Results From the EVEREST II Trial

Percutaneous mitral valve repair using the MitraClip System is a safe and effective treatment for patients with significant mitral regurgitation (MR). Two established strategies for the treatment of significant MR are medical management, which controls symptoms but does not address underlying pathophysiology or disease progression, and surgical repair or replacement, which is effective but invasive. Thus far, there is an unmet need for a less invasive treatment option, particularly among the elderly and in the presence of comorbidities. Ted E. Feldman, MD, Evanston Hospital, Evanston, IL, presented findings from the Endovascular Valve Edge-to-Edge Repair Study (EVEREST II; NCT00209274), which investigated a noninvasive mitral repair option for MR.

EVEREST II was a randomized, multicenter, controlled trial that included 279 patients (MitraClip Device, n=184; Control of Surgical Repair/Replacement, n=95) with moderate to severe (3+) or severe (4+) MR according to American College of Cardiology/American Heart Association guidelines who were candidates for mitral valve surgery. Patients in both groups were well matched at baseline. It is important to note that 73% of patients had degenerative MR and 27% of patients had functional MR in both groups.

The primary safety endpoint was major adverse event (MAE) rate at 30 days using a superiority hypothesis and per-protocol cohort. The primary effectiveness endpoint was clinical success rate or freedom from the combined outcome of death, mitral valve surgery or reoperation for mitral valve dysfunction, or MR >2+ at 12 months using a noninferiority hypothesis and per-protocol cohort. Additional analyses included intention-to-treat (ITT) for safety (MAE rate at 30 days) and effectiveness (freedom from composite of death, mitral valve surgery > 90 days or reoperation for mitral valve dysfunction >90 days postindex procedure, or MR >2+ at 12 months) and clinical benefit assessment using MR severity, left ventricular function, NYHA Functional Class, and quality of life (SF-36) survey as measures of clinical benefit.

The MitraClip device demonstrated superiority over control with regard to safety (p<0.0001). MAEs were observed in 9.6% of patients in the device group compared with 57.0% in the control group, an observed difference of 47.4% at 30 days (Table 1). Additionally, the MitraClip device was noninferior to control with regard to clinical success rate at 12 months (72.4% for the device group vs 87.8% for the control group; p=0.0012). Results of the safety and clinical success rates in the ITT analysis were similar to those of the per-protocol cohort. The device group demonstrated safety superiority (p<0.0001) and effectiveness noninferiority (p=0.0005) compared with control in the ITT analysis.

Table 1. EVEREST II - 30-Day MAEs.

30 Day MAE, non-hierarchical	# Patients experiencing event	
	Device Group (n=136)	Control Group (n=79)
Death	0	2 (2.5%)
Major Stroke	0	2 (2.5%)
Re-operation of Mitral Valve	0	1 (1.3%)
Urgent/Emergent CV Surgery	0	4 (5.1%)
Myocardial Infarction	0	0
Renal Failure	0	0
Deep Wound Infection	0	0
Ventilation >48 hrs	0	4 (5.1%)
New Onset Permanent AF	0	0
Septicemia	0	0
GI Complication Requiring Surgery	1 (0.7%)	0
All Transfusions ≥2 units*	12 (8.8%)	42 (53.2%)
Total % of Patients with MAE	9.6%	57.0%
	p<0.0001* (95% CI, 34.4% to 60.4%)	
*p<0.0001 if include major bleeding only		

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Clinical benefit was observed in the MitraClip and mitral valve surgery patients through 12 months. These patients demonstrated improvements in left ventricular function, NYHA Functional Class, and quality of life.

Based on these findings, the MitraClip procedure may be a feasible therapeutic option for selective patients with significant mitral regurgitation, and surgery remains an option after MitraClip procedure. Results from EVEREST II are promising with regard to safety, efficacy, and clinical benefit. However, MitraClip is an investigational device only and is not currently available for sale in the United States.

The Safety and Tolerability of Betrixaban Therapy

The oral direct factor Xa inhibitor betrixaban, at doses of 40 mg, 60 mg, and 80 mg once daily, is safe and well tolerated compared with dose-adjusted warfarin in patients with nonvalvular atrial fibrillation (AF) or atrial flutter. Michael D. Ezekowitz, MD, PhD, Vice President, Lankenau Institute for Medical Research, Thomas Jefferson Medical College, Wynnewood, PA, presented results from the Phase II, randomized, multicenter EXPLORE-Xa Trial (NCT00742859).

Dr. Ezekowitz pointed out a few important characteristics of betrixaban, including its effective half-life of approximately 20 hours and the fact that it is being codeveloped with an antidote. No dose adjustments for renal impairment or major drug interactions were anticipated during this trial, because betrixaban is excreted mostly unchanged through bile, with minimal renal excretion, and it is not a substrate for the CYP450 system.

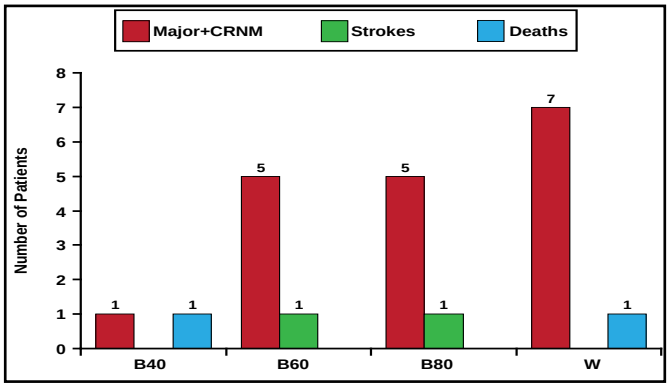
In EXPLORE-Xa, 508 patients with nonvalvular AF and at least one risk factor for stroke were randomized to receive betrixaban 40 mg (n=127), 60 mg (n=127), or 80 mg (n=127) or open-label warfarin (n=127) with an international normalized ratio goal of 2 to 3. The mean age was 74 years, and the median follow-up was 4.9 months (minimum follow-up 3 months; maximum follow-up 12 months). Patients were excluded from participation in the study if they had active endocarditis, AF due to reversible cases or mechanical heart valve, scheduled major surgery or pulmonary vein ablation, or repeated systolic blood pressure >160 mmHg; had received hemodialysis within one year; or experienced a recent ischemic stroke, systemic embolic event, or acute coronary syndrome within 30 days. The primary endpoint was occurrence of major or clinically relevant nonmajor bleeding. The secondary endpoints were time to occurrence of any bleeding (major, clinically relevant nonmajor, and minimal) and time to occurrence of death, stroke, myocardial infarction (MI), or other systemic embolism.

At 3 months, the rate of major or clinically relevant nonmajor bleeding in the betrixaban 40-mg group (n=1) was significantly less than in the warfarin group (n=4). Bleeding rates in the groups that received betrixaban 60 mg (n=4) and 80 mg (n=5) were comparable with rates that were observed in the warfarin group. The number of strokes and deaths was low in all treatment groups (Figure 1). Patients who received the 40-mg betrixaban dose demonstrated a slight increase in d-dimer from baseline, and there was a trend toward a dose response with d-dimer activity across the dose spectrum.

Adverse events were equally distributed among the groups, with the exception of gastrointestinal adverse events. The incidence of vomiting, nausea, and diarrhea was more common in patients who received betrixaban. There was no difference in the incidence of alanine aminotransferase >2x the upper limit of normal in any of the groups (2.4% for betrixaban and warfarin groups).

Betrixaban 40 mg, 60 mg, and 80 mg appear to be well tolerated in patients with AF or atrial flutter. There was a dose-dependent effect on the primary endpoint of major or clinically relevant nonmajor bleeding that was associated with betrixaban therapy. More comprehensive evaluation in a larger study population is needed to determine the safety and efficacy of betrixaban therapy.

Figure 1. Bleeds, Strokes, and Deaths.



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Pooled Analysis of the REAL-LATE and ZEST-LATE Trials

Dual antiplatelet therapy (aspirin plus clopidogrel) did not appear to be more effective than aspirin alone in reducing the rate of cardiac death or myocardial infarction (MI), according to pooled data from the Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Artery Thrombotic Events (REAL-LATE; NCT00484926) and Evaluation of the Long-Term Safety After Zotarolimus-Eluting Stent, Sirolimous-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions Late Coronary Arterial Events (ZEST-LATE; NCT00590174) Trials. The two trials were merged due to their design similarity and slow enrollment, and merged results were presented by Seung-Jung Park, MD, PhD, Asan Medical Center, Seoul, Korea.

Current guidelines recommend the use of clopidogrel 75 mg daily for at least 12 months post-drug-eluting stent (DES) implantation, provided that the patient is not at high risk of bleeding. While early discontinuation of dual antiplatelet therapy is associated with a higher risk of late stent thrombosis in patients with DES, there is no consistent data regarding the appropriate treatment duration and the long-term outcomes that are associated with dual antiplatelet therapy in these patients. The merged data analysis by Dr. Park and colleagues sought to compare antiplatelet strategies in patients on dual antiplatelet therapy who were free of major adverse cardiovascular events (MACEs) and major bleeding for at least 12 months post-DES implantation.

Patients in these two open-label trials were randomized to receive either clopidogrel 75 mg daily plus low-dose aspirin (100 to 200 mg daily; n=1357) or low-dose aspirin alone (n=1344). Patients were well matched at baseline. However,