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# Extended Use of Percutaneous Edge-to-Edge Mitral Valve Repair Beyond EVEREST (Endovascular Valve Edge-to-Edge Repair) Criteria

## 30-Day and 12-Month Clinical and Echocardiographic Outcomes From the GRASP (Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation) Registry

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## ABSTRACT

**OBJECTIVES** This study sought to compare, in high-risk patients with 3+ to 4+ mitral regurgitation (MR) dichotomized by baseline echocardiographic features, acute, 30-day, and 12-month outcomes following percutaneous mitral valve repair using the MitraClip.

**BACKGROUND** The feasibility and mid-term outcomes after MitraClip implantation in patients with echocardiographic features different from the EVEREST (Endovascular Valve Edge-to-Edge Repair) I and II trials have been scarcely studied.

**METHODS** Clinical and echocardiographic outcomes through 12-month follow-up of consecutive patients who underwent MitraClip implantation were obtained from an ongoing prospective registry. Two different groups, divided according to baseline echocardiographic criteria (investigational group [$EVEREST_{OFF}$] and control group [$EVEREST_{ON}$]), were compared.

**RESULTS** Seventy-eight patients were included in $EVEREST_{OFF}$ and 93 patients in $EVEREST_{ON}$ groups. Important and comparable acute reductions in MR and no clip-related complications were revealed. The primary safety endpoint at 30 days was comparable between groups (2.6% vs. 6.5%, respectively, $p = 0.204$); in addition, MR reduction was mostly sustained, whereas equivalent improvement in New York Heart Association functional class were demonstrated. Kaplan-Meier freedom from death, surgery for mitral valve dysfunction, or grade ≥3+ MR at 12 months was demonstrated in 71.4% and 76.2%, respectively, in the $EVEREST_{OFF}$ and $EVEREST_{ON}$ groups (log rank $p = 0.378$). Significant improvements in ejection fraction and reduction in left ventricle volumes were demonstrated in both groups over time, but the baseline between-group differences were sustained.

**CONCLUSIONS** MitraClip implantation in patients with expanded baseline echocardiographic features, compared with the control group, was associated with similar rates of safety and efficacy through 12-month follow-up. Further validation of our findings is warranted. (J Am Coll Cardiol Intv 2015;8:74–82) © 2015 by the American College of Cardiology Foundation.

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Severe mitral regurgitation (MR) leads to incremental left ventricle (LV) dysfunction and increasing rates of hospitalization for heart failure (1). Although mitral valve surgery is the gold standard therapy in patients with moderate-to-severe (3+) or severe (4+) MR associated with symptoms or evidence of LV dysfunction (2), its benefits are controversial in functional MR, where lack of survival benefit and high rates of recurrence have been demonstrated (3). In addition, morbidity and mortality among high-risk patients that undergo mitral valve surgery are relevant in this setting (4,5), which explains why a substantial proportion of patients is referred to isolated medical management rather than surgery in daily clinical practice. Notably, although medical therapy mitigates symptoms, it does not modify the progression of the disease (6).

Percutaneous edge-to-edge mitral valve repair with the MitraClip system (Abbott Vascular, Abbott Park, Illinois) recently emerged as a viable, less invasive, therapeutic option in patients with 3+ or 4+ MR associated with high surgical risk (7). Patients from the initial experience, as well as the ones included in the only randomized controlled trial conducted so far, however, had to fulfill strict echocardiographic criteria to be considered suitable for MitraClip therapy, which largely limited its indications (7,8). Conversely, real-world registries broadened the indications for MitraClip implantation and a significant amount of included patients did not meet the previously established echocardiographic criteria (9,10), but data regarding early and mid-term outcomes in this subset are lacking. On this background, we aimed at assessing the 30-day and 12-month clinical and echocardiographic outcomes after MitraClip implantation in real-world patients who did not meet the key echocardiographic eligibility criteria determined by the EVEREST (Endovascular Valve Edge-to-Edge Repair) I and II studies (7,8).

**ABBREVIATIONS AND ACRONYMS**

**EF** = ejection fraction

**LV** = left ventricle

**MR** = mitral regurgitation

**NYHA** = New York Heart Association

## METHODS

**PATIENTS AND PROCEDURES.** Patients with symptoms or signs of LV deterioration and 3+ or 4+ MR determined by combined transthoracic and transesophageal echocardiogram (11) considered to be at high surgical risk by an interdisciplinary team of cardiologists, interventional cardiologists, cardiac surgeons, and anesthesiologists underwent percutaneous edge-to-edge mitral valve repair with MitraClip at Ferrarotto Hospital, University of Catania, Catania, Italy, from August 1, 2008 to December 31, 2013 as part of the ongoing GRASP (Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation) registry; the results of which have been partly published elsewhere (9). After receiving a complete oral and written explanation of the issues surrounding the procedure, all patients included in the study provided written consent. The study was approved by the local ethics committee. Qualifying inclusion and exclusion criteria for MitraClip therapy (clinical and echocardiographic), as well as details of the procedure have been previously reported (12). Data were obtained from the MitraClip electronic database of Ferrarotto Hospital. Echocardiographic data were separately analyzed by a team of 2 expert echocardiographists and reviewed by a third reader for consensus when there was disagreement. The study groups were defined based on previously published echocardiographic criteria from the EVEREST I and II trials (7,8) as follows: 1) valve geometry features: coaptation length ≥2 mm, coaptation depth <11 mm, flail gap <10 mm, flail width <15 mm; and 2) ventricle function/geometry: ejection fraction [EF] >25%, and LV end-systolic diameter ≤55 mm. Patients that did not fulfill these criteria represented the investigational group (i.e., $EVEREST_{OFF}$ group), whereas patients that fulfilled these criteria represented the control group (i.e., $EVEREST_{ON}$ group). Clinical and echocardiographic outcomes, which were prospectively collected at 30-day and 12-month follow-ups, were then compared between the 2 groups.

**ENDPOINTS.** Acute device success was defined as residual MR ≤2+ after clip implantation. The primary safety endpoint was the incidence of major adverse events at 30 days, defined as the composite of death, myocardial infarction, reoperation for failed MitraClip implantation, nonelective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, mechanical ventilation for >48 h, gastrointestinal complication requiring surgery, new-onset of permanent atrial fibrillation, septicemia, and transfusion of 2 U of blood. The primary efficacy

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endpoint was freedom from death, surgery for mitral valve dysfunction, or grade ≥3+ MR at 12-month follow-up after clip implantation, whereas the same parameters were evaluated as a secondary efficacy endpoint at 30 day.

**STATISTICAL ANALYSIS.** Continuous variables following a normal distribution are presented as mean ± SD and were compared using the Student unpaired *t* test for comparisons between groups and paired *t* test for within-group comparisons. Variables that did not follow a normal distribution were compared with a Mann-Whitney *U* test for comparisons between groups and a Wilcoxon signed rank test for within-group comparisons. Categorical variables are presented as counts and percentages and were compared by the chi-square or the Fisher exact test. Survival curves were generated using the Kaplan-Meier method, and log-rank tests were used to evaluate differences between groups. A 2-way repeated-measures analysis of variance was used to evaluate the effects of time (baseline vs. 30-day follow-up vs. 12-month follow-up) and group ($EVEREST_{OFF}$ vs. $EVEREST_{ON}$) on echocardiographic and clinical variables, and post-hoc analysis was performed with Bonferroni correction. All p values reported are 2-sided, and p values <0.05 were considered significant. All data were processed using the Statistical Package for the Social Sciences (version 21 (SPSS Inc., Chicago, Illinois).

**TABLE 1 Baseline Characteristics**

| | $EVEREST_{OFF}$ (n = 78) | $EVEREST_{ON}$ (n = 93) | p Value |
|---|---|---|---|
| Age, yrs | 71.65 ± 9.13 | 71.86 ± 10.40 | 0.887 |
| Male | 52 (66.7) | 54 (58.1) | 0.248 |
| Hypertension | 59 (75.6) | 68 (73.1) | 0.707 |
| Diabetes | 28 (35.9) | 32 (34.4) | 0.839 |
| Atrial fibrillation | 35 (44.9) | 32 (34.4) | 0.163 |
| COPD | 19 (24.4) | 18 (19.4) | 0.429 |
| Previous PCI | 26 (33.3) | 28 (30.1) | 0.651 |
| Previous cardiac surgery | 16 (20.5) | 29 (31.2) | 0.115 |
| Renal failure | 41 (52.6) | 41 (44.1) | 0.269 |
| Previous myocardial infarction | 29 (37.2) | 29 (31.2) | 0.409 |
| Previous stroke | 8 (10.3) | 6 (6.5) | 0.366 |
| Logistic EuroSCORE II | 7.45 ± 6.35 | 8.10 ± 7.12 | 0.541 |
| STS score mortality | 6.06 ± 6.76 | 6.92 ± 7.17 | 0.425 |
| Functional MR | 68 (87.2) | 78 (83.9) | 0.542 |
| LVEF, % | 32.18 ± 12.83 | 40.17 ± 11.99 | <0.001 |
| LVEDV, ml | 205.79 ± 80.62 | 132.33 ± 38.56 | <0.001 |
| LVESV, ml | 148.25 ± 74.23 | 78.23 ± 33.54 | <0.001 |
| LVESD, mm | 52.57 ± 13.05 | 37.80 ± 8.96 | <0.001 |
| LVEDD, mm | 66.43 ± 10.67 | 54.92 ± 7.44 | <0.001 |
| Left atrial volume, ml | 106.92 ± 54.20 | 89.29 ± 36.64 | 0.026 |
| Mitral valve area, $cm^2$ | 4.11 ± 0.91 | 4.06 ± 0.77 | 0.718 |
| Mitral valve gradient, mm Hg | 1.82 ± 1.00 | 1.91 ± 0.97 | 0.586 |
| MR grade | | | 0.062 |
| 1+ | 0 (0) | 0 (0) | |
| 2+ | 1 (1.3) | 4 (4.3) | |
| 3+ | 31 (39.7) | 50 (53.8) | |
| 4+ | 46 (59) | 39 (41.9) | |
| NYHA functional class | | | 0.632 |
| I | 0 (0) | 1 (1.1) | |
| II | 13 (16.7) | 18 (19.4) | |
| III | 54 (69.2) | 65 (69.9) | |
| IV | 11 (14.1) | 9 (9.7) | |

Values are mean ± SD or n (%).

COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; $EVEREST_{OFF}$ = investigational group of Endovascular Valve Edge-to-Edge Repair trial; $EVEREST_{ON}$ = control group of Endovascular Valve Edge-to-Edge Repair trial; MR = mitral regurgitation; LVEDD = left ventricle end-diastolic diameter; LVEDV = left ventricle end-diastolic volume; LVEF = left ventricle ejection fraction; LVESD = left ventricle end-systolic diameter; LVESV = left ventricle end-systolic volume; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.

## RESULTS

**BASELINE CHARACTERISTICS.** A total of 171 consecutive patients were included. Among the 78 patients included in the $EVEREST_{OFF}$ group, 35 patients had EF ≤25%, 28 patients had LV end-systolic diameter >55 mm, 34 patients had coaptation depth ≥11 mm, and 10 patients had the flail width ≥15 mm. Baseline clinical characteristics were well balanced between the groups, whereas marked differences were demonstrated in echocardiographic parameters, as follows: significantly larger dimensions of LV and left atrium, as well as lower EF and a nonsignificant trend toward more MR grade 4+ were identified in the $EVEREST_{OFF}$ (n = 78) than in the $EVEREST_{ON}$ (n = 93) group. No differences were noted, however, in the baseline distribution of New York Heart Association (NYHA) functional classes between the groups (Table 1).

**ACUTE AND 30-DAY OUTCOMES.** Remarkable and comparable reductions in MR were observed in the vast majority of patients in both groups immediately after the procedure (MR grade ≤ 1+: 78.4% and 75.5%; MR grade 2+: 19.4% and 24.5%; MR grade 3+: 2.2% and 0%; and MR grade 4+: 0% and 0%, respectively, for the $EVEREST_{OFF}$ and $EVEREST_{ON}$ groups, p for all comparisons = 0.523). Accordingly, the rates of acute device success were high and equivalent between the 2 groups (97.8% vs. 100.0%, respectively, p = 0.294). Post-procedure mitral valve areas (2.57 ± 0.7 2 $cm^2$ vs. 2.71 ± 0.65 $cm^2$, respectively, for $EVEREST_{OFF}$ and $EVEREST_{ON}$ groups, p = 0.265) and gradients (3.28 ± 1.63 mm Hg vs. 3.42 ± 1.78 mm Hg, respectively, p = 0.633) were also comparable. All the clips were deployed without complications, including clip embolization, cardiac tamponade or periprocedural

stroke. In the $EVEREST_{OFF}$ group, the implantation of only 1 clip was sufficient to achieve procedural success in 38 patients (48.7%), whereas in the $EVEREST_{ON}$ group, this number was increased to 58 (62.4%), leading to a trend toward a higher number of clips per patient in the former $EVEREST_{OFF}$ group ($p = 0.073$). Four patients received more than 2 clips (3 patients in the $EVEREST_{OFF}$ group [2 patients received 3 clips and 1 patient received 4 clips] and 1 patient in the $EVEREST_{ON}$ group [i.e., patient received 3 clips]). The maximum mitral valve gradient observed among them was 4.5 mm Hg.

Thirty-day follow-up data were available in 100% of the patients (Table 2). The primary safety endpoint (30-day major adverse events) was identified in 2 patients (2.6%) and 6 (6.5%) in the $EVEREST_{OFF}$ and $EVEREST_{ON}$ groups, respectively ($p = 0.204$). Freedom from death, surgery for mitral valve dysfunction, or grade ≥3+ MR (secondary efficacy endpoint) was detected in 72 patients (90.1%) and 82 (93.5%), respectively ($p = 0.427$). Compared with post-procedure, MR reduction was mostly sustained and equivalent between groups (Figure 1, Table 2), whereas marked improvements in NYHA class compared with baseline were revealed in both groups (Figure 2, Table 2). Rehospitalizations for heart failure were rarely observed in both groups through 30 days (2 patients [2.6%] vs. 1 patient [1.1%], respectively, in the $EVEREST_{OFF}$ and $EVEREST_{ON}$ groups, $p = 0.437$).

**12-MONTH OUTCOMES.** Data from 154 patients (90%) were available (i.e., the remaining 10% of the patients did not have sufficient time elapsed from the index procedure) at 12-month follow-up. Kaplan-Meier freedom from death, surgery for mitral valve dysfunction, or grade ≥3+ MR at 12 months (primary efficacy endpoint) was demonstrated in 71.4% and 76.2%, respectively, in the $EVEREST_{OFF}$ and $EVEREST_{ON}$ groups (log rank $p = 0.378$) (Figure 3). The components of the primary efficacy endpoint were also similar between the 2 groups (Table 3).

Paired echocardiographic assessment in patients with echocardiographic data available at 12 months ($n = 134$; i.e., 20 patients from the total of 154 who were eligible for 12-month follow-up died in the time frame [9 cardiac and 11 noncardiac deaths], hence, did not have echocardiographic data available) demonstrated improvement in the EF and reduction in LV volumes in both groups comparing baseline and 12-month follow-up. Nonetheless, all the observed between-group baseline differences in echocardiographic parameters were sustained over time. A numerical, albeit not statistically significant, reduction in left atrial volume was revealed in both groups (Figure 4). Significant reduction in mitral valve area at 12-month follow-up compared with baseline ($p < 0.001$ for both) led to statistically significant, although not clinically concerning increase in mean mitral valve gradient in both groups (Table 3). Importantly, ~90% of the living patients in both groups exhibited MR ≤2+ through 12-month follow-up (Figure 1, Table 3), whereas ~78% were in NYHA functional class ≤II in the same time frame (Figure 2, Table 3).

The rehospitalization rates for heart failure in the surviving patients were low and comparable between groups (5 patients [7.1%] vs. 7 patients [8.3%], respectively, for $EVEREST_{OFF}$ and $EVEREST_{ON}$ groups, $p = 0.784$). No surgical mitral valve intervention was required during the study period, whereas an additional clip was implanted in only 2 patients from the $EVEREST_{ON}$ group. These reinterventions for additional MitraClip implantation were not associated with adverse events.

We performed a subanalysis of the investigational group (i.e., $EVEREST_{OFF}$) to check whether different characteristics of inclusion could lead to different impacts on outcomes through 12-month follow-up. Three groups were analyzed, as follows:

**TABLE 2 30-Day Outcomes**

| | $EVEREST_{OFF}$ (n = 78) | $EVEREST_{ON}$ (n = 93) | p Value |
|---|---|---|---|
| Death | 1 (1.3) | 2 (2.2) | 0.566 |
| Myocardial infarction | 0 (0) | 0 (0) | – |
| Surgery for failed MitraClip | 0 (0) | 0 (0) | – |
| Emergent cardiovascular surgery | 0 (0) | 0 (0) | – |
| Deep wound infection | 0 (0) | 0 (0) | – |
| Mechanical ventilation for >48 h | 0 (0) | 0 (0) | – |
| Gastrointestinal complication requiring surgery | 0 (0) | 0 (0) | – |
| Stroke | 1 (1.3) | 0 (0) | 0.447 |
| Renal failure after MitraClip | 0 (0) | 0 (0) | – |
| New onset of atrial fibrillation | 0 (0) | 2 (2.2) | 0.305 |
| Septicemia | 0 (0) | 1 (1.1) | 0.556 |
| Blood transfusion | 1 (1.3) | 1 (1.1) | 0.695 |
| Rehospitalization for heart failure | 2 (2.6) | 1 (1.1) | 0.437 |
| MR grade (n = 168)* | | | 0.318 |
| 1+ | 41 (53.2) | 38 (41.8) | |
| 2+ | 32 (41.6) | 46 (50.5) | |
| 3+ | 4 (5.2) | 7 (7.7) | |
| 4+ | 0 (0) | 0 (0) | |
| NYHA functional class (n = 168)* | | | 0.048 |
| I | 31 (40.3) | 27 (29.7) | |
| II | 25 (32.5) | 45 (49.5) | |
| III | 18 (23.4) | 19 (20.9) | |
| IV | 3 (3.9) | 0 (0) | |

Values are n (%). Dashes indicate that p values are not applicable. *Results expressed based on 168 patients (i.e., dead patients were not included).

Abbreviations as in Table 1.

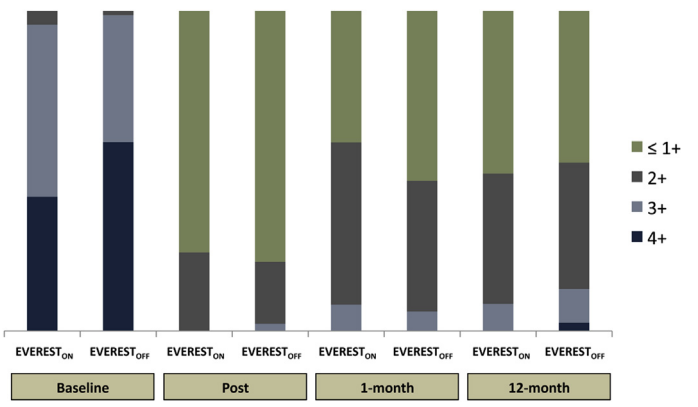


**FIGURE 1 Longitudinal Assessment of MR**

Longitudinal assessment of mitral regurgitation (MR) in the investigational (EVEREST$_{OFF}$) and control (EVEREST$_{ON}$) groups. EVEREST = Endovascular Valve Edge-to-Edge Repair trial.

1) valve geometry; 2) ventricle function/geometry; and 3) combined group. Although the combined group revealed numerically lower efficacy (primary efficacy endpoint 76.2%, 75%, and 62.5%, respectively, p = 0.521), higher rates of MR ≥3+ (14.5%, 12.5%, and 20.8%, p = 0.710), as well as higher death rates (9.5%, 12.5%, and 25%, respectively, p = 0.312), these differences did not reach statistical significance.

## DISCUSSION

The initial clinical experience with the MitraClip therapy for severe MR demonstrated promising safety and efficacy results, but highly selective echocardiographic criteria substantially limited its indications (7,8,13). In addition, most of the patients initially treated with the MitraClip system presented with preserved EF and degenerative MR, features that do not completely characterize the broader "real-world" population that could obtain greater benefit from this therapy (8). Indeed, observational data from a large North American institution revealed that 53% of 1,095 patients with severe MR and heart failure were medically managed; among them, the mean EF was 27 ± 15%, whereas 90% had functional MR, likely due to controversial results of MV surgery in this setting (1,3). Recently, European and North American studies including higher risk patients, mostly with functional MR, confirmed excellent safety and efficacy profiles of MitraClip implantation in more complex clinical scenarios, therefore contributing to fill the gap left by the initial experience (9,10,14,15). Nevertheless, the early and mid-term clinical and echocardiographic outcomes of the specific subgroup of patients that do not fulfill the previously established EVEREST echocardiographic criteria are poorly understood (16), hence, the rationale for our investigation.

We were able to demonstrate high rates of successful MitraClip implantation coupled with low rates of in-hospital adverse events, regardless of the broadened inclusion echocardiographic criteria, including larger LV dimensions and poorer LV function (i.e., EVEREST$_{OFF}$ group features), which strongly indicates that the favorable safety rates previously demonstrated for this relatively novel procedure could be reproduced in more complex settings (9,14). Goel et al. (1) previously showed high rates of hospitalization (41%) and mortality (20%), as well as progressive increase in the use of medications at 12-month follow-up in nonoperated patients with severe functional MR and heart failure. The investigators moreover identified, using EVEREST echocardiographic criteria as reference (i.e., EVEREST$_{ON}$), a role for MitraClip implantation in 36% of those patients. Our results are, therefore, insightful in this context, as they suggest potential room for expansion of MitraClip therapy indications in patients that would otherwise be clinically managed, likely carrying poor long-term prognosis (1). Elderly patients, in whom surgical treatment of MR is associated with elevated perioperative mortality, poor long-term survival, and uncertain benefit in quality of life (5), could as well benefit from broader indications of MitraClip therapy, as advanced age per se is a frequent cause for surgery denial, whereas if apparently does not pose a negative impact on the benefits of MitraClip implantation (17). In fact, the

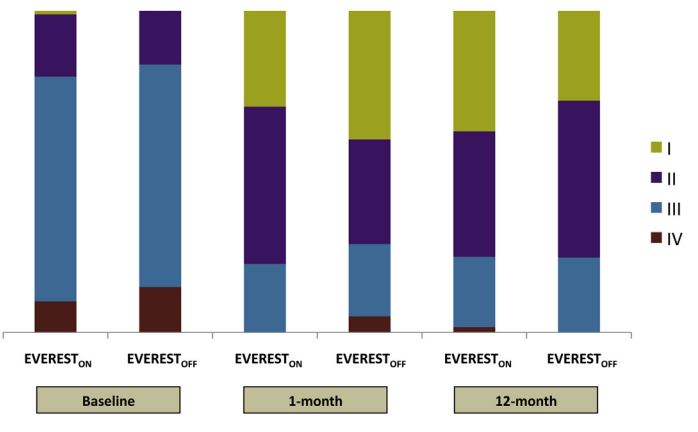


**FIGURE 2 Longitudinal Assessment of NYHA Functional Class**

Longitudinal assessment of New York Heart Association (NYHA) functional class in EVEREST$_{OFF}$ and EVEREST$_{ON}$ groups. Abbreviations as in Figure 1.

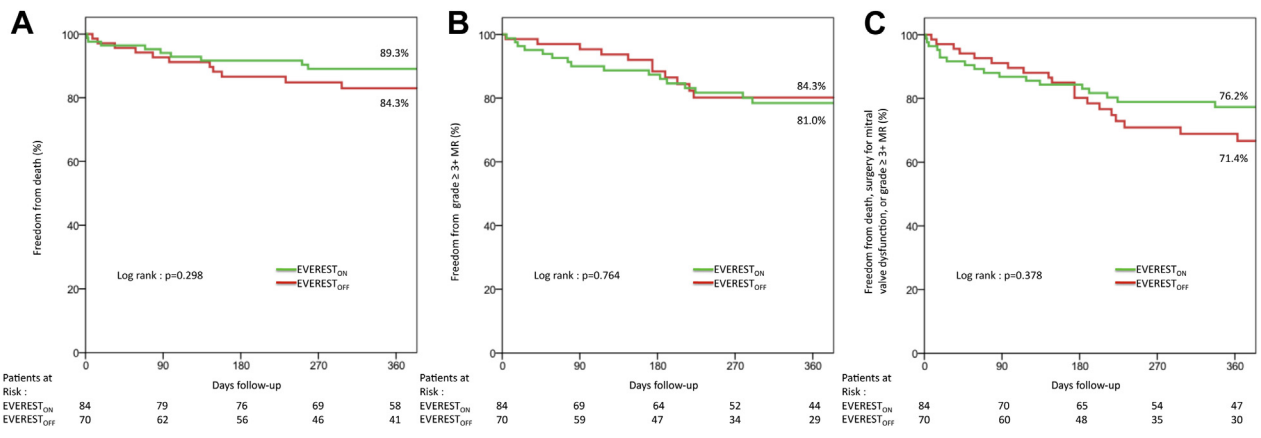


**FIGURE 3** Kaplan-Meier Estimates at 12-Month Follow-Up

Kaplan-Meier curves demonstrate **(A)** freedom from death and **(B)** freedom from MR ≥3+. **(C)** The combined primary efficacy endpoint is depicted. Abbreviations as in Figure 1.

4-year follow-up of the EVEREST II trial suggested a benefit of MitraClip over surgery in patients ≥70 years of age (13). Further investigations are required, however, to evaluate whether MitraClip implantation leads to better outcomes compared with surgery in patients with comparable characteristics to our investigational group (i.e., EVEREST$_{OFF}$).

Another critical result of the present investigation was the marked and comparable improvement in MR obtained after the procedure in both groups (i.e., ~98% of patients with MR ≤2+), regardless of the different baseline echocardiographic features. This finding is particularly important because low grades of MR after MitraClip implantation (i.e., ≤2+) lead to better reverse remodeling (18) and are inversely correlated with long-term survival after the intervention (15,19). Furthermore, the significant improvement in MR remained comparable between EVEREST$_{OFF}$ and EVEREST$_{ON}$ groups at 30-day (i.e., ~95% of living patients with MR ≤2+) and 12-month (i.e., ~90% of living patients with MR ≤2+) follow-up ($p = 0.402$ for between-group comparison over time). Recently, Whitlow et al. (14) reported 78% of MR grade ≤2+ at 12-month follow-up after MitraClip implantation in a population characterized by high baseline clinical risk (~60% functional MR); likewise, Maisano et al. (10) described 78.9% of MR grade ≤2+ at 12-month follow-up in a population in which ~77% of individuals had functional MR. The results obtained for MR reduction in the EVEREST$_{OFF}$ group, despite its broader echocardiographic inclusion criteria, are therefore encouraging. Longer term follow-up is warranted to better characterize the stability/durability of MR reduction in this scenario.

Grayburn et al. (18) recently demonstrated, in a substudy of the EVEREST trials, LV reverse remodeling after reduction of MR to grade 1+ or 2+ secondary to MitraClip implantation in patients with baseline functional MR. In line with those data, our control group (i.e., EVEREST$_{ON}$) exhibited improvement in EF, as well as significant reduction in LV volumes; importantly, the investigational group (i.e., EVEREST$_{OFF}$) also revealed LV reverse remodeling

**TABLE 3** 12-Month Outcomes

| | EVEREST$_{OFF}$ (n = 59) | EVEREST$_{ON}$ (n = 75) | p Value |
|---|---|---|---|
| MR ≥3+* | 11 (15.7) | 16 (19.0) | 0.588 |
| Death* | 11 (15.7) | 9 (10.7) | 0.358 |
| Surgery for mitral valve dysfunction* | 0 (0) | 0 (0) | – |
| MR grade | | | 0.681 |
| 1+ | 29 (49.2) | 39 (52.0) | |
| 2+ | 23 (39.0) | 30 (40) | |
| 3+ | 6 (10.2) | 6 (8.0) | |
| 4+ | 1 (1.7) | 0 (0) | |
| Mitral valve area, cm$^2$ | 2.93 ± 0.81 | 2.86 ± 0.75 | 0.679 |
| Mitral valve gradient, mm Hg | 3.17 ± 1.16 | 3.73 ± 1.72 | 0.087 |
| NYHA functional class | | | 0.388 |
| I | 16 (27.1) | 29 (38.7) | |
| II | 29 (49.2) | 29 (38.7) | |
| III | 14 (23.7) | 16 (21.3) | |
| IV | 0 (0) | 1 (1.3) | |

Values are n (%) or mean ± SD. Dash indicates that the p value is not applicable. *Results expressed based on 154 patients used for the calculation of the primary efficacy endpoint (i.e., including dead patients through 12-month follow-up).

Abbreviations as in Table 1.

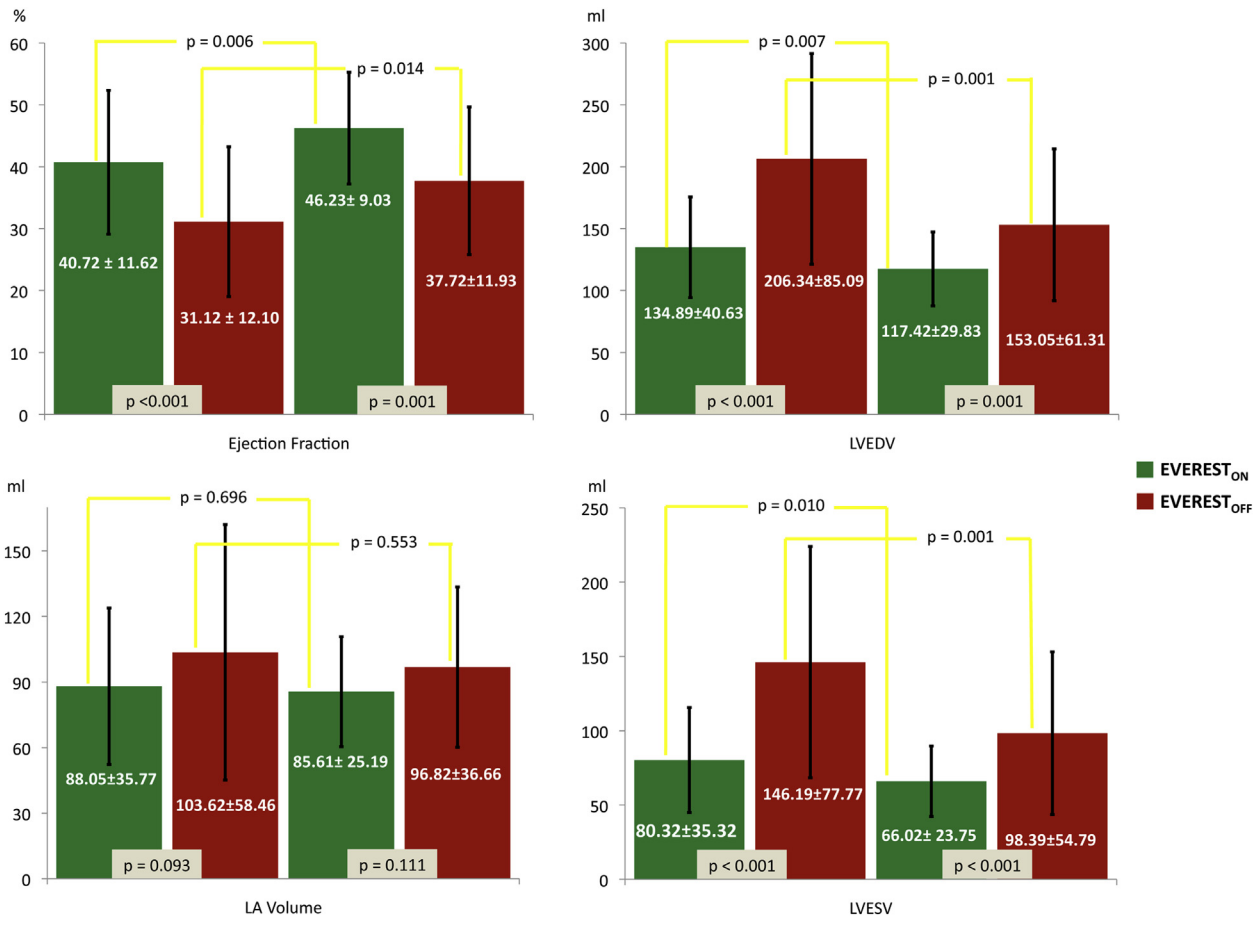


**FIGURE 4 Baseline and 12-Month Follow-Up Echocardiographic Parameters**

The bar graphs demonstrate comparisons between the groups (EVEREST$_{OFF}$ vs. EVEREST$_{ON}$) at baseline and 12-month follow-up (p values for these comparisons are represented in the **light gray square**), as well as intragroup comparisons in the 2 different time points (p values are linked to the correspondent graph bars by **yellow lines**). LA = left atrium; LVEDV = left ventricle end-diastolic volume; LVESV = left ventricle end-systolic volume; other abbreviations as in Figure 1.

through 12-month follow-up (Figure 4) despite its "more complex" baseline echocardiographic features (20), but the baseline between-group differences were sustained over time. Although left atrial volumes demonstrated similar reduction trends observed for LV volumes in both groups, the alterations were not statistically significant. A type II statistical error reflected by the relatively small sample size could be a potential explanation for this finding. Longer term follow-up and larger sample sizes are mandatory to completely elucidate the mechanisms of reverse LV and left atrial remodeling in this setting.

The clinical significance of the reverse LV remodeling observed in both groups was reflected in the considerable improvement in NYHA functional class, which was observed early after MitraClip implantation (Table 2) and persisted through 12-month follow-up in both groups (Table 3) (i.e., > 80% of patients were in NYHA functional class III to IV at baseline, whereas ~78% of patients were in functional class ≤II at 12-month follow-up; p = 0.573 for between-group comparisons over time). In addition, very low rates of death and rehospitalization for heart failure, coupled with infrequent reinterventions for additional clip implantation and no need for surgical mitral valve intervention were revealed. We should acknowledge, however, that the consistent long-term clinical (13) and hemodynamic benefits (21) previously demonstrated after MitraClip implantation in less complex settings warrant further investigation in our study population.

Because the EVEREST I and II echocardiographic features (7,8) used as inclusion criteria for our investigational group combined valve geometry and ventricle function/geometry features, we hypothesized that patients that exhibited those features whether isolated or combined could have different outcomes (i.e., whereas patients with the former could be more likely to have impaired procedural success and long-term efficacy, patients with ventricle function/geometry criteria would eventually reveal worse clinical outcomes). Although no statistically significant differences were observed in our series, the combined group demonstrated numerically lower efficacy and higher rates of death and MR ≥3+ through 12-month follow-up, but our limited sample size and relatively short follow-up period precluded definitive conclusions.

Due to the high anatomical complexity demonstrated by the $EVEREST_{OFF}$ group, we used a number of advanced techniques for clip placement, including "aorta hugging" in cases of extremely deviated posterior leaflet, use of rapid pacing in selected cases, and performing the first grasp close to the larger gap to approximate leaflets and facilitate the second grasp. A detailed description of these techniques will be the subject of a future paper.

Finally, although a trend ($p = 0.073$) toward the implantation of more clips per patient was identified in the $EVEREST_{OFF}$ group, the increased mitral valve gradient observed in both groups at 12-month follow-up was equivalent and not clinically concerning (i.e., most patients with mitral valve gradient <5 mm Hg). These findings, coupled with the stability of MR reduction over time reaffirm that, when needed, the implantation of more than 1 MitraClip can be accomplished in most cases without important concerns regarding prohibitive increase in mitral valve gradient, while keeping the effectiveness in terms of MR reduction (22). The cost-effectiveness of implanting more than 1 clip per patient, though, remains to be determined (23).

The data herewith described are insightful as they suggest a potential room for expanding the indications of MitraClip implantation for the treatment of 3+ to 4+ MR in high-risk surgical patients beyond the initial criteria proposed by the EVEREST I and II studies (7,8); nevertheless, additional research with longer follow-up and larger sample sizes are mandatory before any formal recommendation of broadened indications for MitraClip therapy are considered. Two important ongoing randomized trials that estimate the inclusion of ~1,200 patients will certainly contribute to better elucidation of the role of MitraClip therapy in high surgical risk patients with functional MR (COAPT [Clinical Outcomes Assessment of the MitraClip Therapy Percutaneous Therapy for High Surgical Risk Patients]; NCT01626079) as well as the impact of this novel therapy in patients with functional MR associated with congestive heart failure (NYHA class III or IV and 15% ≤ EF ≤40%) (RESHAPE-HF [A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation]; NCT01772108). Taken together, the results from these studies will shed light on expanded indications of MitraClip implantation, potentially opening a new avenue in the research of percutaneous edge-to-edge treatment of MR (24).

**STUDY LIMITATIONS.** Several things should be considered in the interpretation of our results. First, this was not a randomized controlled trial, therefore, several confounding factors could have influenced our results; nevertheless, the inclusion of consecutive patients with balanced clinical characteristics might have minimized potential selection bias. Second, a relatively small sample size with limited follow-up were included, thus our results should be reproduced in larger populations with longer follow-up periods. Third, the echocardiographic parameters analyzed at 12-month follow-up could have been influenced by survival bias, but equivalent and low rates of mortality exhibited in our study may have attenuated this phenomenon. Fourth, 90% of our patients were available for 12-month follow-up due to insufficient time elapsed since the index procedure. Aiming at minimizing this potential caveat, we made the analyses of the 12-month primary efficacy endpoint and its components separately using Kaplan-Meier estimates. Fifth, the interventions described were undertaken in a center that performs a high volume of MitraClip implantations per year, therefore, our results should not be generalized. Our echocardiographic data were not reviewed by an independent core laboratory as it was performed in a clinical setting, reflecting the real-world practice; however, the analyses were conducted by dedicated, highly experienced physicians (12) using validated methods and were based on consensus.

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## REFERENCES

**1.** Goel SS, Bajaj N, Aggarwal B, et al. Prevalence and outcomes of unoperated patients with severe symptomatic mitral regurgitation and heart failure: comprehensive analysis to determine potential role of MitraClip for this unmet need. J Am Coll Cardiol 2014;63:185–6.

**2.** Vahanian A, Alfieri O, Andreotti F, et al., for the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012;33:2451–96.

**3.** Mihaljevic T, Lam BK, Rajeswaran J, et al. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. J Am Coll Cardiol 2007;49:2191–201.

**4.** Nowicki ER, Birkmeyer NJ, Weintraub RW, et al. Multivariable prediction of in-hospital mortality associated with aortic and mitral valve surgery in Northern New England. Ann Thorac Surg 2004;77:1966–77.

**5.** Andalib A, Mamane S, Schiller I, et al. A systematic review and meta-analysis of surgical outcomes following mitral valve surgery in octogenarians: implications for transcatheter mitral valve interventions. EuroIntervention 2014;9:1225–34.

**6.** Carabello BA. The current therapy for mitral regurgitation. J Am Coll Cardiol 2008;52:319–26.

**7.** Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge Repair Study) cohort. J Am Coll Cardiol 2009;54:686–94.

**8.** Feldman T, Foster E, Glower DD, et al., for the EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011;364:1395–406.

**9.** Grasso C, Capodanno D, Scandura S, et al. One- and twelve-month safety and efficacy outcomes of patients undergoing edge-to-edge percutaneous mitral valve repair (from the GRASP Registry). Am J Cardiol 2013;111:1482–7.

**10.** Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. J Am Coll Cardiol 2013;62:1052–61.

**11.** Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.

**12.** Tamburino C, Ussia GP, Maisano F, et al. Percutaneous mitral valve repair with the MitraClip system: acute results from a real world setting. Eur Heart J 2010;31:1382–9.

**13.** Mauri L, Foster E, Glower DD, et al., for the EVEREST II Investigators. 4-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. J Am Coll Cardiol 2013;62:317–28.

**14.** Whitlow PL, Feldman T, Pedersen WR, et al., for the EVEREST II Investigators. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. J Am Coll Cardiol 2012;59:130–9.

**15.** Sürder D, Pedrazzini G, Gaemperli O, et al. Predictors for efficacy of percutaneous mitral valve repair using the MitraClip system: the results of the MitraSwiss registry. Heart 2013;99:1034–40.

**16.** Franzen O, Baldus S, Rudolph V, et al. Acute outcomes of MitraClip therapy for mitral regurgitation in high-surgical-risk patients: emphasis on adverse valve morphology and severe left ventricular dysfunction. Eur Heart J 2010;31:1373–81.

**17.** Schillinger W, Hünlich M, Baldus S, et al. Acute outcomes after MitraClip therapy in highly aged patients: results from the German Transcatheter Mitral Valve Interventions (TRAMI) Registry. EuroIntervention 2013;9:84–90.

**18.** Grayburn PA, Foster E, Sangli C, et al. Relationship between the magnitude of reduction in mitral regurgitation severity and left ventricular and left atrial reverse remodeling after MitraClip therapy. Circulation 2013;128:1667–74.

**19.** Lim DS, Reynolds MR, Feldman T, et al. Improved functional status and quality of life in prohibitive surgical risk patients with degenerative mitral regurgitation following transcatheter mitral valve repair. J Am Coll Cardiol 2014;64:182–92.

**20.** Sénéchal M, MacHaalany J, Bertrand OF, et al. Predictors of left ventricular remodeling after surgical repair or replacement for pure severe mitral regurgitation caused by leaflet prolapse. Am J Cardiol 2013;112:567–73.

**21.** Gaemperli O, Biaggi P, Gugelmann R, et al. Real-time left ventricular pressure-volume loops during percutaneous mitral valve repair with the MitraClip system. Circulation 2013;127:1018–27.

**22.** Alegria-Barrero E, Chan PH, Foin N, et al. Concept of the central clip: when to use one or two MitraClips. EuroIntervention 2014;9:1217–24.

**23.** Mealing S, Feldman T, Eaton J, Singh M, Scott DA. EVEREST II high risk study based UK cost-effectiveness analysis of MitraClip in patients with severe mitral regurgitation ineligible for conventional repair/replacement surgery. J Med Econ 2013;16:1317–26.

**24.** Rosenhek R. Reverse remodeling in the perspective of decision making for mitral valve repair with the MitraClip. Circulation 2013;128:1600–1.

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