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**Title:** Transcatheter Edge-to-Edge Repair for Secondary Mitral Regurgitation with 3rd Generation Devices in Heart Failure Patients–Results from the Global EXPAND Post-Market Study

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## ABSTRACT

**Aims:** Mitral valve transcatheter edge-to-edge repair (M-TEER) is a guideline-recommended treatment option for patients with secondary mitral regurgitation (SMR). The purpose of this analysis is to report contemporary real-world outcomes in SMR patients treated with 3rd generation MitraClip systems.

**Methods and Results.** EXPAND is a prospective, multi-center, international, single arm study with 1041 patients treated for MR with MitraClip NTR/XTR, with 30-day and 1-year follow-up (FU). All echocardiograms were analyzed by an independent echocardiographic core lab. Study outcomes included: procedural outcomes, durability of MR reduction, and major adverse events including all-cause mortality and hospitalizations for heart failure (HFH). A subgroup of 413 symptomatic patients (age 74.7±10.1 years, 58% male) with severe SMR were included. MR reduction to MR≤1+ and MR≤2+ was achieved in 93.0% and 98.5% of patients, respectively, which was sustained at 1-year-FU. All-cause mortality was 17.7% at 1-year-FU, and the combined endpoint of all-cause mortality or 1st HFH occurred in 34% of patients. This combined endpoint was significantly less frequently observed in MR≤1+ patients (Kaplan-Maier-estimates: 29.7% vs. 69.9% for MR≤1+ vs. MR≤2+; p<0.0001). NYHA functional class improved significantly from baseline (NYHA≤II:17%) to 1-year-FU (NYHA≤II:78%) (p<0.0001). While MR reduction was comparable between NTR-only vs. XTR-only treated patients, less XTR clips were required for achieving MR reduction.

**Conclusions.** Under real-world conditions, optimal sustained MR reduction to MR≤1+ was achieved in a high percentage of patients with 3rd generation MitraClip, which translated into symptomatic improvement and low event rates. These results appear to be comparable with recent randomized clinical trials.

**Keywords:** MitraClip; TEER; TMVr; mitral regurgitation; SMR; heart failure



**Abbreviations List**

ECL = Echocardiography Core Lab

CEC = Clinical Events Committee

EROA = effective regurgitant orifice area

HFH = hospitalizations for heart failure

KCCQ = Kansas City Cardiomyopathy Questionnaire

MAE = major adverse event

M-TEER = mitral valve transcatheter edge-to-edge repair

NYHA = New York Heart Association

SLDA = single leaflet device attachment

SMR = secondary mitral regurgitation

## INTRODUCTION

Mitral regurgitation (MR) is a major cause for valvular heart failure, causes substantial morbidity and mortality (1,2), and in contrast to aortic valve disease, is significantly undertreated (3). In particular secondary MR (SMR) poses a therapeutic challenge due to the underlying atrio-ventricular dysfunction which leads to progressive, mutual deterioration of left ventricular (LV) and valve function (4,5). Recent advances in medical and transcatheter therapies are significantly enhancing our treatment options for SMR (6,7). Eminently, the *Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation* (COAPT) trial has shown that mitral valve transcatheter edge-to-edge repair (M-TEER) with the 2nd generation of the MitraClip system improves prognosis and quality of life in heart failure patients with reduced LV ejection fraction and SMR (8). Current technical development in the field of M-TEER aims at refining device design and expanding device sizes to further reduce MR and optimize procedural outcome in challenging mitral valve (MV) anatomies. These advances could translate into amelioration of heart failure symptoms and potentially improved prognosis in SMR patients, who would otherwise be denied M-TEER due to anatomic difficulties. Initial single-center reports not explicitly distinguishing primary MR and SMR patients have indicated that different clip sizes are effective for MR reduction, with one study showing that larger clips could potentially cause more frequently leaflet injury (9). The present investigation aimed to evaluate the real-world experience with two different sizes of the 3rd generation of MitraClip devices in patients with secondary MR (SMR) from the Global EXPAND study with centrally adjudicated clinical and echocardiographic outcomes.

## METHODS

### Study design and patients

The Global EXPAND study (NCT03502811) is a post-market, prospective, observational, multicenter study of the commercially available 3rd generation MitraClip NTR and XTR M-TEER system. The EXPAND study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice, and regional clinical study guidelines. The study was approved by each local institutional review board and the health authorities of the participating centers. A minimum of 1000 consecutive consented subjects with symptomatic moderate-to-severe and severe primary MR or SMR (as assessed by the sites) were planned to be enrolled at up to 60 sites. Patients enrolled to the study if they met the inclusion criteria: symptomatic severe MR and eligible for M-TEER by the local investigator and Heart Team according to the approved MitraClip indication for use in their country. All patients provided written informed consent, prior to study enrollment.

### Transcatheter Edge-to-Edge Repair Procedure

The procedure was performed under general anesthesia. Each MitraClip was introduced via transfemoral venous access, through the interatrial septum into the left atrium and implanted into the MV by leaflet grasping to achieve MR reduction. The MitraClip NTR has a 9 mm arm length and 5 mm width, and the MitraClip XTR a 12 mm arm length and 5 mm width. The MitraClip XTR is equipped with six frictional elements instead of the previously four of the NTR. Clip selection guidelines generated by expert physicians on the EXPAND Steering Committee for this study recommended at least 6 mm of leaflet length for use of NTR and at least 9 mm of leaflet length for use of XTR (Supplementary Table 1). Other reasons for determining implant size selection for the first clip was mainly dependent on site assessment of anatomy, MR severity, MR etiology and valve area.

Study endpoints and data adjudication:

The primary endpoint was assessment of safety as a composite of major adverse events (MAEs) at 30 days, including all-cause death, myocardial infarction, stroke, or non-elective cardiovascular surgery for device related complications. A *Clinical Events Committee* (CEC) centrally adjudicated all reported MAE up to 30 days. Single leaflet device detachment (SLDA) and leaflet damage/injury reported up to 1 year were adjudicated by an independent physician committee (11). Adverse events through 1 year were based on site reporting. Key performance measures include MR reduction to grade ≤2+ and grade ≤1+ at 30 days and 1-year follow-up. These endpoints were descriptively compared to outcomes from the landmark COAPT and MITRA-FR trials. MR severity and etiology, and other echocardiographic parameters, at baseline and follow-up were assessed by an independent echocardiography core lab (ECL), in accordance with the chamber quantification and evaluation of valvular regurgitation guidelines (10). Additional performance measures include: acute procedural success defined as successful device implantation with resulting MR ≤2+ at discharge, and acute device success defined as successful device implantation without device-related complications such as device embolization, SLDA, bleeding, or perforation at discharge. Clinical and echocardiogram outcomes, improvement in New York Heart Association (NYHA) functional class and quality of life as assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ) score through 1 year are also reported in this study.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR). Categorical variables were presented as number and relative percentages. Paired analysis was performed using Student t-test or Bowker's test as appropriate. Kaplan-Meier curves with log-rank test were used for all-cause death, first hospitalization for heart failure (HFH), and combined all-cause death and first HFH analysis. The rate of HFH in

the year before M-TEER and post procedure was compared with the Poisson regression model. Statistical analyses were performed using SAS version 9.4 (SAS Institute., Cary, NC), a p-value of <0.05 was considered significant.

## RESULTS

### Population and Baseline characteristics

The EXPAND study enrolled a total of 1041 patients from 57 centers (22 sites in the USA; 35 European sites) who underwent M-TEER. Four hundred thirteen (US: 28%, Europe: 72%) patients were identified by the ECL to have SMR, and further analyses and results are based on these 413 patients. The mean age was 74.7 ±10.1 years; 58% were men; mean EuroSCORE II was 9.8 ±9.4 and STS repair score was 7.2 ±7.3; chronic lung disease was present in 25% of patients, diabetes in 30%, and chronic renal failure in 47% (Table 1). The majority of patients were in NYHA class III (69%) and IV (14%), with an impaired KCCQ Score of 44 ±24. A high proportion of patients were reported to be taking heart failure medications (Table 1 and Supplementary Table 2): 88.6% (366/413) on beta-blockers, 37.8% (156/413) on ACE-Inhibitors, 22.3% (92/413) on angiotensin receptor blockers, 36.6% (151/413) on mineralocorticoid receptor antagonist, and 85.7% (354/413) on diuretics (any type). An angiotensin receptor-neprilysin inhibitor was taken in 11.6% (48/413). Thirty seven percent (152/411) of patients had a previous implantable cardioverter defibrillator and 10.2% (42/410) reported to have cardiac resynchronization therapy.

### Echocardiographic baseline characteristics

The ECL assessed that 92% of SMR patients had 3+ or 4+ MR per ESC guidelines (19); 48.3% of SMR patients had 3+ or 4+ MR per ASE guidelines (Table 2) (10). Mean left ventricular ejection fraction (LVEF) was 39.4 ±13.5%, LV end-diastolic volume (LVEDV) was 181 ±80 ml and LVEDV index was 97.5 ±41.6 ml/$m^2$. Mean vena contracta and effective regurgitant

orifice area (EROA) were 0.53 ±0.13 cm and 0.30 ±0.12 $cm^2$, respectively. At least moderate (≥2+) tricuspid regurgitation (TR) was present in 42% of patients. Echocardiographic systolic pulmonary artery pressure (Echo-SPAP) was 54 ±15mmHg.

Procedural Characteristics

Implant rate was 99% (410/413 patients). Acute procedural success was achieved in 97% (399/410) of patients (Table 3). Mean procedure time was 86.8 ± 46.7 minutes. The XTR clip was exclusively implanted in 169 (41%) patients, NTR exclusively in 181 (44%) patients, while 60 (14.6%) patients received both XTR and NTR clips. In XTR-treated patients, 73% received 1 clip and 27% received 2 or more clips (Graphical Abstract). In patients treated with NTR device, 57% received 1 clip and 43% received 2 or more clips. Proportion of patients treated with 1 vs. 2 clips was higher in XTR-treated patients than in NTR ($p<0.01$). In 29.9% of cases, the leaflet length was the major criteria for selecting the first device size. XTR was selected as the first clip implanted in 56% (229/411) of subjects, whereas NTR was the first clip implanted in 44% (182/411). At discharge, 99% (389 of 393 patients with discharge assessment) had MR ≤2+, and 92% (362/393) had MR ≤1+.

Echocardiographic and Clinical Outcomes

*Safety and Performance Evaluation*

The safety endpoint of 30-day MAE occurred in 3.6% (15/412). There were 11 cardiovascular deaths, 1 subject had ischemic stroke and 4 patients underwent non-elective cardiovascular surgery for device-related complications, including for SLDA of NTR clip (n=1), iatrogenic atrial septum defects that required closure (n=2) and MV replacement (n=4) (Supplementary Table 3). SLDA was confirmed in 8 patients (1.9%), 3 with XTR and 5 with NTR: 2 reported during the procedure, 3 reported at discharge, and 3 reported at 30-day follow-up. Only one SLDA event resulted in a MAE as described, and the other cases were resolved with additional

clip placement in an additional procedure to achieve residual MR ≤2+. Reduction to MR ≤2+ at 30 days was accomplished in 331 of 336 (98.5%) patients with echocardiographic follow-up. At 1-year follow-up, 99.6% (225/226) of the SMR patients had maintained MR ≤2+. In 93% of patients, MR grade was reduced to MR ≤1+ and sustained up to 1-year follow-up compared to baseline (p<0.001)(Supplementary Table 2).

*Clinical Outcomes at 1-year Follow-up*

At 1-year, all-cause mortality was 17.7% (n=68), and 26.0% of patients had HFH (Figure 1A and B). One year prior to M-TEER, 64.8% (248/383) of patients had HFH, with an annualized HFH rate reduction of 65% from 1.08 HFH/year before M-TEER to 0.38 after M-TEER (p<0.001)(Supplementary Figure 1). The combined event rate of all-cause death or first HFH occurred in 133 (34.1%) of patients at 1-year (Figure 1C). These event rates are comparable to the results from the COAPT trial and lower than in the MITRA-FR trial (Supplementary Table 2). Reduction to MR ≤1+ at discharge was associated with improved survival and freedom from first HFH at 1-year (Figure 2A-C, Graphical Abstract). Patients with an EROA < 0.3 $cm^2$ vs. ≥ 0.3 $cm^2$ EROA had comparable mortality and HFH rates after M-TEER (Supplementary Figure 2).

NYHA class improved in the majority of patients at 30 days (76% in NYHA ≤II, p<0.001) and 12 months (78% in NYHA ≤II) compared to baseline (p<0.001). The KCCQ score improved by a mean of 19 points at 30 days (p<0.001) and 22 points at 12 months (p<0.001) after M-TEER in surviving patients with follow-up. There was a decrease in beta-blocker intake which was paralleled by an increase in mineralocorticoid receptor antagonist and angiotensin receptor-neprilysin inhibitor intake (Table 4).

*Procedure-Related Events at 1-Year Follow-up*

Device and procedure-related adverse events through 1-year follow-up occurred in 43 patients (10.4%). There are no reports of new leaflet-related adverse events at 1-year follow-up. Six patients underwent MV replacement (1.4%), and 6 patients needed repeat MV reintervention (Supplementary Table 4).

*Echocardiographic Outcomes at 1-Year Follow-up*

285 of the 413 subjects completed 12-month follow-up visit with ECL assessment. At 1-year follow-up, MV area decreased by 28% (<0.001) and mean MV gradient increased from 2.0 ± 1.0 at baseline to 3.4 ± 3.2 mmHg after M-TEER (p<0.001)(Table 5). Systolic anterior-posterior and lateral-medial MV diameters decreased by 5% and 8% (p<0.001). LVEDV and LVESV progressively decreased by 11% and 12% (both p<0.001), while LVEF remained at 40%. Mean pulmonary artery pressure decreased by 3.9 ±1.2 mmHg (p<0.001). The number of patients with at least moderate TR (≥2+) decreased significantly to 24% (p<0.001).

Patients treated with NTR vs. XTR device

The summary of baseline echo parameters of patients treated with NTR-only vs. XTR-only clips are shown in Table 6. Baseline MR parameters were comparable between groups: vena contracta (0.53 cm for both, p=0.86), EROA (0.29 $cm^2$ vs. 0.30 $cm^2$, p=0.54), regurgitant volume (46 ml vs. 44 ml, p=0.38) and PISA radius (0.70 cm vs. 0.72 cm, p=0.27) for NTR-only vs. XTR-only, respectively. LVEF was lower in the XTR-only group (NTR-only vs. XTR-Only: 41% vs. 38%, p=0.027), while LV volumes and dimensions were larger in the XTR-only group (LVEDV NTR-only vs. XTR-only: 169.5 ml vs. 190.3 ml, p = 0.023; LVESV: 106.1 ml vs. 123.8 ml, p=0.022; LVESD: 4.83 cm vs. 5.09 cm, p = 0.043).

While differences in clip usage were observed for LV size and function, clip use differed also for certain MV anatomical considerations. Larger coaptation depth (0.71 cm vs. 0.79 cm, for NTR vs. XTR, respectively, p=0.005) and tenting area (1.46 $cm^2$ vs. 1.60 $cm^2$ for NTR vs.

XTR, respectively, p=0.07) showed the trend for usage of XTR in MV with more severe tenting. Mean MV area was 3.90 $cm^2$ vs. 3.96 $cm^2$ for NTR-only vs. XTR-only groups (p=0.73) with a similar proportion of patients having a MVA ≥ 4$cm^2$ in both groups (41% with NTR vs. 46% with XTR, p=0.39). Mean MVG was 2.1 mmHg with NTR vs. 2.1 mmHg with XTR (p=0.78). MV annular dimensions were not different between groups. Baseline TR with at least moderate degree (≥2+) was also not significantly different between groups (NTR: 40.6% vs. XTR: 40.8%, p=0.9).

No significant difference was seen in clinical outcomes at 1-year follow-up based on clip size used. Reduction to MR ≤2+ at 30 days was accomplished in 99.3% of NTR-only patients and 97.8% XTR-only patients with echocardiographic follow-up. At 1-year follow-up, 100% NTR-only patients and 99.2% XTR-only patients had maintained MR ≤2+. In 98.1% NTR-only patients and 88.5% of XTR-only patients, MR grade was reduced to MR ≤1+ at 1-year follow-up. All-cause mortality rate was 19.2% vs. 16.6% (p = 0.54) and HFH rate was 23.0% vs. 28.1% (p = 0.29) in the NTR- vs. XTR-only clip use groups, respectively (Supplementary Table 5). Regardless of clip size used, a similar improvement was seen in NYHA functional class at 1-year follow-up (NYHA ≤ II, NTR: 80.7% vs. XTR: 75.7%, p = 0.64) as well as quality of life (ΔKCCQ score, NTR: 20.5 ± 26.2 vs. XTR: 23.2 ± 25.6, p = 0.42). Use of either clip size resulted in significant reduction in anterior-posterior systolic and diastolic dimensions (APsys and APdia) from baseline to 1-year follow-up: (ΔAPsys: NTR: -0.17 ±0.59cm, p=0.005; XTR: -0.13 ±0.57cm, p=0.014; and ΔAPdia: NTR: -0.14 ±0.64cm, p=0.04; XTR: -0.14 ±0.57cm, p=0.0071). Reduction in LV volume at 1-year follow-up was comparable despite the differences in LV volume and dimensions at baseline: (ΔLVEDV; NTR: -25.2± 63.1 ml; XTR: -23.7 ± 43.9 ml, p = 0.56; and ΔLVESV: NTR: -17.6± 59.1 ml; XTR: -14.4 ± 39.7 ml, p = 0.31).

## DISCUSSION

This is the first and largest study to assess outcomes and echocardiographic characteristics in SMR patients treated with two different MitraClip sizes in a prospective trial with core-lab reviewed data. The EXPAND trial confirmed the safety and efficacy of both MitraClip sizes in patients with SMR. Clinical outcome including all-cause mortality and HFH were comparable in patients treated with either NTR or XTR device. Patients treated with NTR vs. XTR devices differed primarily in left heart anatomy. The LV was more dilated and LV function was more impaired in XTR-treated patients. Patients treated with the XTR clip had relatively larger coaptation depths and tenting, however, the observed difference in tenting area was not statistically significant.

Recently, M-TEER has become the guideline-recommended interventional therapy for patients with severe SMR and impaired LVEF <50% on top of GDMT in the US. In Europe, M-TEER is also indicated as a class IIa guideline recommended treatment similar to the COAPT population and not eligible for surgery (16). Since the majority of patients with SMR have LVEF <50% and/or are at high surgical risk, M-TEER has become a major pillar of valvular heart failure therapy for this vulnerable patient group in both the US and Europe. Notably, the decision to favor M-TEER is based on the positive outcome of M-TEER in the COAPT trial and the unsatisfactory outcome of surgical MV repair for this indication, with substantial MR recurrence even in low-risk patients in the latter case. With the projected further expansion in use of M-TEER comes the encounter of challenging anatomies in an expanding patient population, for which a single MitraClip size might not have been enough to achieve effective MR reduction. Therefore, availability of multiple device sizes offers a tailored approach for the treatment of MR as part of the comprehensive personalized heart failure therapy.

As such, the EXPAND trial results show that procedural MR reduction was extremely effective and associated with improved survival and freedom from first HFH after 1 year, with reduction to grade ≤1+ in 93% of patients sustained through 1-year follow-up. This percentage

of patients with sustained reduction of MR ≤1+ is higher than both COAPT and MITRA-FR trial results. Additionally, 97.3% of patients having received at least one device and achieved reduction to MR ≤2+ at discharge, a rate that was maintained at 30 days (98.5%) and 1-year follow-up (99.2%). This rate of MR reduction is remarkable, since the randomized *Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation* (MITRA-FR) trial showed that <85% of patients had MR ≤2+ after 12 months, 95% in COAPT and >95% in the *European Registry of Transcatheter Repair for Secondary Mitral Regurgitation* (EuroSMR). As shown in COAPT and the EuroSMR registry, effective MR reduction with lowest possible residual MR is key to improve outcomes after M-TEER (17,18).

Notably, the estimated 1-year mortality rate of EXPAND with 17.7% is comparable to COAPT (19%), MITRA-FR (24%) and EuroSMR registry (20%). The potentially lower mortality compared to MITRA-FR (24%) could be due to the procedural results in EXPAND and further emphasizes that MR reduction is strongly associated with mortality outcomes (Graphical Abstract). A contributor to this outcome could be the significant MR reduction in EXPAND, potentially achieved by individual device selection of either NTR or XTR clips. The option for device size selection based on individual patient anatomy was not available yet in COAPT, MITRA-FR, or EuroSMR. Nevertheless, other contributors to mortality such as baseline characteristics and patient selection could have influenced outcomes of all studies.

Of relevance for the application of different clip sizes could be the reported association of usage of a larger device with more SLDAs and leaflet tears (9). Leaflets adverse events within EXPAND have been further analyzed by an expert panel (20). Reassuringly, only 2 peri-procedural SLDA were reported, with further 6 SLDA through 30 days and no other leaflet related adverse events through 1 year. This 1.9% rate of SLDA is lower than the very early experience with different MitraClip devices reported before (9,15). This could be due to the etiology of SMR. In SMR, the prevalence of fragile and degenerative leaflets or extensive mitral

annulus calcifications should be low. As such, the study by Doldi et al. pointed at a potential effect in primary MR, not in SMR (9). Leaflet injury and SLDAs seem to be rather acute events, as both studies did not report any delayed SLDAs after 30 days (9,15). The documented leaflet injuries and SLDAs occurred in a very early application phase after the XTR clip was available. Therefore, a steep learning curve could have contributed to the lower incidence of SLDAs in our subsequent study.

The majority of participating cardiac valve centers in this study had prior experience in characterizing SMR by comprehensive echocardiographic protocols and thus optimally treating SMR patients with M-TEER procedure. Therefore, these results might not be representative of the learning curve of centers starting their M-TEER program. The growing operator experience over the years in addition to improved pre- and periprocedural imaging and careful patient selection are likely to have contributed to the procedural results in this trial. Another limitation of this study is the echocardiographic follow-up rate of 69%, which could have influenced the interpretation of results, however this follow-up rate is comparable to the COAPT trial. Lastly, definitions of severe SMR differ between both past and current European and US guidelines. This needs to be reflected if trial results are interpreted. The selection criteria for NTR and XTR implantation are still under investigation. The criteria recommended here by the Expand Steering Committee are based on expert knowledge. However, a recent echocardiographic analysis confirmed that the NTR clip is more suitable for smaller mitral valve areas (21). This supports the recommendation in this study to use the NTR clip if mitral valve area is below 4 $cm^2$.

As expected, EXPAND results demonstrate that 3$^{rd}$ generation clip designs are effective treatment options in experienced heart valve centers for treatment of a variety of patient anatomies. Both the XTR clip and the NTR clip were implanted in comparable numbers of patients. Also, the combination of both clip designs was feasible in a substantial number of

patients. Notably, if patients were treated with the NTR clip, almost 40% of them received ≥2 clips in contrast to only 27% of the XTR-treated patients receiving ≥2 clips. As shown by the echocardiographic differences between NTR- and XTR-treated patients, the implantation of larger clips in larger ventricular anatomies could overcome the potential challenges to achieve optimal SMR reduction with the smaller size first-generation clips. Currently, fourth generation devices have been developed with wider clip arms and independent leaflet grasping, which are now in use for MR patients, but broad 1-year clinical data has not been gathered yet. This is in contrast to the large patient number presented here in this study.

This analysis represents ECL-assessed echocardiographic and clinical events committee-assessed clinical outcomes in patients with SMR treated with the 3rd generation MitraClip (NTR/XTR) system. Results from this real-world contemporary setting confirm that repair with either the NTR or XTR MitraClip alone or in combination is associated with a favorable safety profile and good clinical outcomes. The real-world efficacy of SMR treatment with MitraClip NTR/XTR was shown by MR reduction to grade ≤2+ in 99.6% of patients and reduction to grade ≤1+ in 93% of patients that sustained through 1-year follow-up. Moreover, these results show that continuous improvements in treatment of MR with M-TEER have been achieved since the introduction of the 1st generation MitraClip. In experienced heart valve centers, NTR and XTR MitraClip devices extend the options for the heart team to achieve optimal procedural results in different SMR anatomies to assure prognostic benefit.

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**CONFLICT OF INTEREST**

Dr. Orban has received speaker fees from Tomtec Imaging Systems. Prof. Rottbauer has received consulting fees/speaker honoraria from Abbott, Bayer Healthcare, Boston Scientific, Daiichi Sankyo, Edwards Lifesciences, and Medtronic. He is a member in the steering committee of the EXPAND G4 Study (Abbott) and Encourage AF Study (Daiichi Sankyo). Dr. Williams has received research funding from Abbott, Medtronic, BSC and Edwards Lifesciences. Dr. Mahoney serves as consultant and proctor for Medtronic, Edwards Lifesciences and Boston Scientific. He is a consultant for Abbott. He has received research support from Edwards, Medtronic, Abbott, and Boston Scientific. He has no equity or personal financial interest in any company. Dr. von Bardeleben has served in unpaid trial activities for Abbott, Edwards Lifesciences, University of Göttingen (IIT), and advisory or speaker bureau for Abbott Cardiovascular, Bioventrix, Boston Scientific, Cardiac

Dimensions, Edwards Lifesciences, Neochord. Dr. Price has received consulting fees from AstraZeneca, Chiesi USA, Medtronic, Boston Scientific, Abbott, and WL Gore outside of the submitted work. Dr. Grasso serves as a proctor for Abbott, Boston Scientific and has received fees as speaker from Edwards Lifesciences. Prof. Lurz has served as a consultant, received institutional fees and research grants from Abbott, Edwards Lifescience, Medtronic, ReCor, and Occlutech. Dr. Zamorano has received speaker honoraria from Pfizer, Amgen and Daichii, and research grants from Abbott and Edwards Lifesciences. Dr. Asch has no personal disclosures. His work as Director of an Academic Core laboratory is through institutional research grants (MedStar Health) with Abbott, Boston Scientific, Medtronic, Edwards Lifesciences, Neovasc, Ancora Heart, Livanova, MVRx, InnovHeart, Polares medical, and Aria CV. Prof. Maisano has received grant and/or institutional research support from Abbott, Medtronic, Edwards Lifesciences, Biotronik, Boston Scientific Corporation, NVT, Terumo. He received consulting fees, honoraria personal and institutional from Abbott, Medtronic, Edwards Lifesciences, Xeltis, Cardiovalve. He has received royalty income/IP rights from Edwards Lifesciences. He is a shareholder (including share options) of Cardiogard, Magenta, SwissVortex, Transseptalsolutions, Occlufit, 4Tech, Perifect. Dr. Kar has received grants and institutional research support from Abbott, Boston Scientific and Edwards Lifesciences, consulting fees/honoraria from Abbott, Boston Scientific, W.L. Gore and Medtronic, and steering committee member of TRILUMINATE Study (Abbott), national principle investigator of EXPAND Study (Abbott) and the REPAIR MR Study (Abbott). Prof. Hausleiter has received research support from Abbott Vascular and Edwards Lifesciences.

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## FIGURE LEGENDS

**Figure 1. Clinical Outcome after M-TEER.** All-cause mortality (A), heart failure hospitalization (B), and combined all-cause mortality and heart failure hospitalization (C) through 1 year follow up for EXPAND SMR population. Event rates are Kaplan-Meier time to first event estimates. HF, heart failure; M-TEER, mitral valve transcatheter edge-to-edge repair; SMR, secondary mitral regurgitation.

**Figure 2. Clinical Outcome after M-TEER according to ECL Assessed Discharge MR.** All-cause mortality (A), heart failure hospitalization (B), and combined all-cause mortality and heart failure hospitalization (C) through 1 year follow up for EXPAND SMR population as stratified by discharge residual MR >1+ and <=1+ as assessed by ECL. Event rates are Kaplan-Meier time to first event estimates. ECL, echocardiography core lab; MR, mitral regurgitation; M-TEER, mitral valve transcatheter edge-to-edge repair; SMR, secondary mitral regurgitation.

**Graphical Abstract.** Subject consort diagram (A). Illustrations showing MitraClip NTR Clip, which is identical to the original MitraClip NT/Classic Clip and MitraClip XTR Clip which has longer clip arms for easier grasp and better reach (B). Number of devices implanted with NTR only and XTR only showing more single clip use when XTR is used (C). Combined all-cause mortality and heart failure hospitalization through 1 year follow up for EXPAND SMR population as stratified by discharge residual MR >1+ and ≤1+ as assessed by ECL; Event rates are Kaplan-Meier time to first event estimates (D). ECL, echocardiography core lab; MR, mitral regurgitation; M-TEER, mitral valve transcatheter edge-to-edge repair; SMR, secondary mitral regurgitation.

**Supplementary Figure 1. Hospitalizations for Heart Failure before and after M-TEER.** Percentage and number of patients with heart failure hospitalizations before (lower bar) and after (upper bar) M-TEER are shown. Annualized rates are shown below each graph.

**Supplementary Figure 2. Clinical Outcome after M-TEER according to Baseline EROA.** All-cause mortality (A), heart failure hospitalization (B), and combined all-cause mortality and heart failure hospitalization (C) through 1 year follow up for EXPAND SMR population as stratified by effective regurgitant orifice area (EROA) < 0.3 cm2 and ≥ 0.3 $cm^2$. Event rates are Kaplan-Meier time to first event estimates.

## TABLES

**Table 1. Baseline Patient Characteristics MitraClip**

| | **(N=413)** |
|---|---|
| Age, years | 74.7 ± 10.1 (413) |
| Male, % | 58.4% (241/413) |
| Body Mass Index, kg/m$^2$ | 26.04 ± 4.87 (411) |
| EuroSCORE II | 9.83 ± 9.36 (234) |
| STS Replacement Score | 8.83 ± 7.47 (261) |
| STS Repair Score | 7.20 ± 7.34 (283) |
| Cardiac Arrhythmia, % | 68.8% (282/410) |
| Prior Cardiac Surgeries, % | 34.9% (144/413) |
| Prior percutaneous coronary intervention, % | 45.5% (184/403) |
| Permanent Pacemaker , % | 20.7% (85/410) |
| CRT, % | 10.2% (42/410) |
| Previous ICD, % | 37.0% (152/411) |
| Prior Heart Failure Hospitalization within 1yr, % | 64.8% (248/383) |
| Chronic Lung Disease, % | 25.2% (100/397) |
| Diabetes, % | 29.5% (120/407) |
| Renal Failure, % | 47.1% (192/408) |
| On Dialysis / dialysis dependent | 4.7% (19/189) |
| Prior Valve procedure, % | 11.5% (47/410) |
| Prior MV procedure, % | 27.7% (13/47) |
| MV Repair – Surgical | 15.4% (2/13) |
| Mitral Annuloplasty Ring - Surgical | 7.7% (1/13) |
| MV Transcatheter Intervention | 84.6% (11/13) |
| Prior AV procedure | 70.2% (33/47) |
| Prior TV procedure | 2.1% (1/47) |

| **Medication Data, %** | |
|---|---|
| Betablockers | 88.6% (366/413) |
| ACE-Inhibitors | 37.8% (156/413) |
| Angiotensin receptor blockers | 22.3% (92/413) |
| Mineralocorticoid receptor antagonist | 36.6% (151/413) |
| Diuretic (any type) | 85.7% (354/413) |
| Angiotensin receptor-neprilysin inhibitor | 11.6% (48/413) |
| **Functional Class and QOL** | |
| NYHA ≤II, % | 16.9% (70/413) |
| NYHA ≤III, % | 83.1 % (343/413) |
| KCCQ Score | 43.7 ± 23.7 (389) |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; AV, aortic valve; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association functional class; MV, mitral valve; New York Heart Association; STS, Society of Thoracic Surgeons; TV, tricuspid valve.

**Table 2. Baseline Echocardiographic Characteristics**

| MR Parameters | Baseline |
|---|---|
| **MR grades (ESC Guidelines)*, %** | |
| 2+: Moderate | 7.5% (24/404) |
| 3+: Moderate-to-Severe | 27.4% (113/404) |
| 4+: Severe | 64.8% (267/404) |
| Vena Contracta, cm | 0.53 ± 0.13 (297) |
| EROA (PISA), $cm^2$ | 0.30 ± 0.12 (298) |
| Regurgitant Volume, ml | 44.8 ± 19.4 (298) |
| **MV and LV Parameters** | |
| MVA, $cm^2$** | 3.93 ± 1.16 (290) |
| MVA < 4 $cm^2$, % | 56.2% (163/290) |
| MVA ≥ 4 $cm^2$, % | 43.8% (127/290) |
| MPG, mmHg | 2.11 ± 1.13 (286) |
| MPG ≤ 5mmHg, % | 96.9% (277/286) |
| MPG > 5mmHg, % | 3.1% (9/286) |
| LVEF, % | 39.4%± 13.5 (377) |
| Left Ventricular End Systolic Dimension, cm | 4.98 ± 1.14 (393) |
| Left Ventricular End Diastolic Dimension, cm | 6.07 ± 0.94 (396) |

| | |
|---|---|
| Left Ventricular End Systolic Volume, ml | 115.6 ± 69.0 (378) |
| Left Ventricular End Diastolic Volume, ml | 181.2 ± 80.4 (377) |
| Mean Pulmonary Artery Pressure, mmHg | 24.9 ± 9.2 (375) |
| Systolic Pulmonary Artery Pressure, mmHg | 54.4 ± 14.9(363) |
| Anterior Posterior Systolic Diameter, cm | 3.08 ± 0.48 (395) |
| Anterior Posterior Diastolic Diameter, cm | 3.40 ± 0.49 (396) |
| Lateral medial Systolic Diameter, cm | 3.03 ± 0.46 (383) |
| Lateral medial Diastolic Diameter, cm | 3.31 ± 0.49 (381) |
| **Coaptation depth** | |
| Mean, cm | 0.76 ± 0.27 (373) |
| Coaptation Depth ≤ 1.10 cm, % | 89.0% (332/373) |
| Coaptation Depth > 1.10 cm, % | 11.0% (41/373) |
| **Coaptation length** | |
| Mean, cm | 0.35 ± 0.16 (341) |
| Coaptation Length ≤ 0.2 cm, % | 9.7% (33/341) |
| Coaptation Length > 0.2 cm, % | 90.3% (308/341) |
| **Tricuspid Regurgitation, %** | |
| None | 6.8% (25/368) |
| Mild | 51.1% (188/368) |

| | |
|---|---|
| Moderate | 22.6% (83/368) |
| Severe | 13.6% (50/368) |
| Massive | 6.0% (22/368) |

* MR Severity assessed by ECL based on 2017 ESC Guidelines [19]. Retrospective assessment of baseline MR by ECL according to ASE guidelines [10] was MR 1+: 9.2% (38/412), MR 2+: 42.5% (175/412), MR 3+: 33.0% (136/412), MR 4+: 15.3% (63/412). ** MVA was assessed per pressure half time estimation.
ECL, Echocardiography Core Lab; ESC, European Society of Cardiology; EROA, effective regurgitant orifice area; LVEF, left ventricular ejection fraction; MPG, mean mitral valve pressure gradient; MR, mitral regurgitation; MV, mitral valve; MVA, mitral valve area; PISA, proximal isovelocity surface area.

**Table 3. Procedure Data and Patient Discharge Status**

| | MitraClip (N=413) |
|---|---|
| Acute Procedural Success | 97.3% (399/410) |
| Implant Rate | 99.3% (410/413) |
| Acute Device Success | 98.1% (405/413) |
| Device Time, min | 54.5 ± 39.9 (413) |
| Procedure Time, min | 86.8 ± 46.7 (413) |
| Fluoroscopy Time, min | 19.7± 12.0 (413) |
| Median (Q1, Q3) | 16.7 (11.4, 25.0) |
| Length of Stay in Hospital for Index Procedure, days | 7.8 ± 7.3 (413) |
| Post-Procedure PACU/ CCU/ICU Duration, hours | 46.3± 64.7 (299) |

| **MitraClip Usage** | **1 Clip** | **2 Clips** | **3 Clips** |
|---|---|---|---|
| XTR Only (41.2%, 169/410) | 30.0% (123/410) | 11.0% (45/410) | 0.2% (1/410) |
| NTR only (44.1%, 181/410) | 25.4% (104/410) | 17.3% (71/410) | 1.5% (6/410) |
| XTR and NTR (14.6%, 60/410) | 0.0% (0/410) | 10.5% (43/60) | 4.1% (17/410) |
| Total Usage | 55.4% (227/410) | 38.8% (159/410) | 5.9% (24/410) |

CCU, Cardiac care unit; ICU, intensive care unit; PACU, Post anesthesia care unit.

**Table 4. NYHA Functional Class, KCCQ Score and Medication baseline through 1 year**

| NYHA Functional Class, % | Baseline | 30 Days | 1 Year |
|---|---|---|---|
| I | 1.2% (5/413) | 17.1% (58/339) | 22.5% (61/271) |
| II | 15.7% (65/413) | 59.0% (200/339) | 55.4% (150/271) |
| III | 69.5% (287/413) | 21.5% (73/339) | 19.2% (52/271) |
| IV | 13.6% (56/413) | 2.4% (8/339) | 3.0% (8/271) |
| NYHA ≤II | 16.9% (70/413) | 76.1% (258/339)* | 77.9% (211/271)* |
| NYHA ≤III | 83.1% (343/413) | 23.9% (81/339) | 22.1% (60/271) |
| **KCCQ Score** | | | |
| All available | 43.7 ± 23.7 (389) | 64.1 ± 23.9 (342) | 68.3 ± 22.1 (258) |
| Paired baseline vs. 30 Days | 44.8 ± 23.4 (334) | 64.2 ± 23.8 (334) | NA |
| Difference | | 19.5 ± 24.9 (334) † | |
| Paired baseline vs. 1-yr | 46.4 ± 24.1 (252) | NA | 68.5 ± 22.1 (252) |
| Difference | | 22.0 ± 25.8 (252) † | |
| **Medication Data, %** | | | |
| Betablockers | 88.6% (366/413) | | 80.8% (227/281) |
| Mineralocorticoid receptor antagonist | 36.6% (151/413) | | 44.5% (125/281) |
| Diuretic (any type) | 85.7% (354/413) | | 87.5% (246/281) |
| Any ACE-Inhibitors, Angiotensin receptor | | | |

| | | |
|---|---|---|
| blockers, or Angiotensin receptor-neprilysin inhibitor | 71.7% (296/413) | 74.0% (208/281) |
| ACE-Inhibitors | 37.8% (156/413) | 32.0% (90/281) |
| Angiotensin receptor blockers | 22.3% (92/413) | 20.3% (57/281) |
| Angiotensin receptor-neprilysin inhibitor | 11.6% (48/413) | 21.7% (61/281) |

*Significant improvement in NYHA from Baseline to 30-days and baseline to 1-year, (Bowker's Test), p-value of <0.0001 for each comparison
†Significant improvement in KCCQ score from Baseline to 30-days and baseline to 1-year, p-value of <0.0001 for both comparisons
ACE, angiotensin converting enzyme; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association functional class.

**Table 5. Echocardiographic Outcomes at 1-year follow-up.**

| LV Parameters | Baseline | 1 year | p-value |
|---|---|---|---|
| MVA, $cm^2$ | 3.9 ± 1.1 (121) | 2.8 ± 1.0 (121) | <0.0001 |
| MPG, mmHg | 2.0 ± 1.0 (134) | 3.4 ± 3.2 (134) | <0.0001 |
| LVEF, % | 40.2 ± 13.6 (207) | 41.3 ± 14.0 (207) | 0.19 |
| Left Ventricular End Systolic Dimension, cm | 4.97 ± 1.10 (216) | 4.89 ± 1.26 (216) | 0.16 |
| Left Ventricular End Diastolic Dimension, cm | 6.12 ± 0.92 (219) | 5.94 ± 1.07 (219) | 0.0007 |
| Left Ventricular End Systolic Volume, ml | 117.2 ± 72.9 (207) | 101.5 ± 71.8 (207) | <0.0001 |
| Left Ventricular End Diastolic Volume, ml | 185.5 ± 84.1 (207) | 161.0 ± 80.5 (207) | <0.0001 |
| Mean Pulmonary Artery Pressure, mmHg | 24.2 ± 8.2 (182) | 20.3 ± 7.0 (182) | <0.0001 |
| Anterior Posterior Systolic Diameter, cm | 3.09 ± 0.49 (215) | 2.94 ± 0.48 (215) | 0.0002 |
| Anterior Posterior Diastolic Diameter, cm | 3.39 ± 0.51 (216) | 3.25 ± 0.51 (216) | 0.0008 |
| Lateral medial Systolic Diameter, cm | 3.02 ± 0.49 (206) | 2.77 ± 0.46 (206) | <0.0001 |
| Lateral medial Diastolic Diameter, cm | 3.31 ± 0.52 (203) | 3.12 ± 0.52 (203) | <0.0001 |
| Tricuspid Regurgitation, % | | | |
| None | 4.9% (9/183) | 18.0% (33/183) | |
| Mild | 55.8 % (101/183) | 59.0% (107/183) | |
| Moderate | 20.9 % (38/183) | 15.0% (28/183) | <.0001* |

| | | |
|---|---|---|
| Severe | 11.0% (20/183) | 6.6% (12/183) |
| Massive | 7.2 % (13/183) | 1.6% (3/183) |

Paired analysis shown.
*Bowker's test for comparison of TR≥ 2+ vs TR < 2+.
LVEF, left ventricular ejection fraction; MPG, mean mitral valve pressure gradient; MVA, mitral valve area.

**Table 6. Baseline Echocardiographic Characteristics of Subjects Treated with NTR-only vs. XTR-only Clip types**

| Baseline Echo Characteristics | NTR-only (N=181) | XTR-only (N=169) | p-value |
|---|---|---|---|
| MR (ESC Guidelines)*, % | | | |
| None | 0.0% (0/176) | 0.0% (0/168) | 1.00 |
| Mild | 0.0% (0/176) | 0.0% (0/168) | 1.00 |
| Moderate | 6.3% (11/176) | 6.5% (11/168) | 0.91 |
| Moderate-to-Severe | 31.3% (55/176) | 25.0% (42/168) | 0.20 |
| Severe | 62.5% (110/176) | 67.9% (114/168) | 0.30 |
| Vena Contracta, cm | 0.53 ± 0.13 (121) | 0.53 ± 0.13 (127) | 0.86 |
| EROA, $cm^2$ | 0.29 ± 0.10 (128) | 0.30 ± 0.13 (126) | 0.54 |
| Regurgitant Volume, ml | 45.5 ± 18.5 (128) | 43.3 ± 20.4 (126) | 0.38 |
| PISA Radius, cm | 0.70 ± 0.17 (155) | 0.72 ± 0.19 (139) | 0.27 |
| MVA, $cm^2$ | 3.90 ± 1.18 (126) | 3.96 ± 1.15 (120) | 0.67 |
| MVA ≥ 4 $cm^2$, % | 40.5% (51/126) | 45.8% (55/120) | 0.40 |
| MPG, mmHg | 2.1 ± 1.2 (120) | 2.1 ± 1.1 (121) | 0.78 |
| Mean Pulmonary Artery Pressure, mmHg | 26.0 ± 9.5 (165) | 24.4 ± 9.2 (154) | 0.12 |
| Coaptation Depth, cm | 0.71 ± 0.27 (161) | 0.79 ± 0.26 (155) | 0.005 |
| Coaptation Depth >1.1cm, % | 9.3% (15/161) | 13.5% (22/156) | 0.64 |

| | | | |
|---|---|---|---|
| Coaptation Length, cm | 0.34 ± 0.16 (150) | 0.35 ± 0.15 (142) | 0.41 |
| Coaptation Length < 0.2 cm, % | 11.3% (17/150) | 7.7% (11/142) | 0.30 |
| Tenting Area, $cm^2$ | 1.46 ± 0.71 (169) | 1.60 ± 0.68 (157) | 0.07 |
| LVEF, % | 41.1 ± 14.2 (159) | 37.7 ± 12.8 (160) | 0.027 |
| Left Ventricular End Systolic Dimension, cm | 4.83 ± 1.09 (173) | 5.09 ± 1.19 (162) | 0.043 |
| Left Ventricular End Diastolic Dimension, cm | 5.97 ± 0.90 (173) | 6.11 ± 0.98 (164) | 0.17 |
| Left Ventricular End Systolic Volume, ml | 106.1 ± 68.2 (160) | 123.8 ± 70.2 (160) | 0.022 |
| Left Ventricular End Diastolic Volume, ml | 169.5 ± 78.6 (159) | 190.3 ± 84.0 (160) | 0.023 |
| Left Ventricular End Systolic Volume Index, $ml/m^2$ | 58.0 ± 36.8 (160) | 66.4 ± 37.0 (159) | 0.044 |
| Left Ventricular End Diastolic Volume Index, $ml/m^2$ | 92.9 ± 42.0 (159) | 102.1 ± 42.8 (159) | 0.055 |
| Anterior Posterior Systolic Annular Dimension, cm | 3.11 ± 0.47 (168) | 3.07 ± 0.47 (166) | 0.38 |
| Anterior Posterior Diastolic Annular Dimension, cm | 3.42 ± 0.49 (169) | 3.38 ± 0.49 (166) | 0.45 |
| Tricuspid Regurgitation, % | | | |
| None | 6.9% (11/160) | 7.2% (11/152) | 0.90 |
| Mild | 52.5% (84/160) | 52.0% (79/152) | 0.93 |
| Moderate | 17.5% (28/160) | 24.3% (37/152) | 0.14 |

| | | | |
|---|---|---|---|
| Severe | 15.0% (24/160) | 12.5% (19/152) | 0.52 |
| Massive | 8.1% (13/160) | 3.9% (6/152) | 0.12 |
| Baseline TR >moderate, % | 23.1% (37/160) | 16.4% (25/152) | 0.14 |

Paired analysis shown (Categorical using Chi-square test; continuous using t-test
* MR Severity assessed by ECL based on 2017 ESC Guidelines [19].
ECL, Echocardiography Core Lab; ESC, European Society of Cardiology; EROA, effective regurgitant orifice area; LVEF, left ventricular ejection fraction; MPG, mean mitral valve pressure gradient; MR, mitral regurgitation; MVA, mitral valve area; PISA, proximal isovelocity surface area; TR, tricuspid regurgitation.

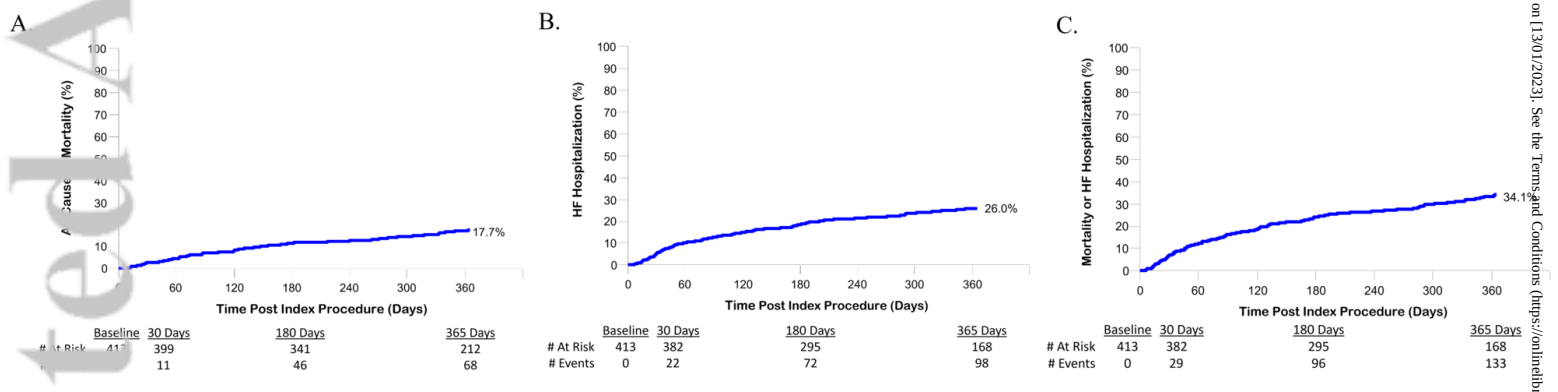


Figure 1 final.tiff

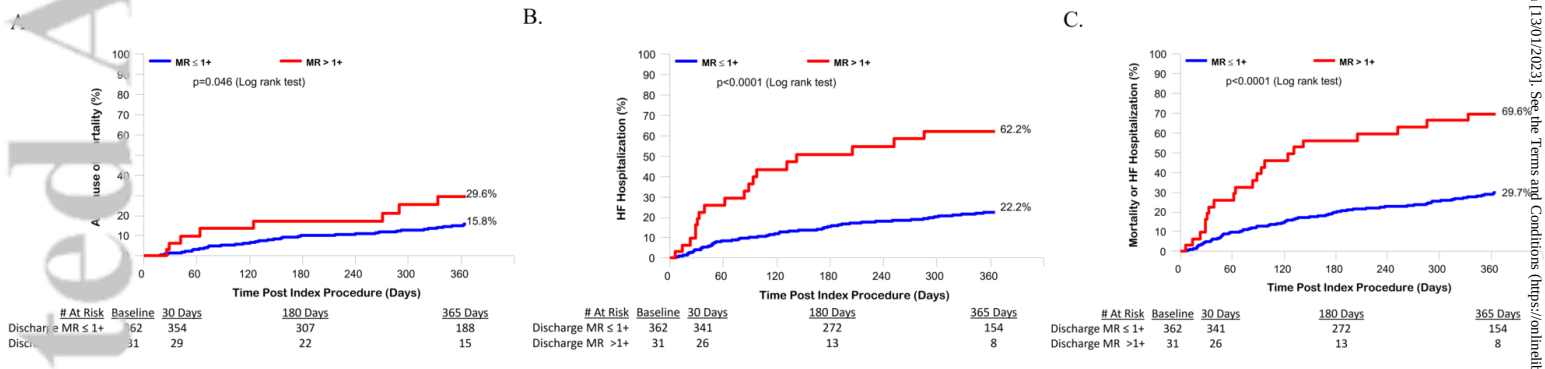


Figure 2 ejhf final.tiff