TEER in Intermediate Risk Primary MR, Will It Follow the TAVR's Footsteps?

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

AFFILIATION/FINANCIAL RELATIONSHIP	COMPANY
Grant/Research Support	Co-Principal investigator of the Repair MR trial
Consulting Fees/Honoraria	Abbott, Boston Scientific, Medtronic,
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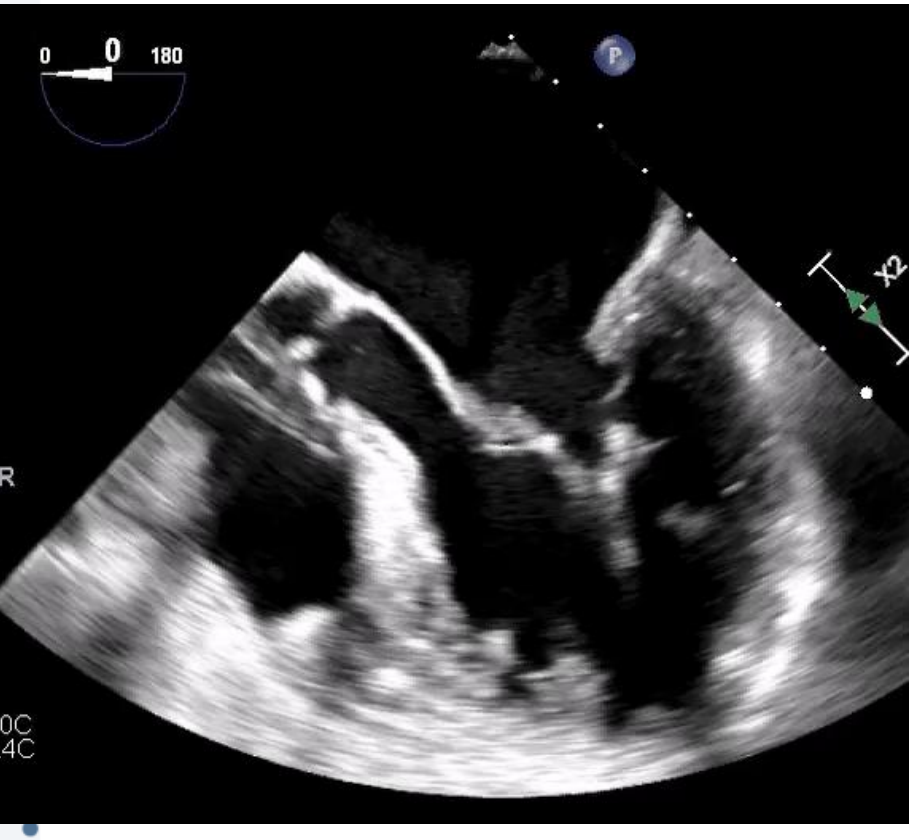
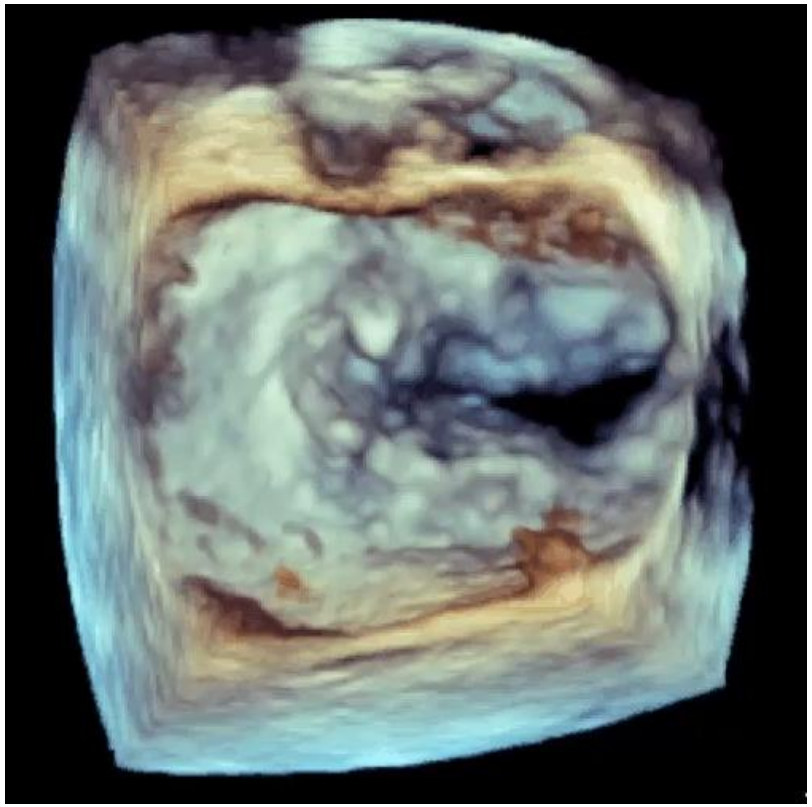
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

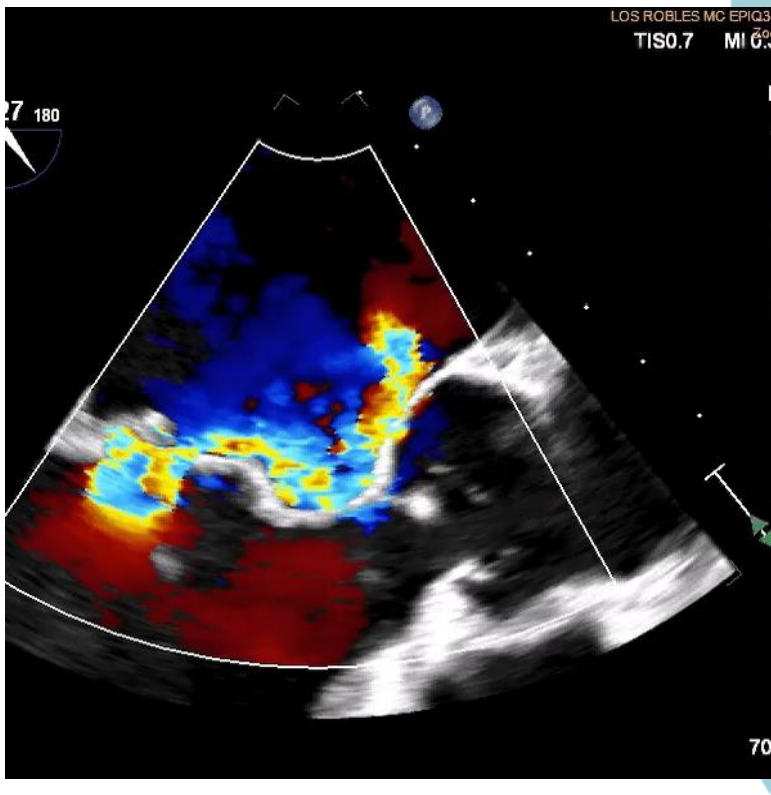
Transcatheter Edge to Edge Repair(TEE) for Primary MR in 2022

- Only approved transcatheter technology for treatment of primary MR in most countries in the world
- It is safe and effective and durable in selected patients
- Used primarily in high surgical/inoperable patients
- Improvements in technology, imaging, and clinical experience has lead to greater efficacy rate
- There is increase in use of this novel technology worldwide
- Physicians and patients are keen for this therapy for lower surgical risk patients

75 year old lady, Jehovah's Witness, mild mitral annular calcification







What Next

- Surgical repair : That is standard of care of low and intermediate surgical risk patients
- Mitral valve replacement: since there is mild mitral annular calcification,
- Transcatheter Edge to Edge Repair (TEER) : Off label since it is not approved for this low or intermediate risk degenerative MR
- Enroll in the REPAIR MR trial (Surgical repair vs TEER): since there is equipoise for this patient

Intervention for Patients with Chronic Primary MR

1	B-NR	1. In symptomatic patients with severe primary MR (Stage D), mitral valve intervention is recommended irrespective of LV systolic function.
1	B-NR	2. In asymptomatic patients with severe primary MR and LV systolic dysfunction (LVEF ≤60%, LVESD ≥40 mm) (Stage C2), mitral valve surgery is recommended.
1	B-NR	3. In patients with severe primary MR for whom surgery is indicated, mitral valve repair is recommended in preference to mitral valve replacement when the anatomic cause of MR is degenerative disease, if a successful and durable repair is possible.
2a	B-NR	4. In asymptomatic patients with severe primary MR and normal LV systolic function (LVEF ≥60% and LVESD ≤40 mm) (Stage C1), mitral valve repair is reasonable when the likelihood of a successful and durable repair without residual MR is >95% with an expected mortality rate of <1%, when it can be performed at a Primary or Comprehensive Valve Center.

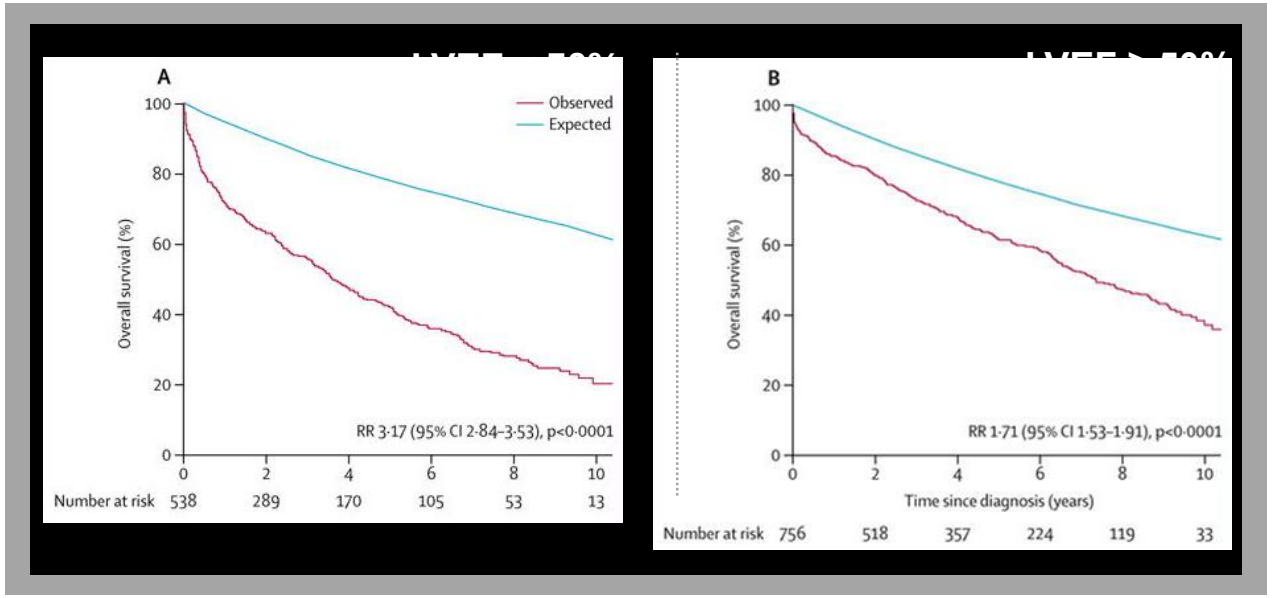
ACC 2021guidelines:Intervention for Patients with Chronic Primary MR (TEER has only a narrow indication)

		Recommendations
2b	C-LD	5. In asymptomatic patients with severe primary MR and normal LV systolic function (LVEF >60% and LVESD <40 mm) (Stage C1) but with a progressive increase in LV size or decrease in EF on ≥3 serial imaging studies, mitral valve surgery may be considered irrespective of the probability of a successful and durable repair.
2a	**B-NR**	**6. In severely symptomatic patients (NYHA class III or IV) with primary severe MR and high or prohibitive surgical risk, transcatheter edge-to-edge repair (TEER) is reasonable if mitral valve anatomy is favorable for the repair procedure and patient life expectancy is at least 1 year.**
2b	B-NR	7. In symptomatic patients with severe primary MR attributable to rheumatic valve disease, mitral valve repair may be considered at a Comprehensive Valve Center by an experienced team when surgical treatment is indicated, if a durable and successful repair is likely
3: Harm	B-NR	8. In patients with severe primary MR where leaflet pathology is limited to less than one half the posterior leaflet, mitral valve replacement should not be performed unless mitral valve repair has been attempted at a Primary or Comprehensive Valve Center and was unsuccessful.

Undertreatment of Degenerative MR in the community

Mitral valve disease continues to be under treated in the community, where only a minority of affected patients undergo mitral surgery, even when surgical treatment options are available.[1]

> Mitral surgery was ultimately done in only 198 (15%) of 1294 patients...in 164 (29%) of 571 with primary regurgitation. Excess mortality and HF and substantial surgical undertreatment underscore the limits of the current mitral regurgitation standards and suggests that new strategies to improve treatment and outcomes of mitral regurgitation should be tested.[1]



Survival after diagnosis of isolated moderate or severe mitral regurgitation, stratified by left-ventricular ejection fraction (LVEF) at diagnosis in Olmsted County residents (median age: 77)

[1]Dziadzko et al. Lancet. 2018; 391: 960–969.

What is Moderate Surgical Risk for Primary MR?

TABLE 8 Risk Assessment for Surgical Valve Procedures

Criteria	Low-Risk SAVR (Must Meet ALL Criteria in This Column)	Low-Risk Surgical Mitr Valve Repair for Prima MR (Must Meet ALL Criteria in This Colum	High Surgical Risk (Any 1 Criterion in This Column)	Prohibitive Surgical Risk (Any 1 Criterion in This Column)
STS=predicted risk of death*	<3% AND	<1% AND	>8% OR	Predicted risk of death or major morbidity (all-cause) >50% at 1 y OR
Frailty†	None AND	None AND	≥2 Indices moderate to severe) OR	≥2 Indices (moderate to severe) OR
Cardiac or other major organ system compromise not to be improved postoperatively‡	None AND	None AND	1 to 2 Organ systems OR	≥3 Organ systems OR
Procedure-specific impediment§	None	None	Possible procedure-specific impediment	Severe procedure-specific impediment

Moderate Risk ?

Otto et al. J Am Coll Cardial. 2021 Feb 2;77(4):450-500.

Impact of Age in Isolated Mitral Valve Repair

J. MAXWELL CHAMBERLAIN MEMORIAL PAPER FOR ADULT CARDIAC SURGERY

Longitudinal Outcome of Isolated Mitral Repair in Older Patients: Results From 14,604 Procedures Performed From 1991 to 2007

Vinay Badhwar, MD, Eric D. Peterson, MD, Jeffrey P. Jacobs, MD, Xia He, MS, J. Matthew Brennan, MD, Sean M. O'Brien, PhD, Rachel S. Dokholyan, MPH, Kristopher M. George, MD, Steven F. Bolling, MD, David M. Shahian, MD, Fredrick L. Grover, MD, Fred H. Edwards, MD, and James S. Gammie, MD

AGE RANGE	OPERATIVE MORTALITY
65-69 years	1.7%
70-74 years	1.9%
75-79 years	3.4%
80+ years	4.3%

Age is a strong predictor of morbidity and mortality in mitral valve repair with an age of 75 years being a key inflection point

Mitral Valve Repair Surgery:

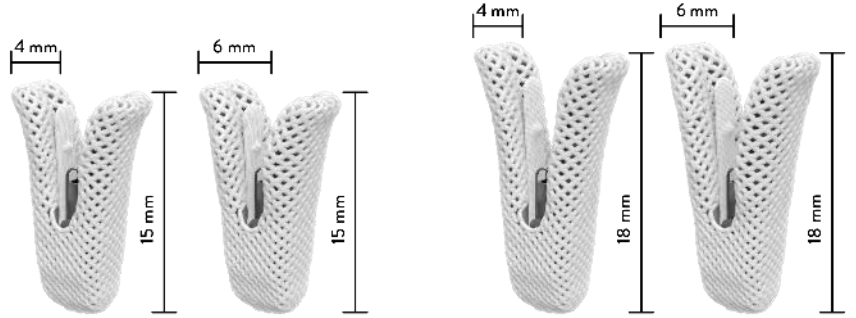
Operative Outcomes

	25th PERCENTILE	50th PERCENTILE	75th PERCENTILE
MV Repair	**0.3%**	**0.6%**	**1.2%**

25% of patients who undergo surgical mitral valve repair have an STS score > 1.2%

Transcatheter Edge-to-Edge Repair for Primary MR

- Despite its safety, effectiveness in select patients, TEER has only a narrow indication for the treatment of primary MR in the US
  - **Primary MR:** Prohibitive risk defined as an STS PROM Repair Score ≥ 6% or frailty or other clinical factors that may introduce a procedure-specific impediment
- Over 150,000 patients treated worldwide
- The MitraClip™ is currently in its 4th generation new features to simplify the procedure, particularly for patients with complex anatomies
- TEER with PASCAL device is current in clinical trial for prohibitive risk primary MR



STANDARD LENGTH ARM
(G4 NT / G4 NTW)

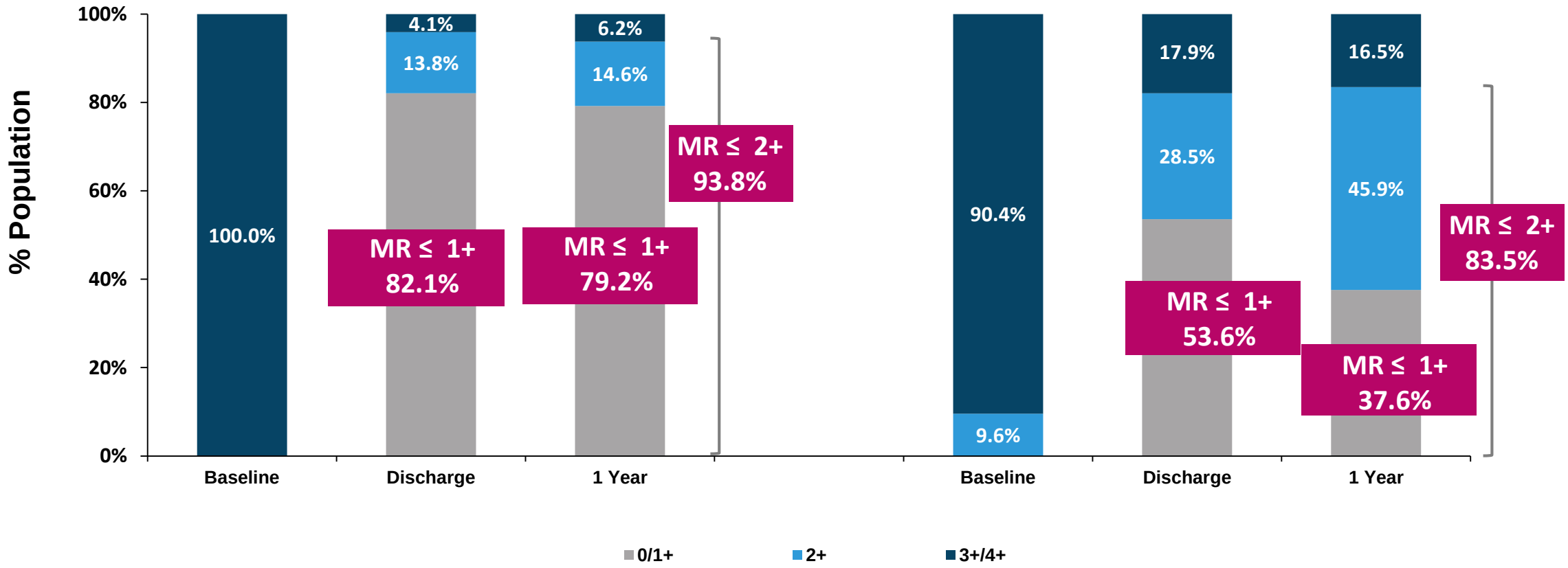
LONG LENGTH ARM
(G4 XT / G4 XTW)

Contemporary MitraClip™ Outcomes:

Improvements in MR Reduction with New Generation MitraClip™ Systems

EXPAND Primary MR Subjects[1] w/ Baseline MR Severity ≥ 3+ (n=279)

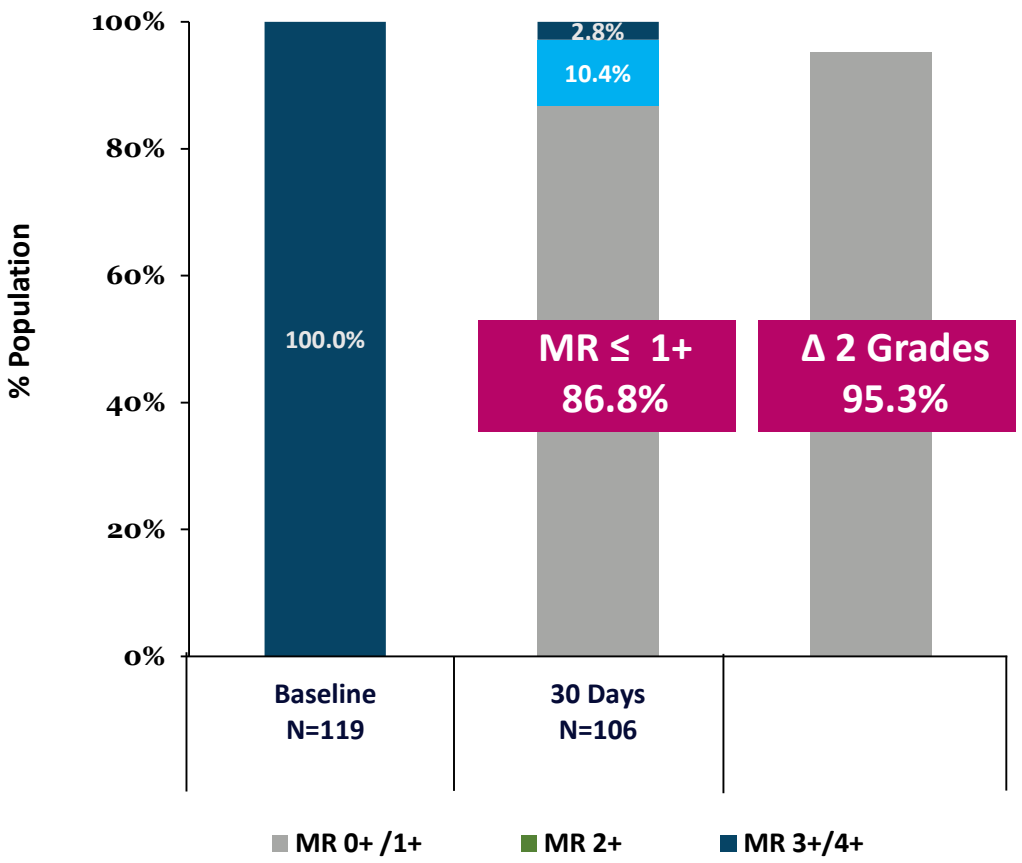
EVEREST/REALISM Prohibitive Risk Primary MR Cohort[2] (n=123)



[1]Kar et al. TCT 2020, Late Breaking Clinical Trial Presentation
[2]Lim et al. ACC 2018 Presentation

Contemporary Outcomes in Lower Risk Patients

Safe Procedure with a Predictable Reduction of MR to ≤ Mild



PARAMETER	VALUE (N=166)
Age	77.2 ± 10.2 years
LVEF	62.5 ± 9.9 %
STS Repair Score	2.9 ± 1.3 %
Implant Rate	98.8%
Procedure Time	77.5 minutes
Al-Cause Death	1.2%
MI	0.0%

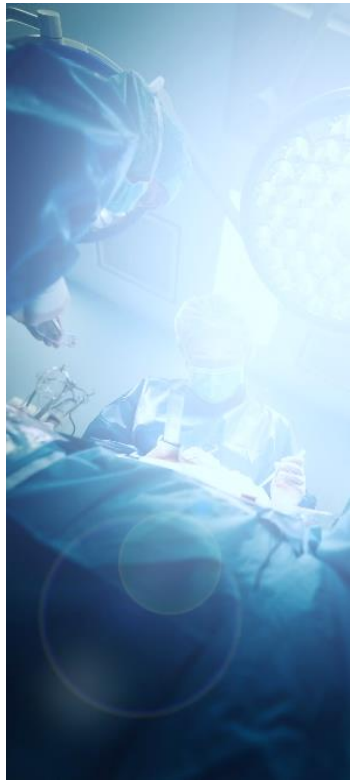
[1]Tang et al. Outcomes of MitraClip Repair in Primary Mitral Regurgitation Patients With STS Repair Score of Less Than 6% and STS Replacement Score of Less Than 8%: Results From the Global EXPAND Study TCT 2020, Outcomes

TEER in Moderate Surgical Risk:

REPAIR MR: Objectives and Design

REPAIR MR TRIAL

SCIENTIFIC OBJECTIVE	Compare the clinical outcome of MitraClip™ device versus surgical repair in patients with severe primary MR who are: • Moderate Surgical Risk • Have a mitral valve conducive to repair
TRIAL DESIGN	• Prospective, randomized, multi-center study, to be conducted in United States, Canada, and Europe • 500 subjects enrolled at up to 60 sites in United States, Canada, & Europe • Principal Investigators: Dr. Patrick McCarthy (Northwestern) and Dr. Saibal Kar (Los Robles) • Echo Core-Laboratory: Medstar Washington University Hospital (Dr. Federico Asch and Dr. Neil Weissman)

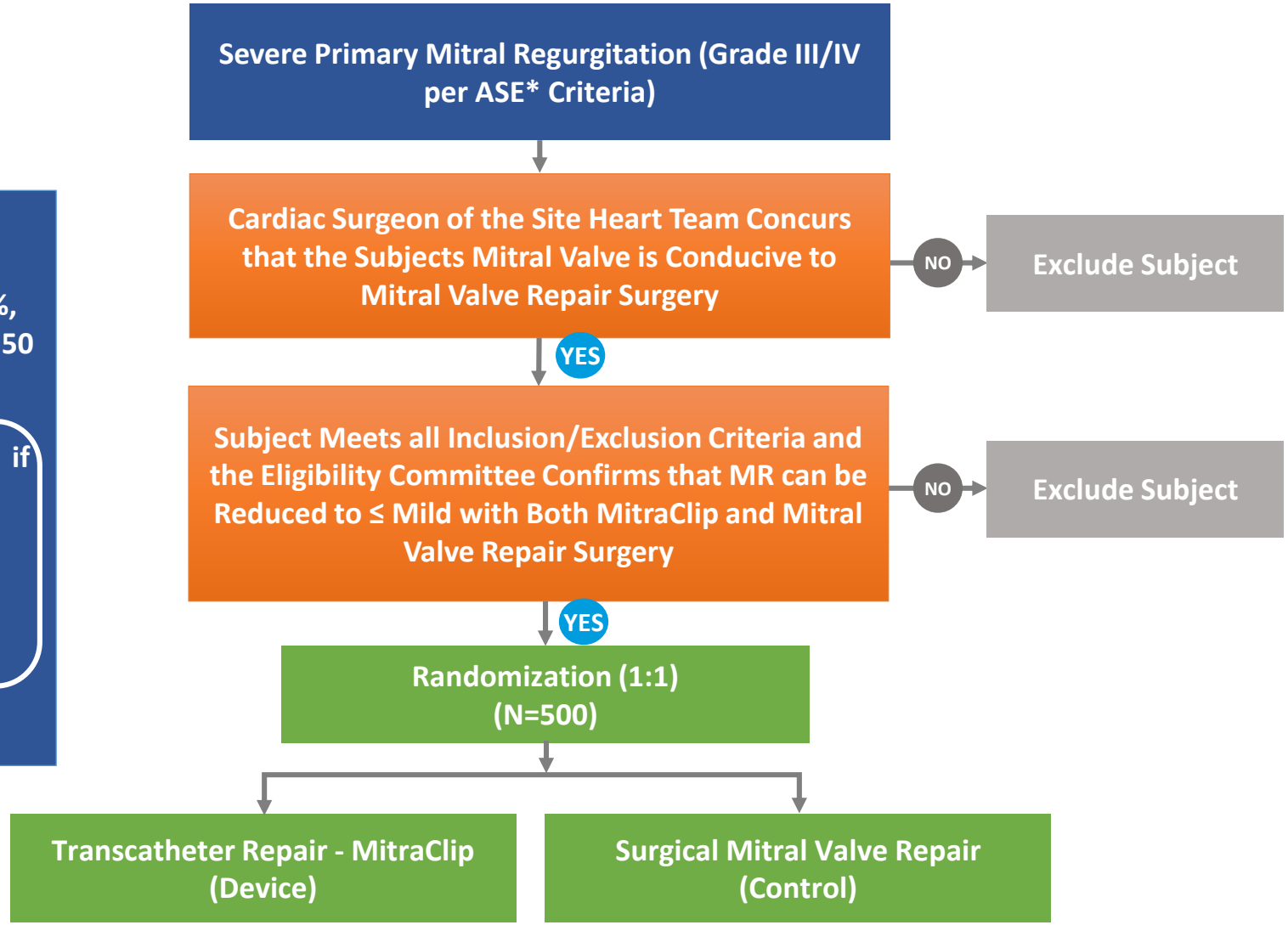


Trial Overview

REPAIR MR TRIAL

Patient Population

- Subject is symptomatic (NYHA Class II/III/IV) or asymptomatic (LVEF ≤ 60%, Pulmonary Artery Systolic Pressure > 50 mmHg, or LVESD > 40 mm)
- Subject is at least 75 years of age, OR if younger than 75 years, then has:
  - STS-PROM Score ≥ 2%, OR
  - Presence of other comorbidities which may introduce a potential surgical specific impediment



**Zoghbi et al. J Am Soc Echocardiogr. 2017 Apr;30(4):303-371.

† Subjects in whom planned surgical procedure is replacement will be excluded

TEER in Moderate Surgical Risk:

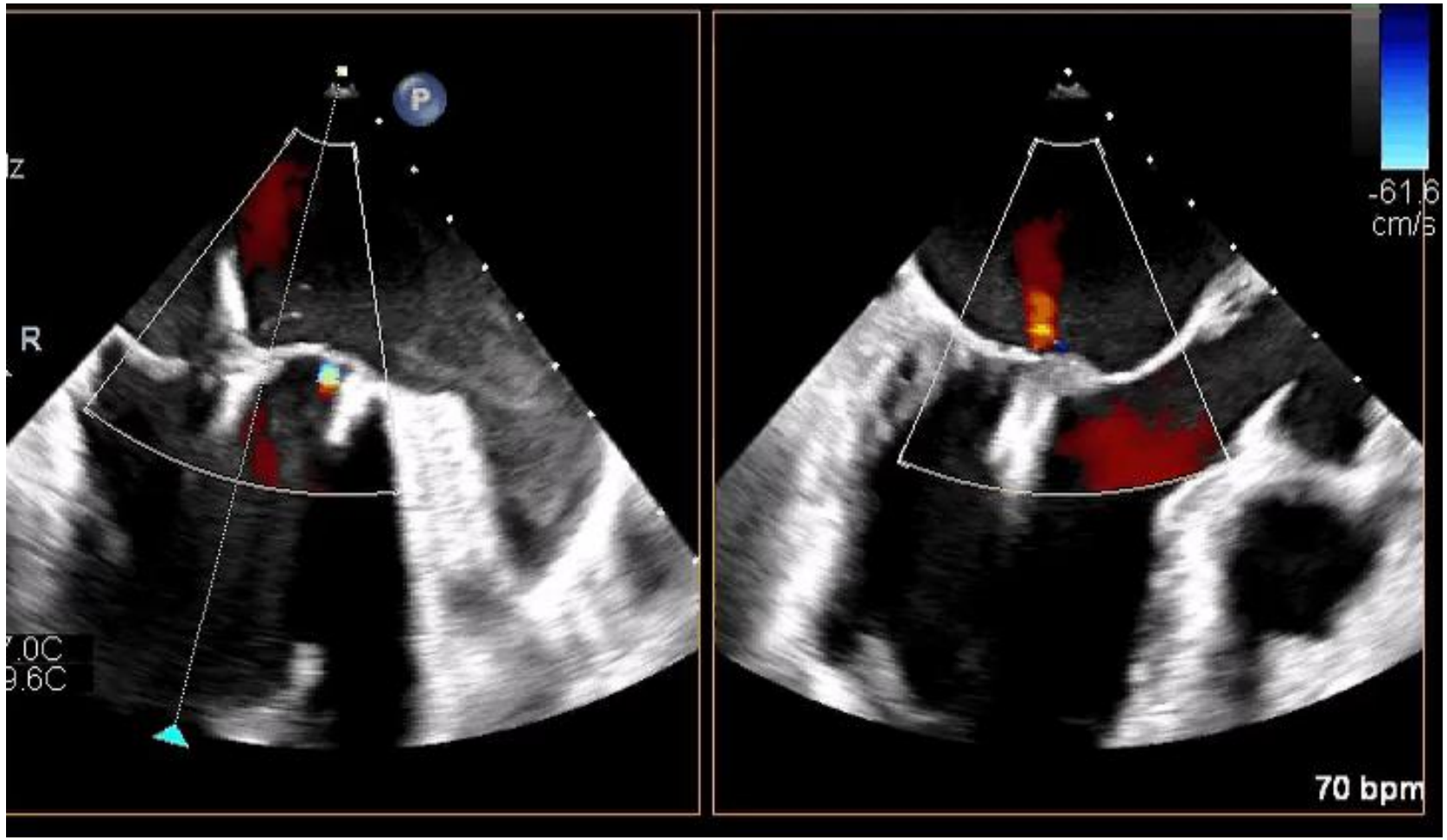
REPAIR MR: Trial Endpoints

REPAIR MR TRIAL

- Co-Primary Endpoint #1: All-cause mortality, stroke, cardiac hospitalization, or acute kidney injury requiring renal replacement therapy at 2 years (any cardiac hospitalizations in the first 30 days post treatment will be excluded).
- Co-Primary Endpoint #2: Proportion of subjects with moderate or less MR (≤2+), without mitral valve replacement, and without recurrent mitral valve intervention (surgical or percutaneous) from the time of index procedure through 2 years.

- Screening, Baseline, Index Procedure, Discharge, 30 days, 6 months, 1 year, 18 months, and annually from 2 to 10 years

Disappearance of MR following one XTW Clip



TEER in for a Intermediate risk primary MR

- Procedural outcomes associated with MitraClip™ has improved significantly since the early EVEREST II experience.[1]

- Mitral valve disease continues to be under treated in the community, where only a minority of affected patients undergo mitral surgery,
  even when surgical treatment options are available.[2]

- With improvements in procedural experience, advanced imaging, and availability of new generation devices, the time is NOW to bring a safe and effective transcatheter treatment option for elderly patients who may be candidates for surgery but may also benefit from a MitraClip!

The Time is NOW to evaluate TEER in Intermediate Risk!

[1] Kar et al. Core Lab Adjudicated Contemporary Clinical Outcomes at 1 Year with MitraClip NTR/XTR System from Global EXPAND Study
[2] Dziadzko et al. Lancet. 2018; 391: 960–969/ Survival after diagnosis of isolated moderate or severe mitral regurgitation, stratified by left-ventricular ejection fraction (LVEF) at diagnosis in Olmsted County residents

Conclusions

- TEER in Intermediate Risk Primary MR, Will Follow the TAVR's Footsteps

- REPAIR MR, as currently designed, is the right trial for primary MR:
  - *The patient population and the associated benefit-risk will help advance patient care for elderly patients*
  - *The randomized nature of the study is intended to increase and improve guideline support for MitraClip™*