for symptomatic heart failure patients with at least moderate-to-severe functional MR, the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) Trial has been designed. Enrolled patients must be determined by a heart team to not be suitable for surgical repair/replacement. The plan is for approximately 610 patients (305 in each arm) to be randomized at up to 100 centers. The anticipated primary completion date is in 2020 with a follow-up completion date of 2024. Preliminary data on the first 51 roll-in subjects has been presented at the Transcatheter Cardiovascular Therapeutics meeting in 2017, demonstrating 94% successful implant, no 30-day mortality, and infrequent complications(8).

Table 1. Inclusion and exclusion criteria of EVEREST and COAPT Trials

Trial	Inclusion	Exclusion	Primary endpoint
EVEREST I	MR≥3+ Symptomatic or asymptomatic with a: LVEF 30-50% and LVESD 50-55mm or LVEF 50-60% and LVESD < 45 mm or LVEF>60 and LVESD 45-55 mm Candidate for surgical repair	LVEF<30%, and/or LVESD >55mm Mitral valve orifice area <4.0 cm^2 Leaflet anatomy which may preclude MitraClip device implantation	Major Adverse Event rate through 30 days
EVEREST II	MR≥3+ Symptomatic with a: LVEF > 25% and LVESD ≤ 55 mm or asymptomatic with a: LVEF 25% to 60% LVESD ≥ 40 mm New onset of atrial fibrillation PASP>50mmHg at rest or >60 mmHg with exercise	LVEF≤25%, and/or LVESD >55mm Mitral valve orifice area <4.0 cm^2 Leaflet anatomy which may preclude MitraClip device implantation	Safety: Major Adverse Event rate through 30 days or discharge, Efficacy: Freedom from death, MV surgery and MR > 2+ at 12 months
EVEREST II high risk	MR≥3+ STS mortality risk ≥12% or judged to be high surgical risk by CT surgeon (using prespecified criteria)	LVEF<20% and/or LVESD>60mm Mitral valve orifice area <4.0 cm2 Leaflet anatomy which may preclude MitraClip device implantation	Safety: Procedural mortality at 30 days
COAPT	Functional MR ≥ 3+ Symptomatic with: NYHA ≥ II Not surgical candidate ≥1 HF hospitalization in last year, or BNP ≥ 300 pg/ml	LVEF<20%, LVEF>50% Leaflet anatomy which may preclude MitraClip device implantation	Safety: Composite of single leaflet device attachment, device embolization, endocarditis requiring surgery, mitral stenosis requiring surgery, LVAD,

			heart transplant, any device complications requiring non-elective cardiovascular surgery <u>Effectiveness:</u> Freedom from death, HF hospitalization

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