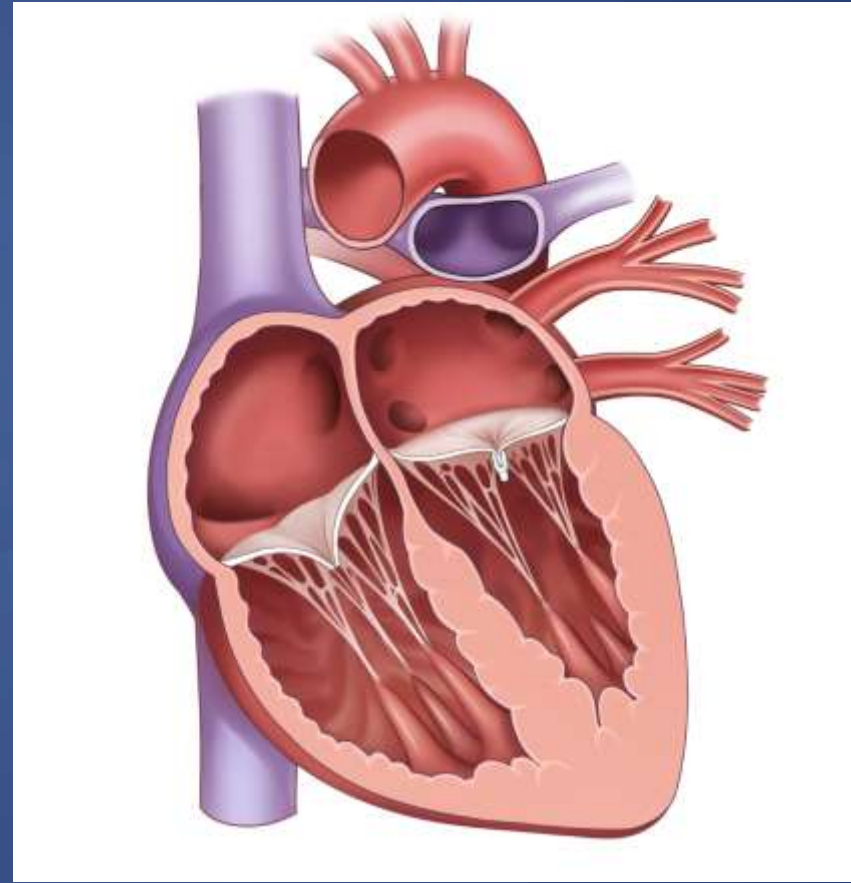
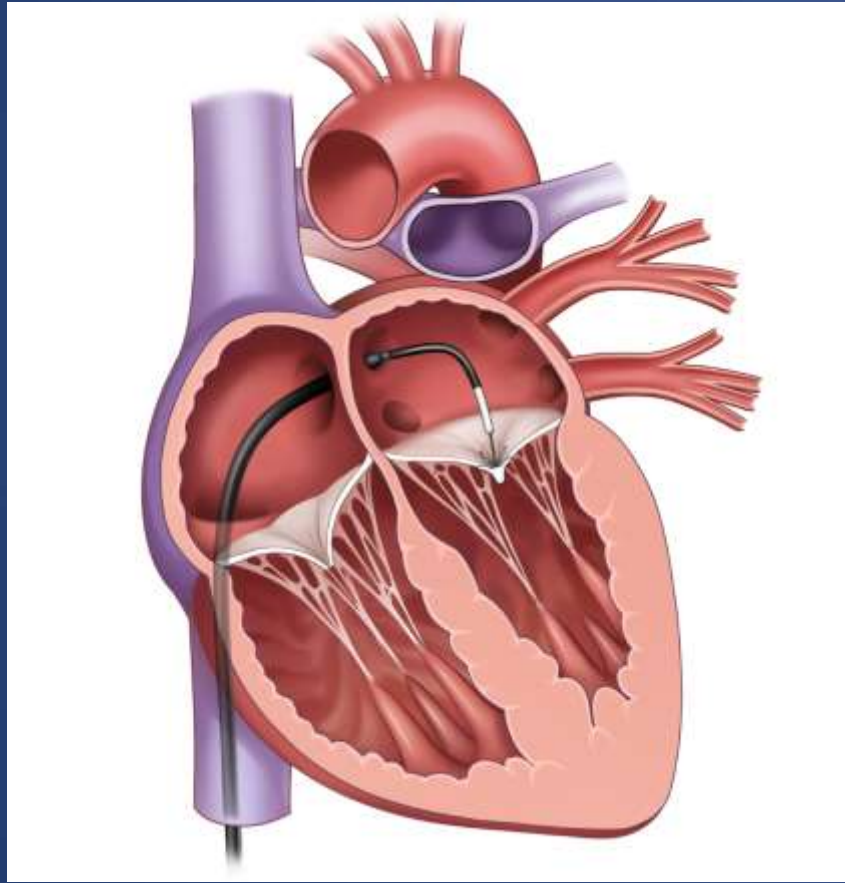


Transcatheter Edge-to-Edge Repair (TEER)

Concept of TEER with MitraClip

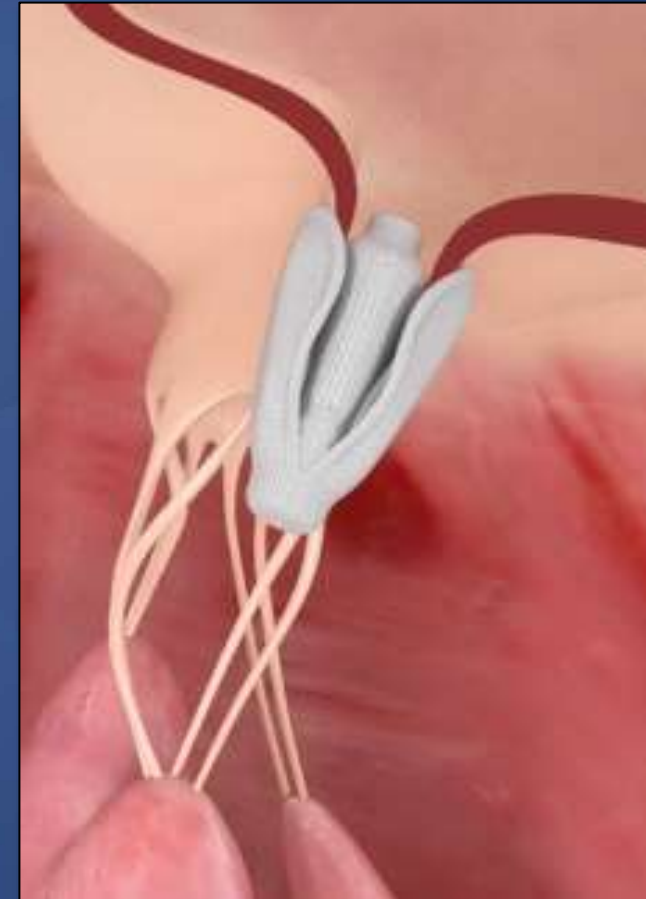


Current Devices of TEER

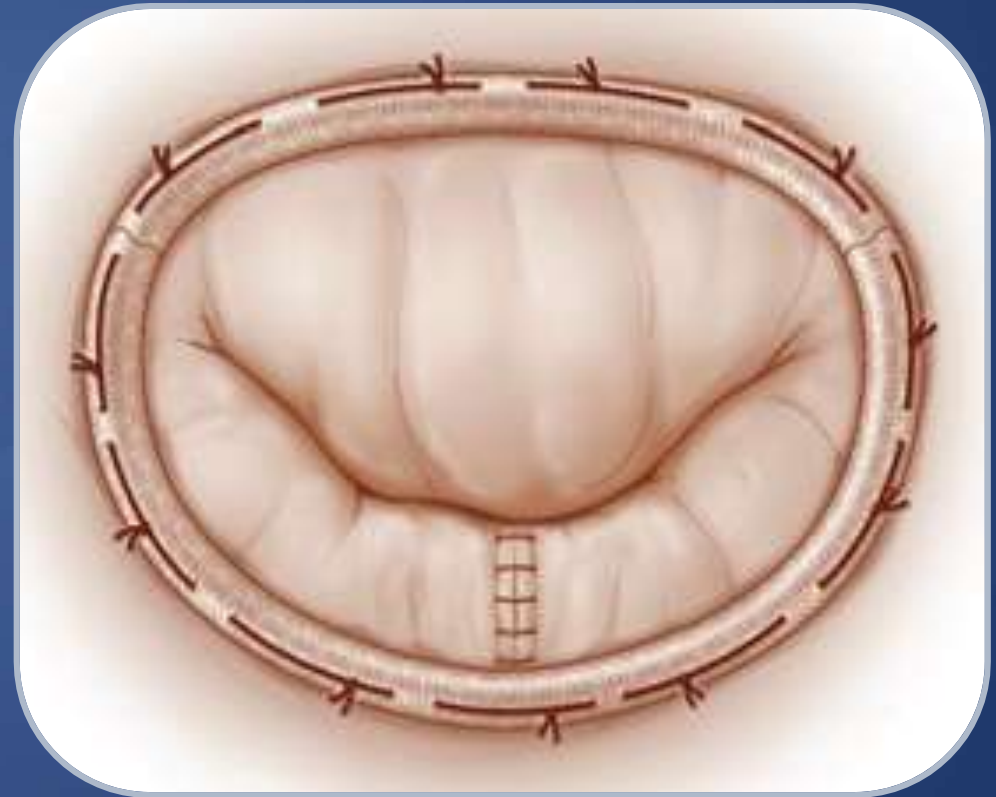
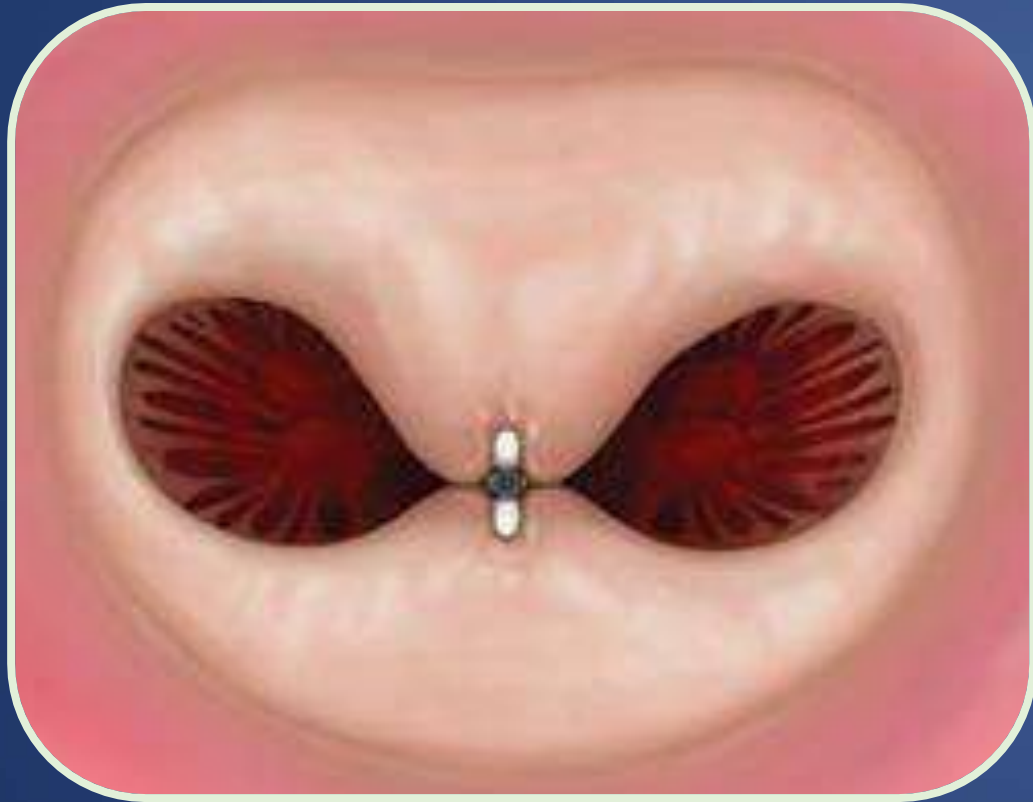
MitraClip (Abbott)
FDA, CE, KFDA approved



PASCAL (Edwards)
CE approved



MitraClip vs. Surgery



Status of MitraClip

EVEREST I
(feasibility trial)

EVEREST II
(RCT vs surgery)

ACCESS-EU registry
REALISM registry

COAPT trial (RCT vs OMT)

2003

2008

2013

2019

2020

2021

First in man

CE Mark

FDA approval
for DMR

FDA approval
for FMR

1st Case
in Korea

G4 Device
launched in
Korea

2020 AHA/ACC Guideline Indication of TEER

- **Primary MR (IIA, B)**
 - Severely symptomatic MR (NYHA III-IV)
 - High or prohibitive surgical risk
 - Favorable anatomy
- **Secondary MR (IIA, B)**
 - Chronic severe symptomatic MR after optimal GDMT (NYHA II-IV)
 - LVEF 20-50% & LVESD \leq 70 mm & PASP \leq 70 mmHg
 - Appropriate anatomy

Two Types of Mitral Regurgitation

Primary (degenerative) MR:
Prolapse/Flail



Secondary (functional) MR:
Ventricular Problem



Evidence of TEER for Primary MR

Mitraclip for Primary MR : EVEREST II RCT

279 patients enrolled at 37 sites

Severe MR (3+ or 4+)

73% DMR, 27% FMR

Specific anatomical criteria

↓
Randomized 2:1

↙ ↘
Device Group
MitraClip System
N=184

↙ ↘
Control Group
Surgical Repair or Replacement
N=95

↓ ↓
Echocardiography Core Lab and Clinical Follow
Baseline, 30 days, 6 months, 1 year, 18 months, and
annually through 5 years

EVEREST II Trial

279 patients 2:1 Randomization to Mitraclip vs Surgery

	Percutaneous Repair N=184	Surgery N=95	P value
Age	67.3 ± 12.8	65.7 ± 12.9	0.32
> 75 yr	55 (30%)	26 (27%)	0.68
Male sex	115 (62%)	63 (66%)	0.60
Congestive heart failure	167 / 184 (91%)	74 / 95 (78%)	0.005
Coronary artery disease	86 / 183 (47%)	44 / 95 (46%)	0.99
Atrial fibrillation	59 / 175 (34%)	35 / 89 (39%)	0.42
Diabetes	14 / 184 (8%)	10 / 95 (11%)	0.50
COPD	27 / 183 (15%)	14 / 95 (15%)	0.99
Previous CABG	38 / 184 (21%)	18 / 95 (19%)	0.87
LV ejection fraction, %	60.0 ± 10.1	60.6 ± 11.0	0.65

EVEREST II Trial

279 patients 2:1 Randomization to Mitraclip vs Surgery

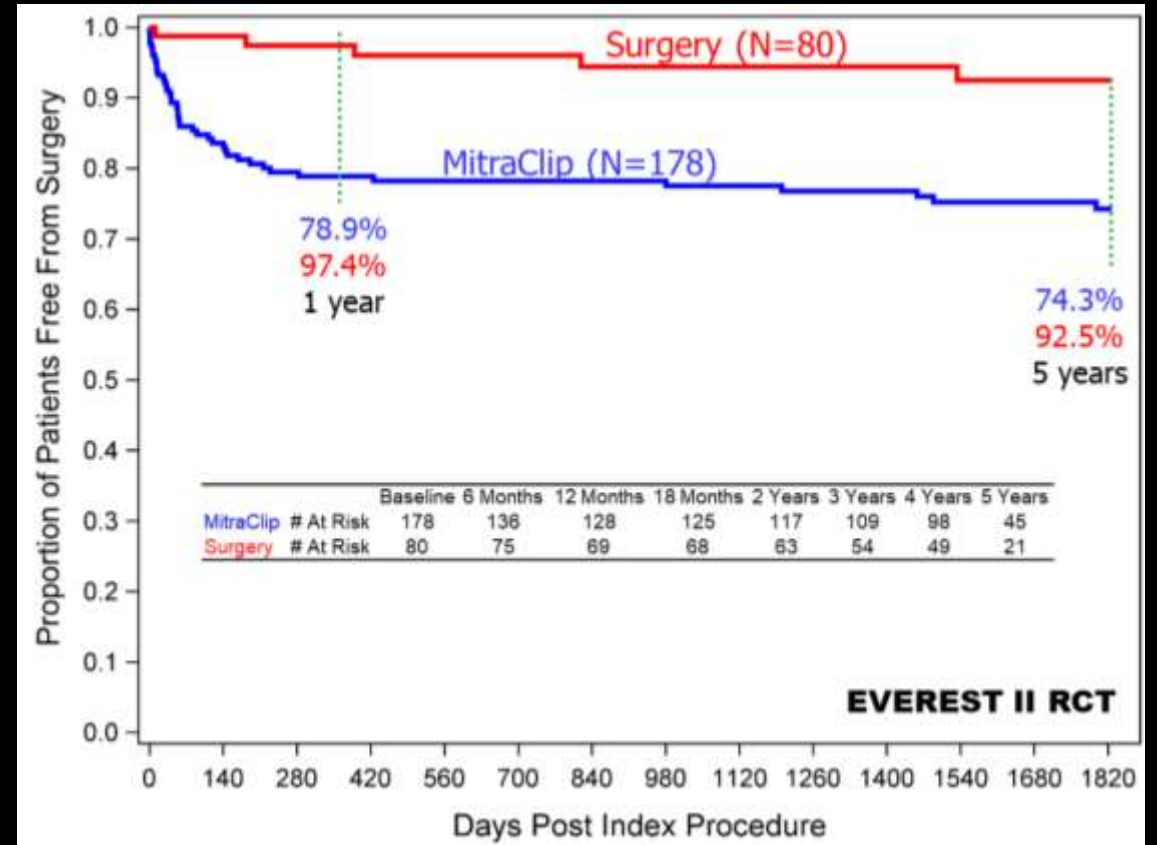
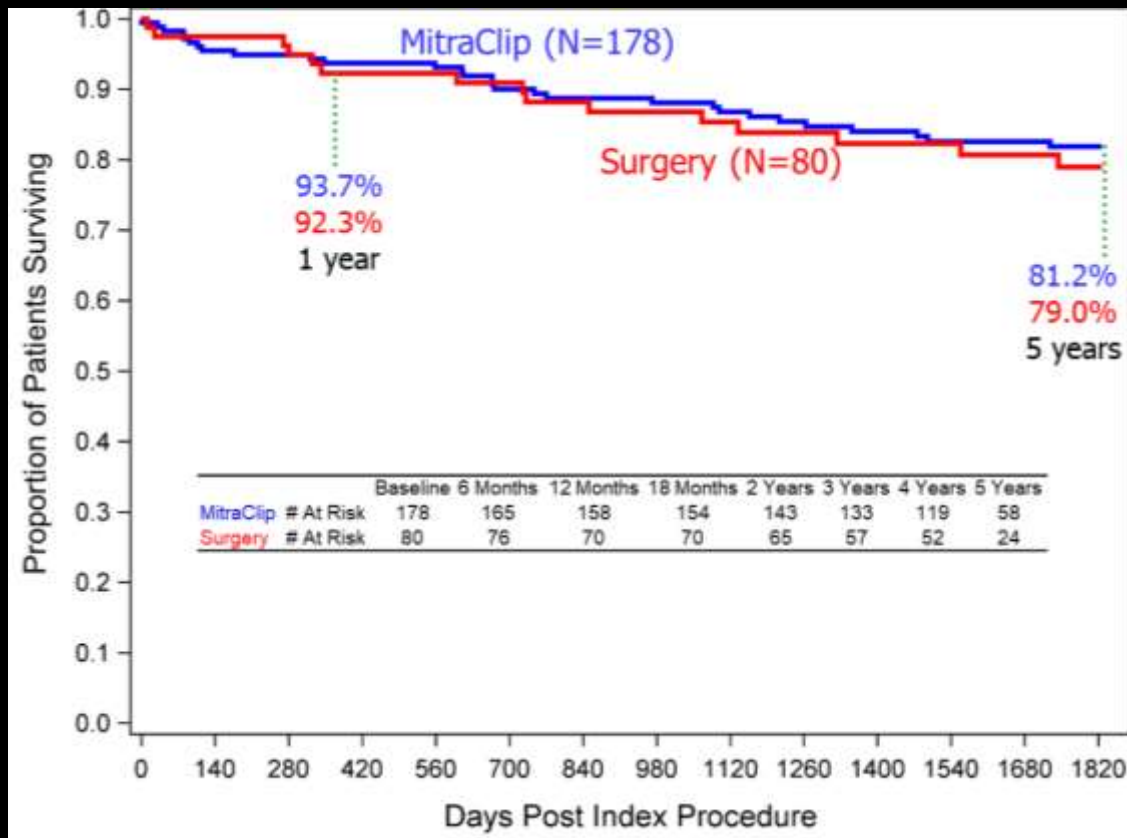
	Percutaneous Repair N=184	Surgery N=95	P value
Primary Efficacy Endpoint at 12 months			
Freedom from death, surgery for MV dysfunction, grade 3+/4+ MR	100 (55%)	65 (73%)	0.007
Death	11 (6%)	5 (6%)	1.00
Surgery for MV dysfunction	37 (20%)	2 (2%)	<0.001
Grade 3+/4+ MR	38 (21%)	18 (20%)	1.00
Major Adverse Event at 30 days	27 (15%)	45 (48%)	<0.001
Any major adverse event excluding transfusion	9 (5%)	9 (10%)	0.23

EVEREST II Trial

279 patients 2:1 Randomization to Mitraclip vs Surgery

Freedom from Mortality

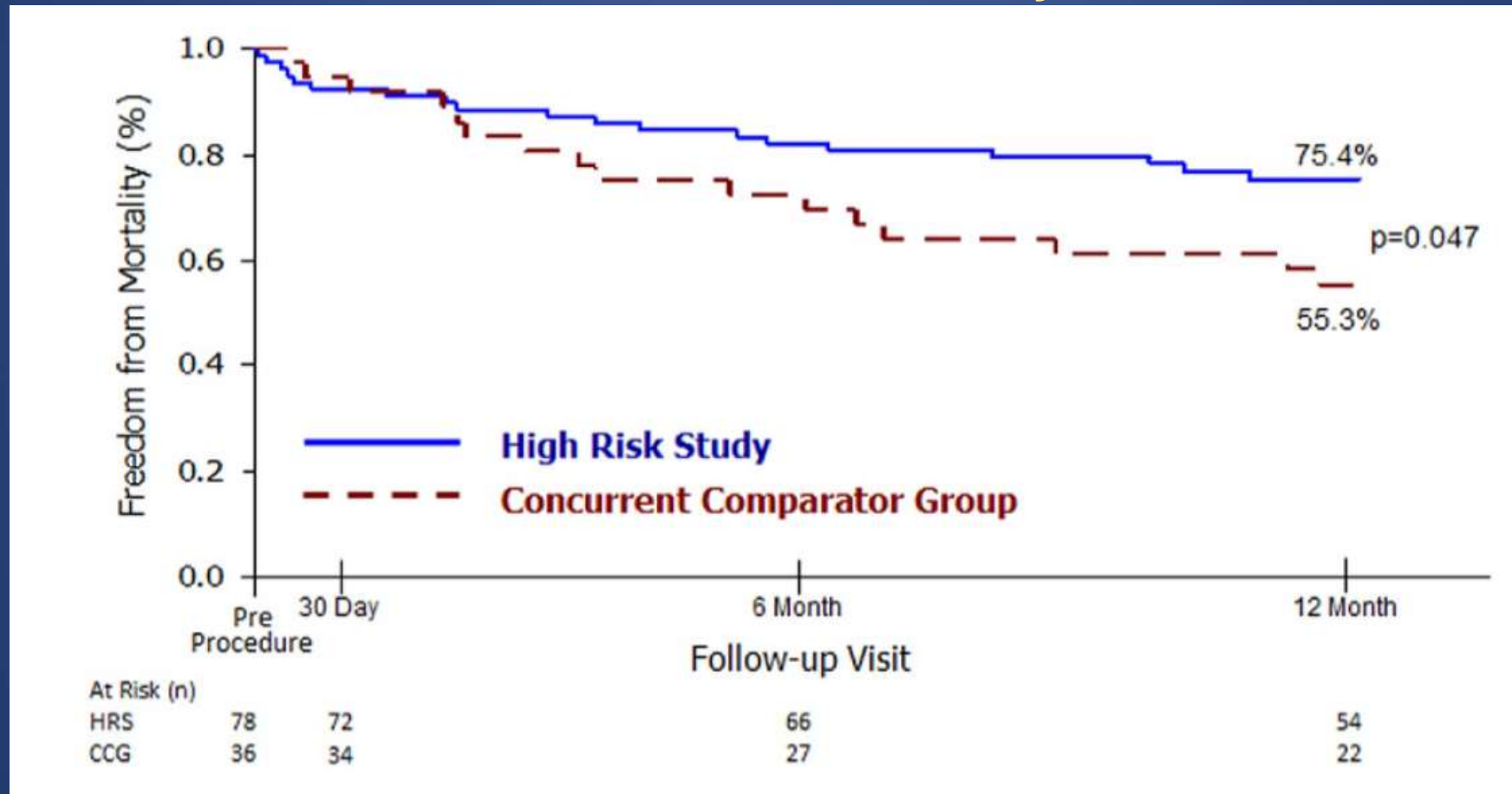
Freedom from MV Surgery or Re-operation



EVEREST II High-Risk Study

76 High Risk Patients compared with 36 Patients with Standard Care

Freedom from Mortality



2014 & 2017 AHA/ACC Guideline, TMVR for Primary MR

- Transcatheter mitral valve repair may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe primary MR (stage D) who have favorable anatomy for the repair procedure and a reasonable life expectancy but who have a prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal GDMT for heart failure (HF)

COR

IIb

LOE

**B-
NR**

2020 AHA/ACC Guideline, TEER for Primary MR

- 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

COR



LOE

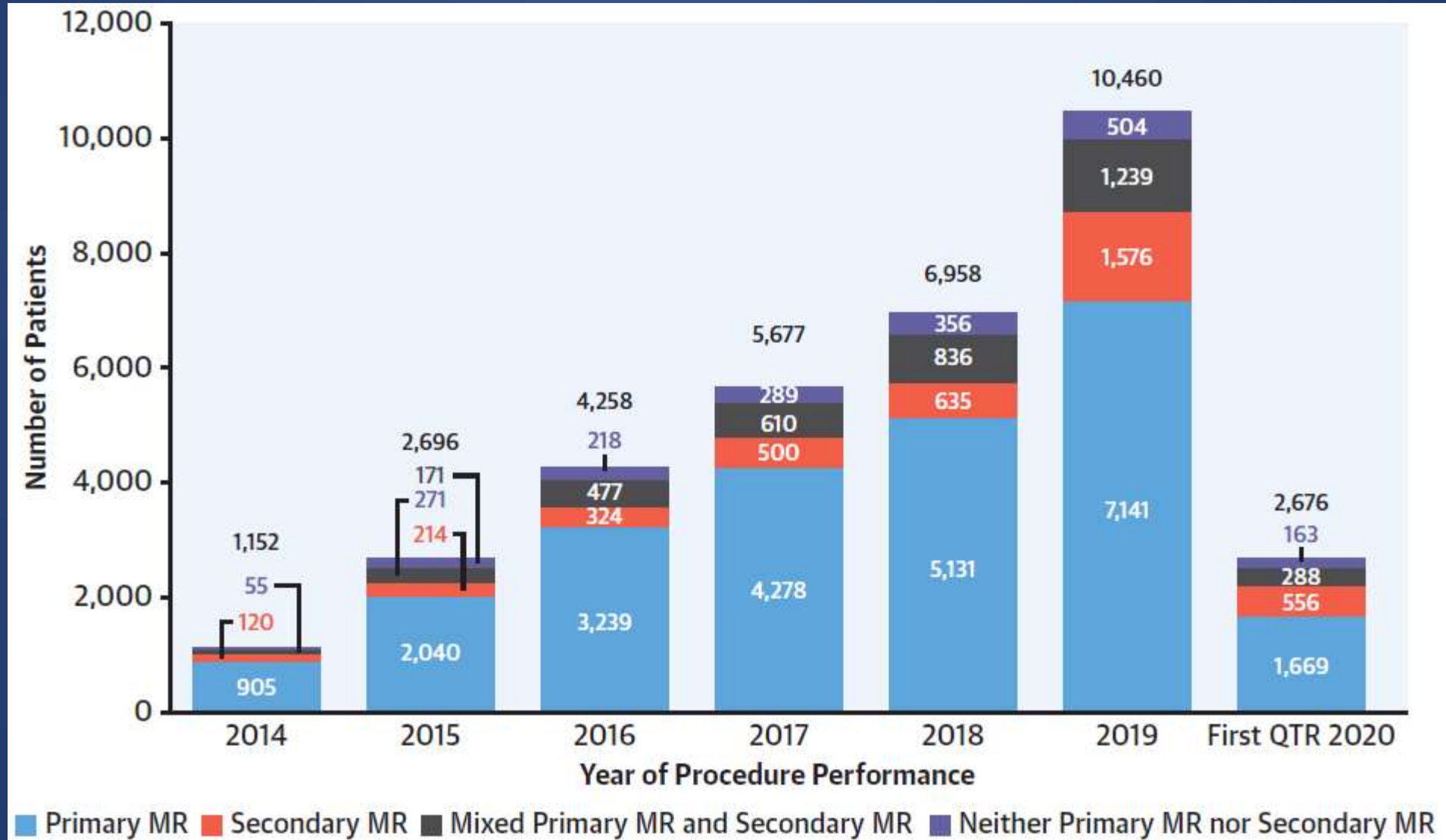


Real-World outcome of TEER

: 2021 STS/ACC TVT Registry Report

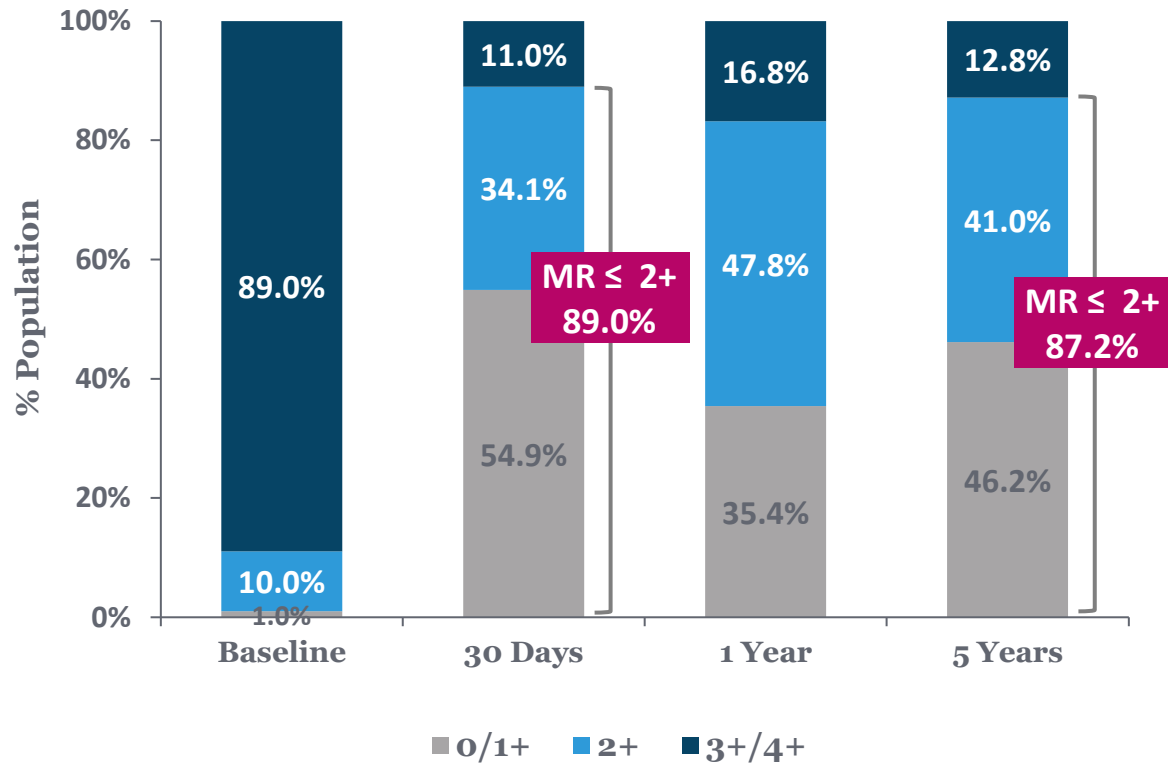
	In-hospital	30-day
Death	2.2%	4.5%
Stroke	0.7%	1.3%
MV reintervention	0.6%	1.1%
Single leaflet device attachment	1.0%	1.3%
Atrial fibrillation	2.1%	2.9%
Major bleeding	2.2%	4.7%
Major vascular access site complications	0.4%	0.5%
Moderate-severe / Severe mitral insufficiency	8.7%	
MV mean gradient > 5 mmHg	26.3%	

Annual TEER Volume in US : 2021 STS/ACC TVT Registry

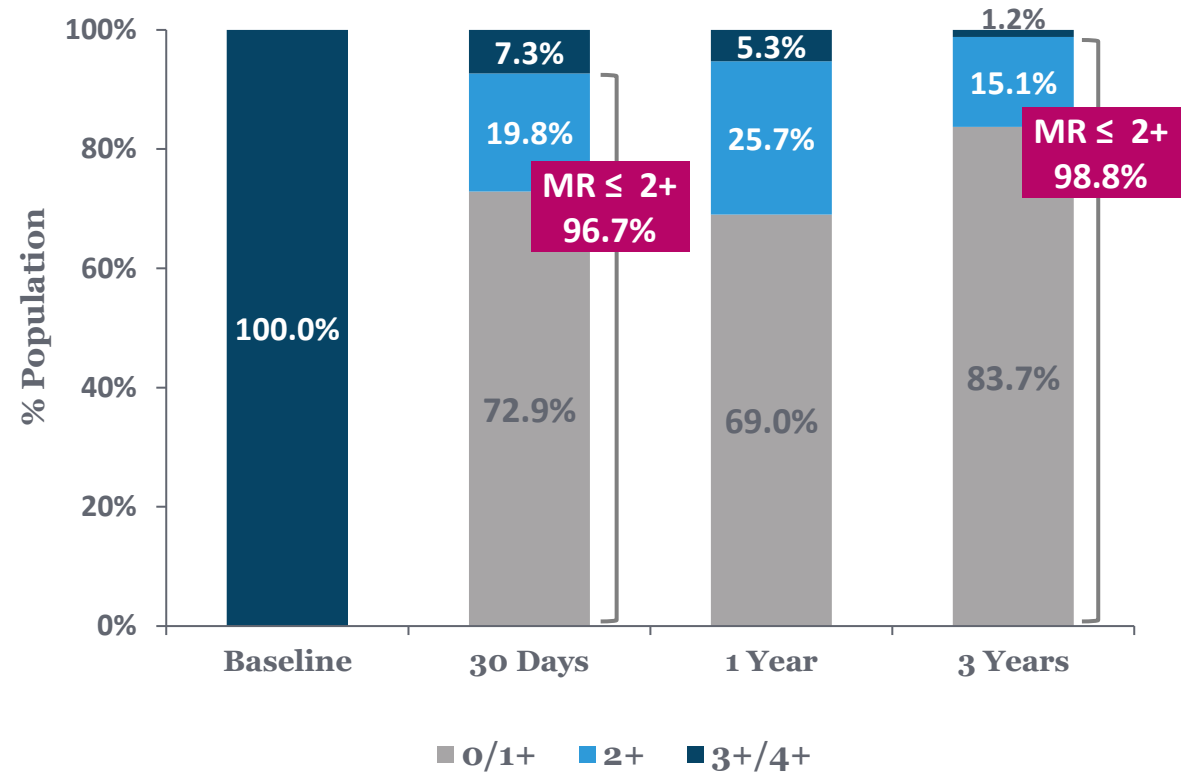


Durable Results in Longer-term FU

EVEREST II REALISM 5 Year Outcomes¹
(n=264)

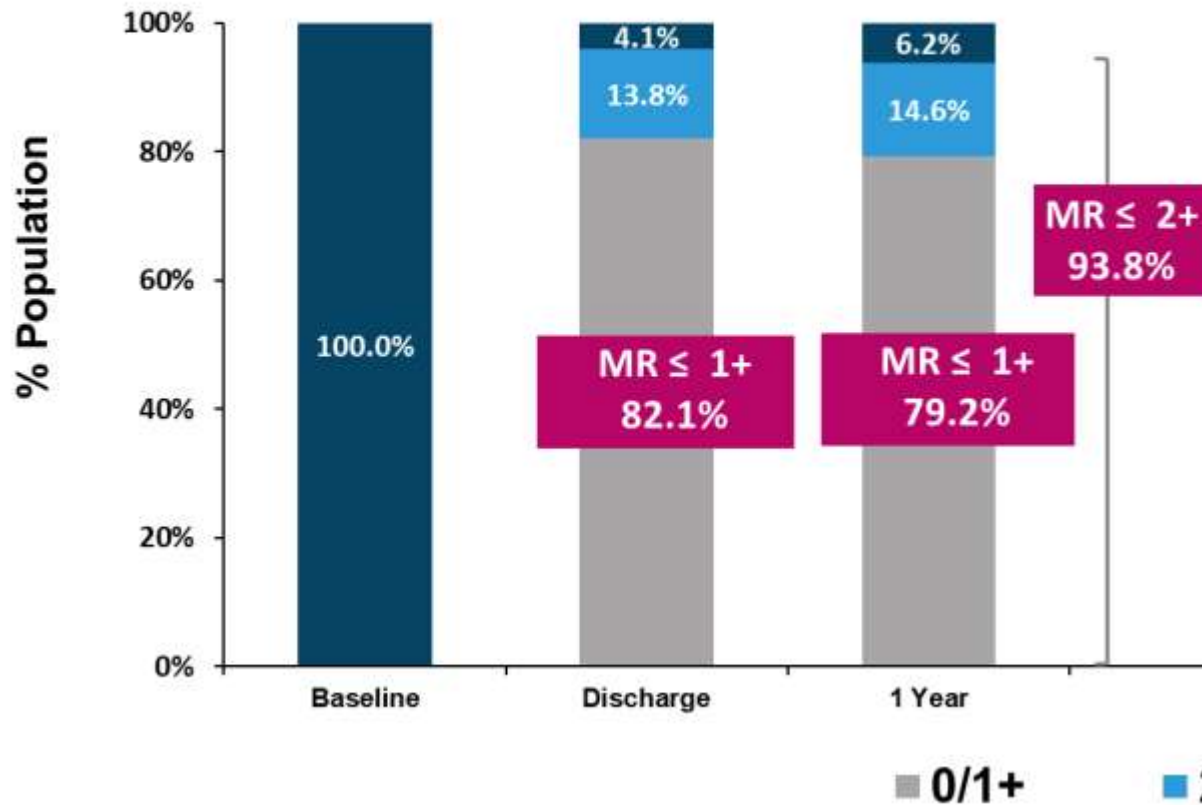


COAPT 3 Year Outcomes²
(n=302)

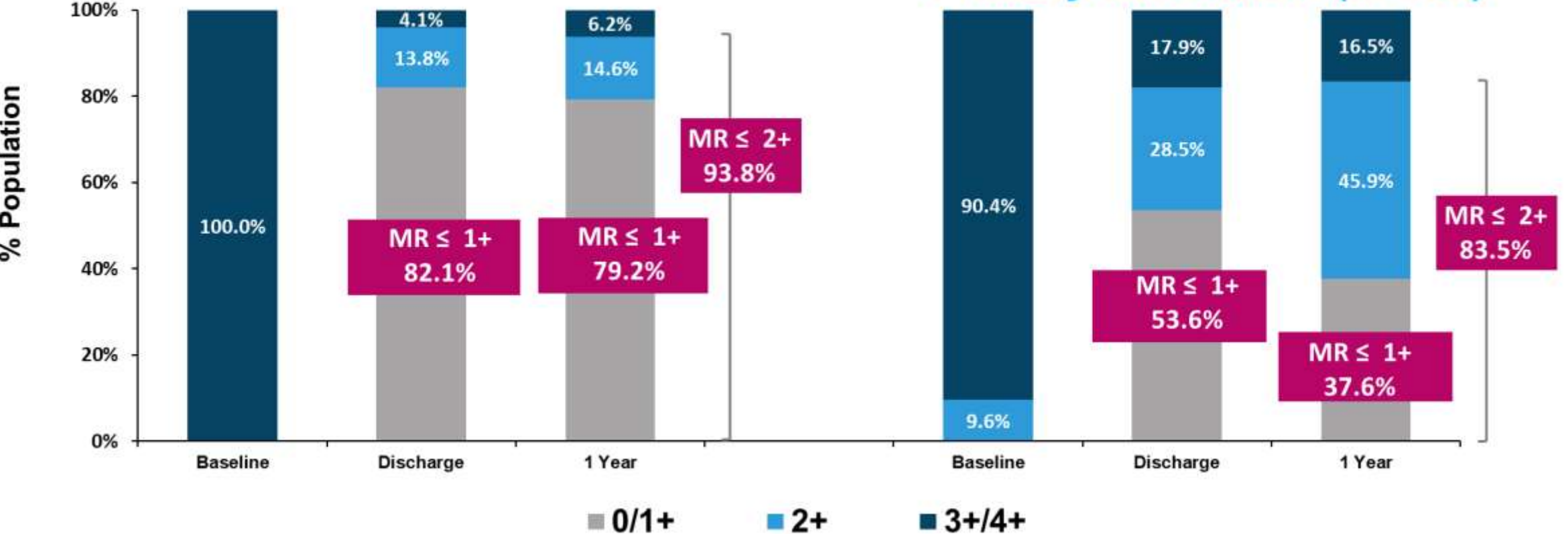


Higher MR Reduction (about 80% MR ≤1+ at 1-year)

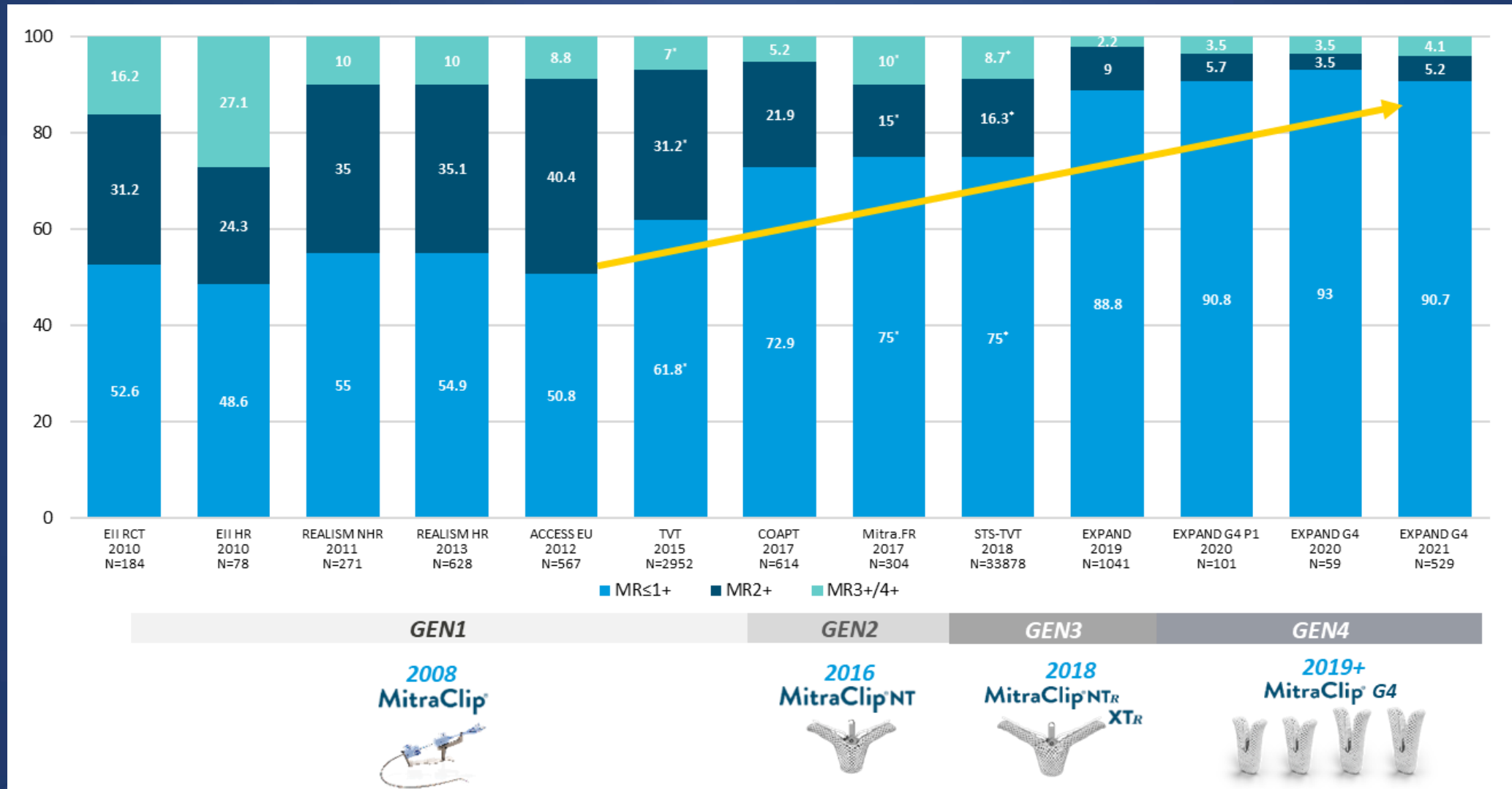
**EXPAND Primary MR Subjects
w/ Baseline MR Severity ≥ 3+ (n=279)**



**EVEREST/REALISM Prohibitive Risk
Primary MR Cohort (n=123)**



Significant Improvement in MR at 30-days post-TEER Implant Over The Past Years



MITRA-HR Trial

MitraClip vs. Surgery for High Surgical Risk Primary MR

Primary Endpoint: All-cause mortality, unplanned hospitalizations for HF and MV reintervention at 12 month (non-inferiority)

Table 1. Inclusion criteria of the MITRA-HR trial.

Primary mitral regurgitation grade 3+ or 4+
New York Heart Association Class II to IV
Mitral valve anatomy appropriate to MitraClip therapy and mitral valve surgery (repair or replacement)
High surgical risk defined by the local Heart Team as: <ul style="list-style-type: none">– age ≥ 75 years and an intermediate MVARC risk (STS score [repair] $\geq 6\%$, or one frailty index [mild]¹, or one compromised major organ system², or one possible procedure-specific impediment³) or– age < 75 years and a high MVARC risk (STS score [repair] $> 8\%$, or two frailty indices [moderate to severe]¹, or no more than two compromised organ systems², or one possible procedure-specific impediment³)
Isolated mitral valve pathology
If revascularisation procedures are required, they must be performed more than 30 days from the intervention (day 0)
Affiliation to French social security
^{1,2,3} details in Supplementary Appendix 1

Randomize 1:1*

MitraClip
N=165

Surgery
N=165

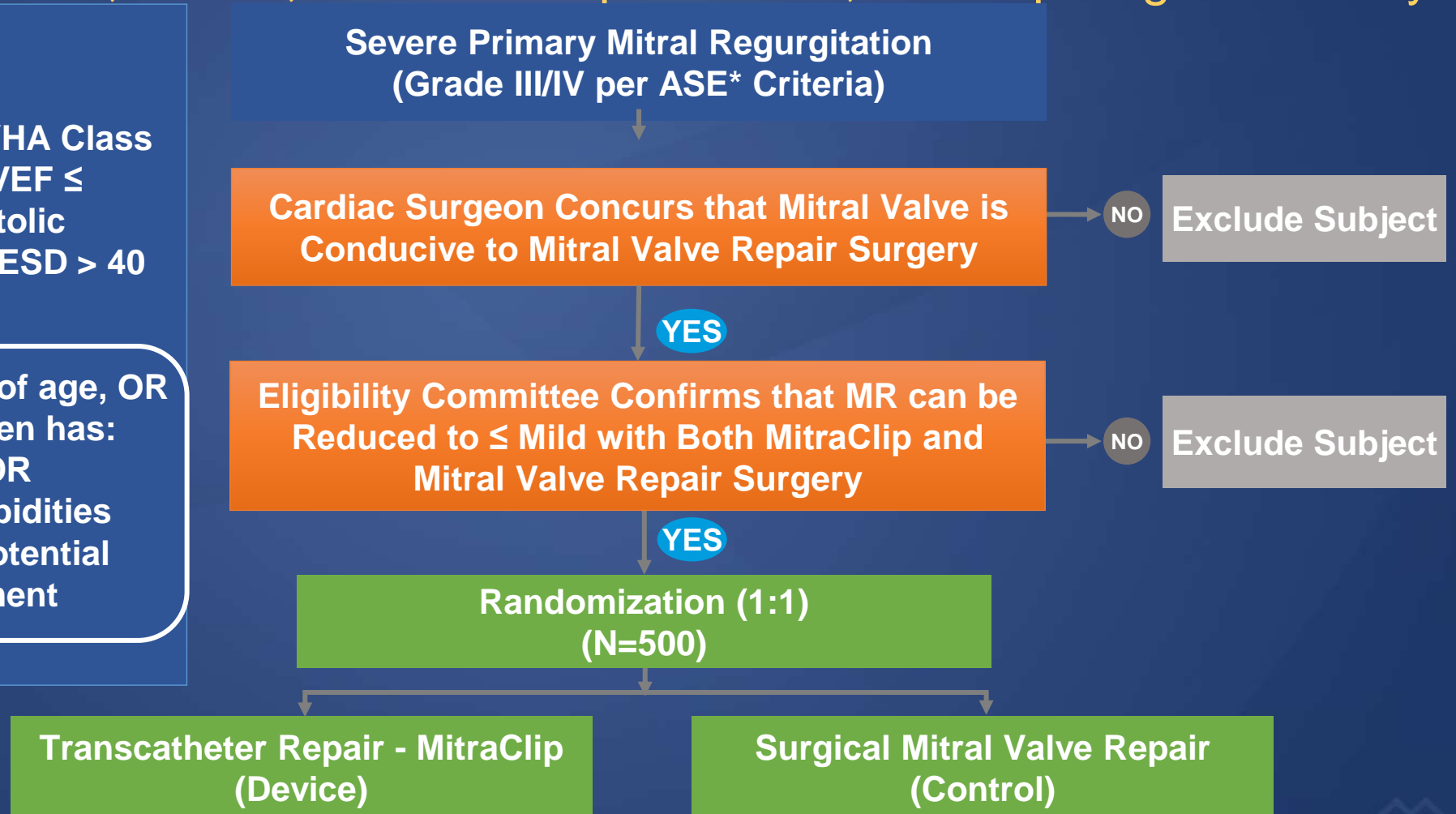
REPAIR-MR Trial

MitraClip vs. Surgery for Moderate Surgical Risk Primary MR

Primary Endpoint: Death, Stroke, Cardiac Hospitalization, AKI requiring RRT at 2 yrs

Patient Population

- Subject is symptomatic (NYHA Class II/III/IV) or asymptomatic (LVEF \leq 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 \geq 2%, OR
 - Presence of other comorbidities which may introduce a potential surgical specific impediment

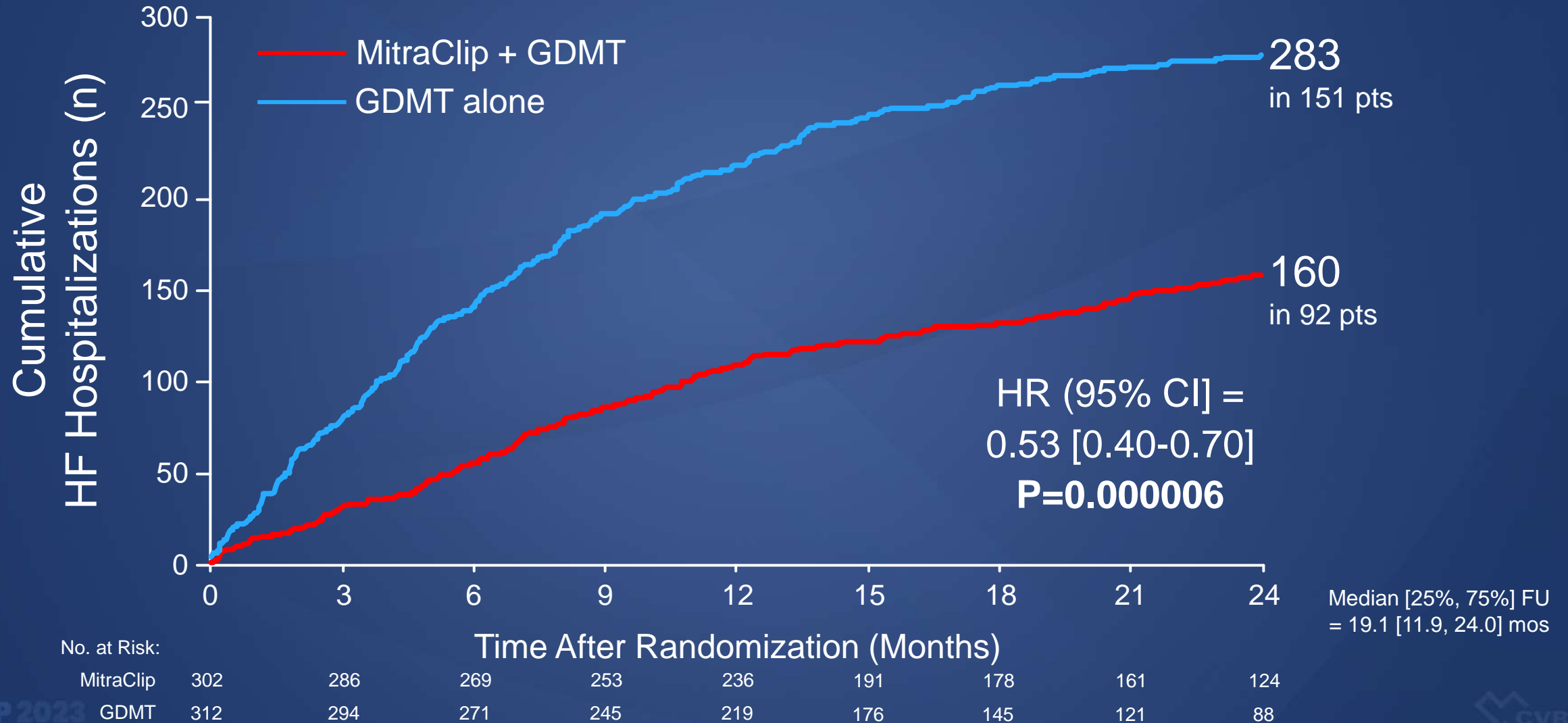


PI : Patrick McCarthy MD, Saibal Kar MD. NCT04198870.

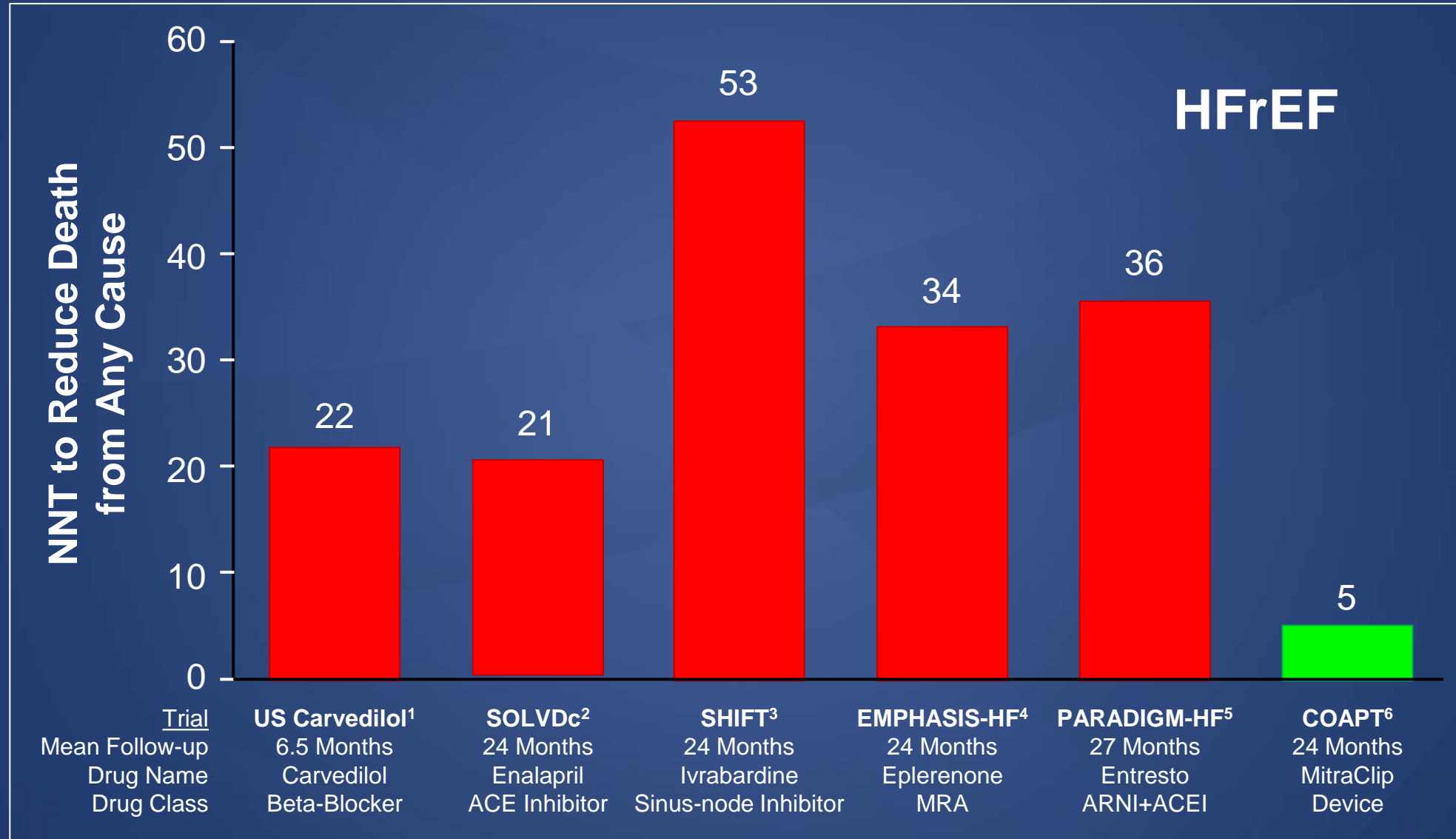
TEER for Secondary MR

COAPT opened a New Era of Mitral Intervention

All Hospitalizations for HF within 24 months

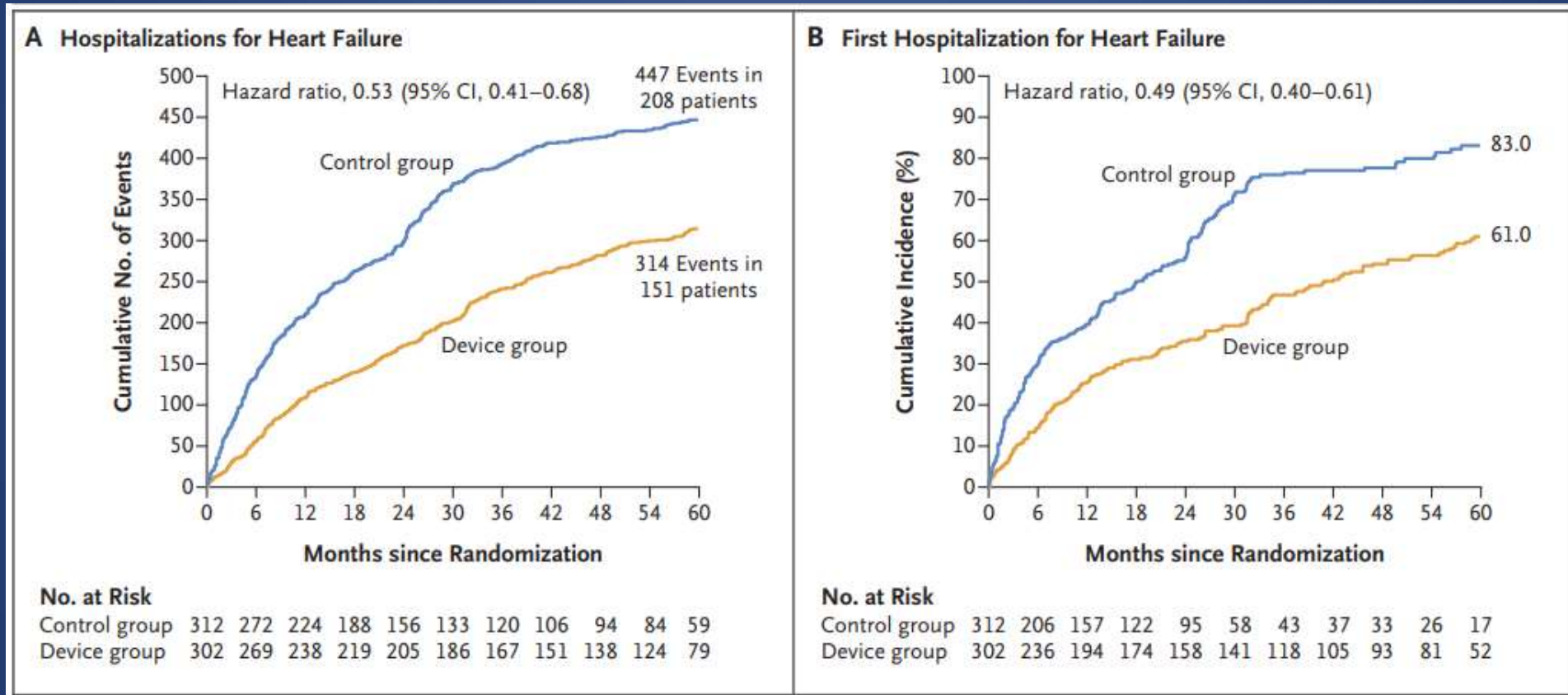


COAPT : Number Needed to Treat to Prevent 1 Death



5-Year follow-up COAPT trial

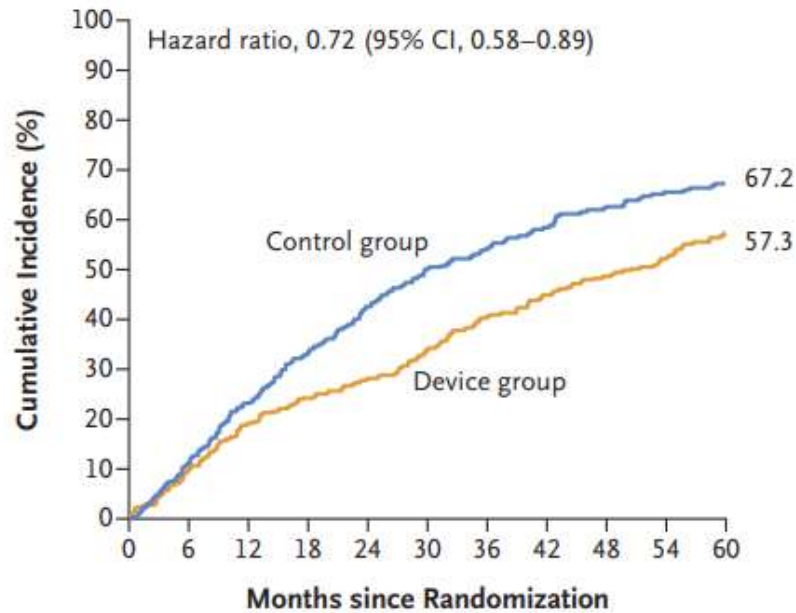
Mitraclip versus GDMT in patients with heart failure and secondary MR Clinical Outcomes of 5-Year follow-up



5-Year follow-up COAPT trial

Mitraclip versus GDMT in patients with heart failure and secondary MR Clinical Outcomes of 5-Year follow-up

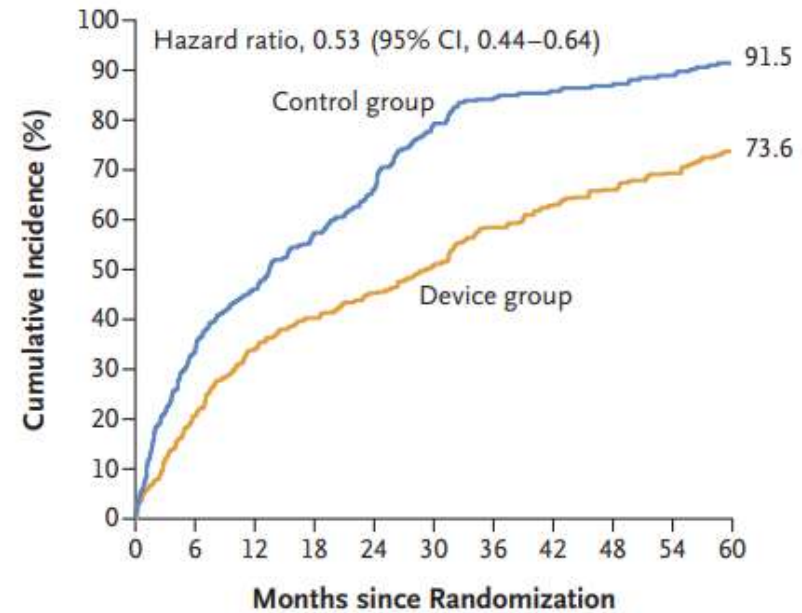
C Death from Any Cause



No. at Risk

Control group	312	272	224	189	157	135	122	107	94	84	59
Device group	302	269	238	219	205	186	167	151	138	124	79

D Death from Any Cause or First Hospitalization for Heart Failure



No. at Risk

Control group	312	206	157	122	95	58	43	37	33	26	17
Device group	302	236	194	174	158	141	118	105	93	81	52

2020 AHA/ACC Guidelines for Secondary MR

- In patients with chronic severe secondary MR related to LV systolic dysfunction (LVEF <50%) who have persistent symptoms (NYHA class II, III, or IV) while on optimal GDMT for HF (Stage D), TEER is reasonable in patients with appropriate anatomy as defined on TEE and with LVEF between 20% and 50%, LVESD ≤ 70 mm, and pulmonary artery systolic pressure ≤ 70 mmHg.
- In patients with chronic severe secondary MR related to LV systolic dysfunction (LVEF <50%) who have persistent severe symptoms (NYHA class III or IV) while on optimal GDMT for HF (Stage D), mitral valve surgery may be considered

COR

IIa

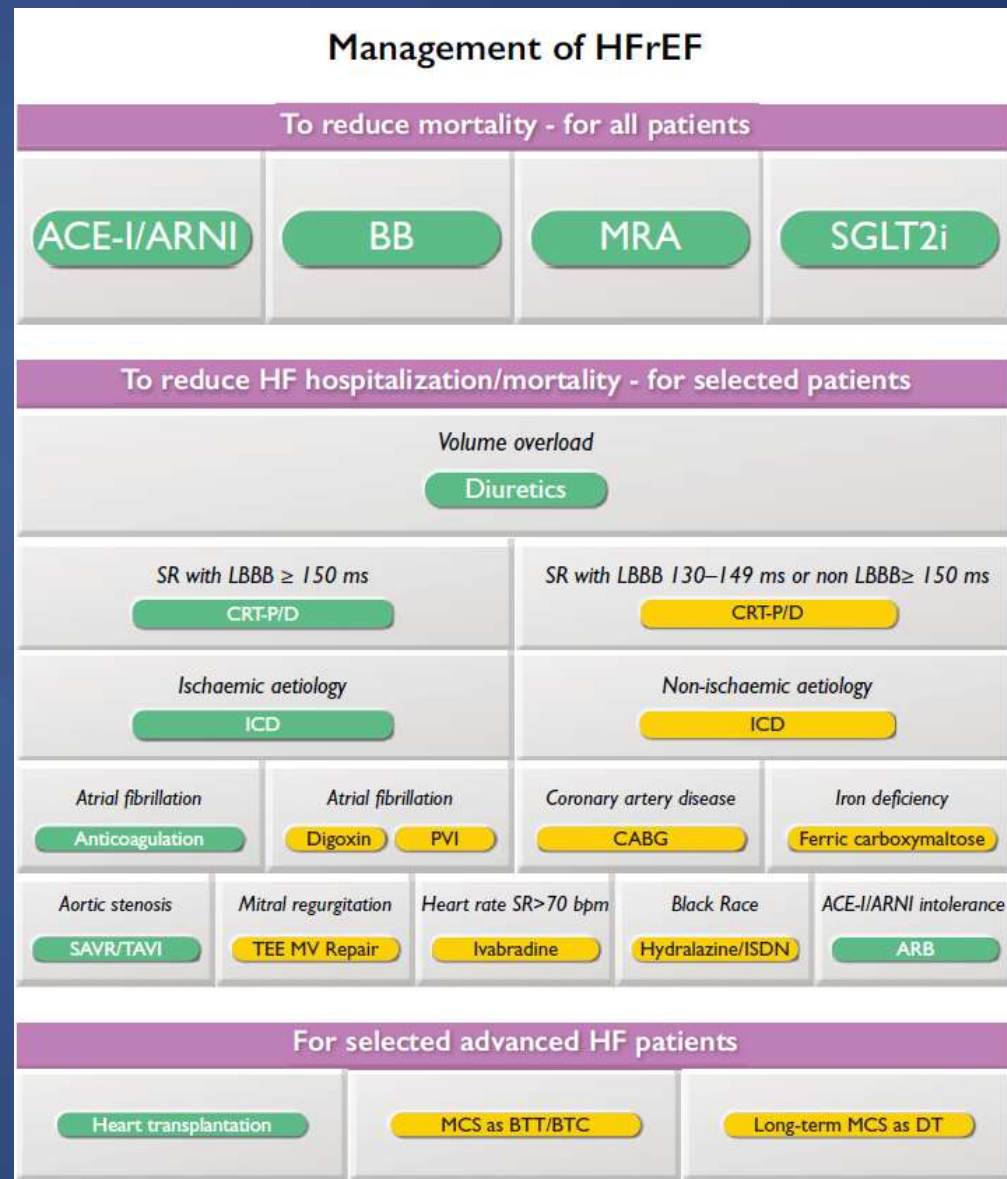
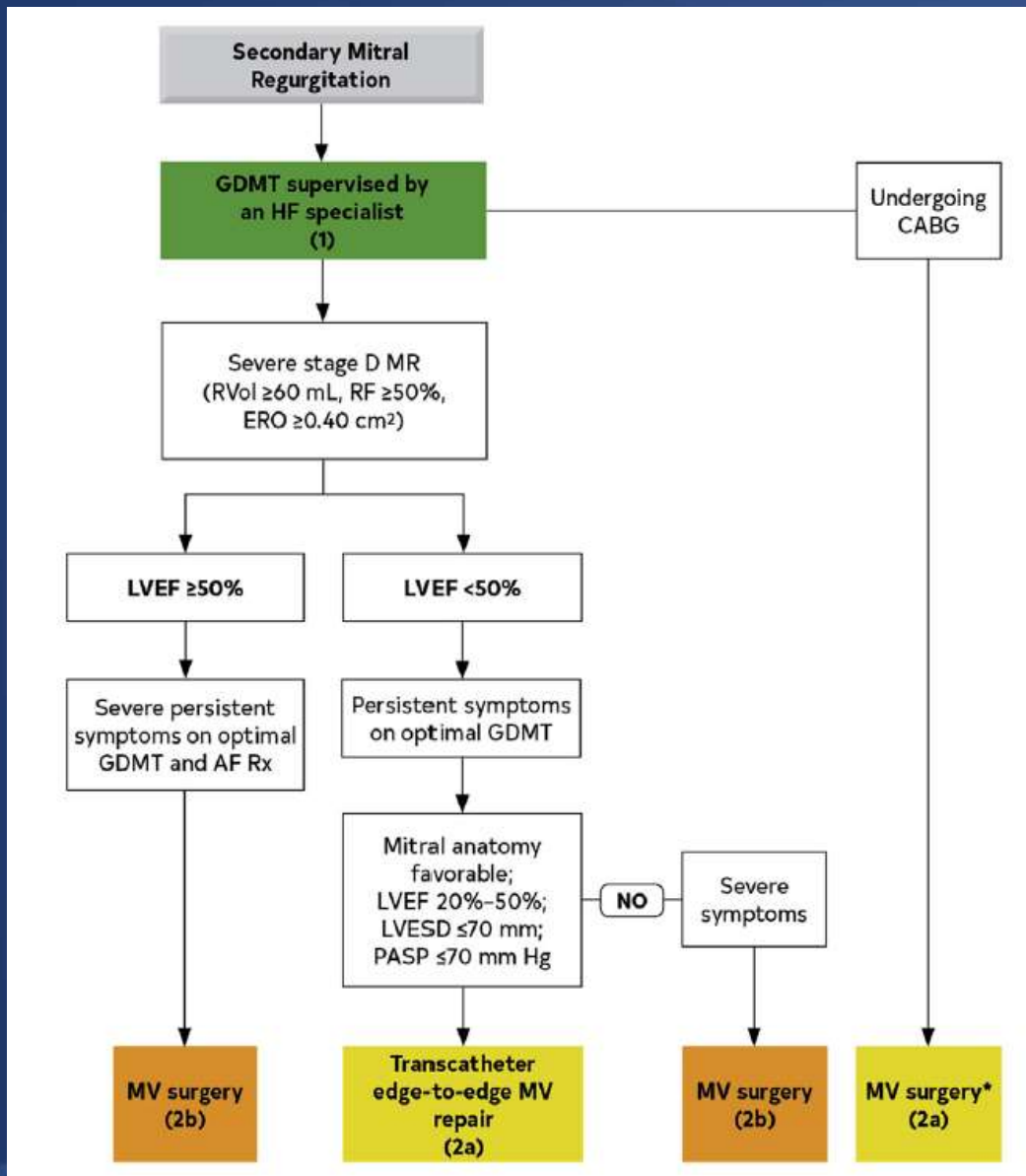
LOE

B-R

IIb

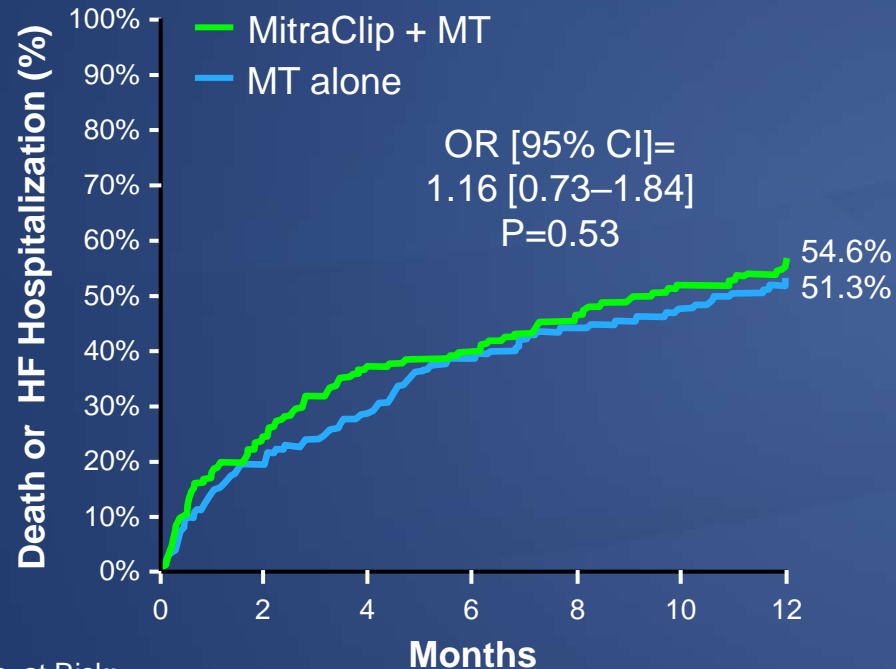
**B-
NR**

TEER in VHD & HF Guidelines



Two Contrasting RCTs of TEER for Secondary MR

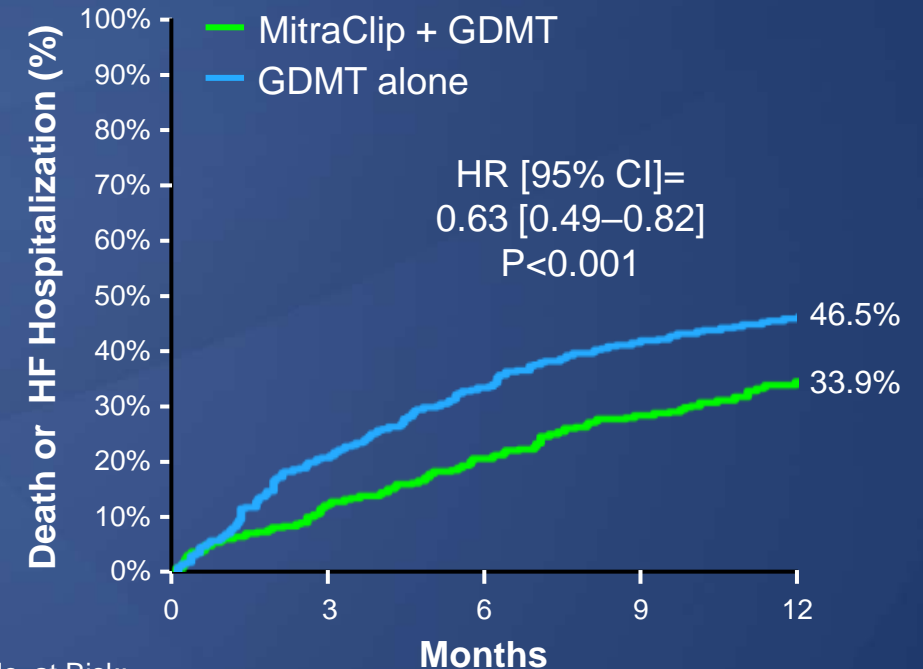
MITRA-FR



No. at Risk:

	0	2	4	6	8	10	12
Control Group	152	123	109	94	86	80	73
Device Group	151	114	95	91	81	73	67

COAPT



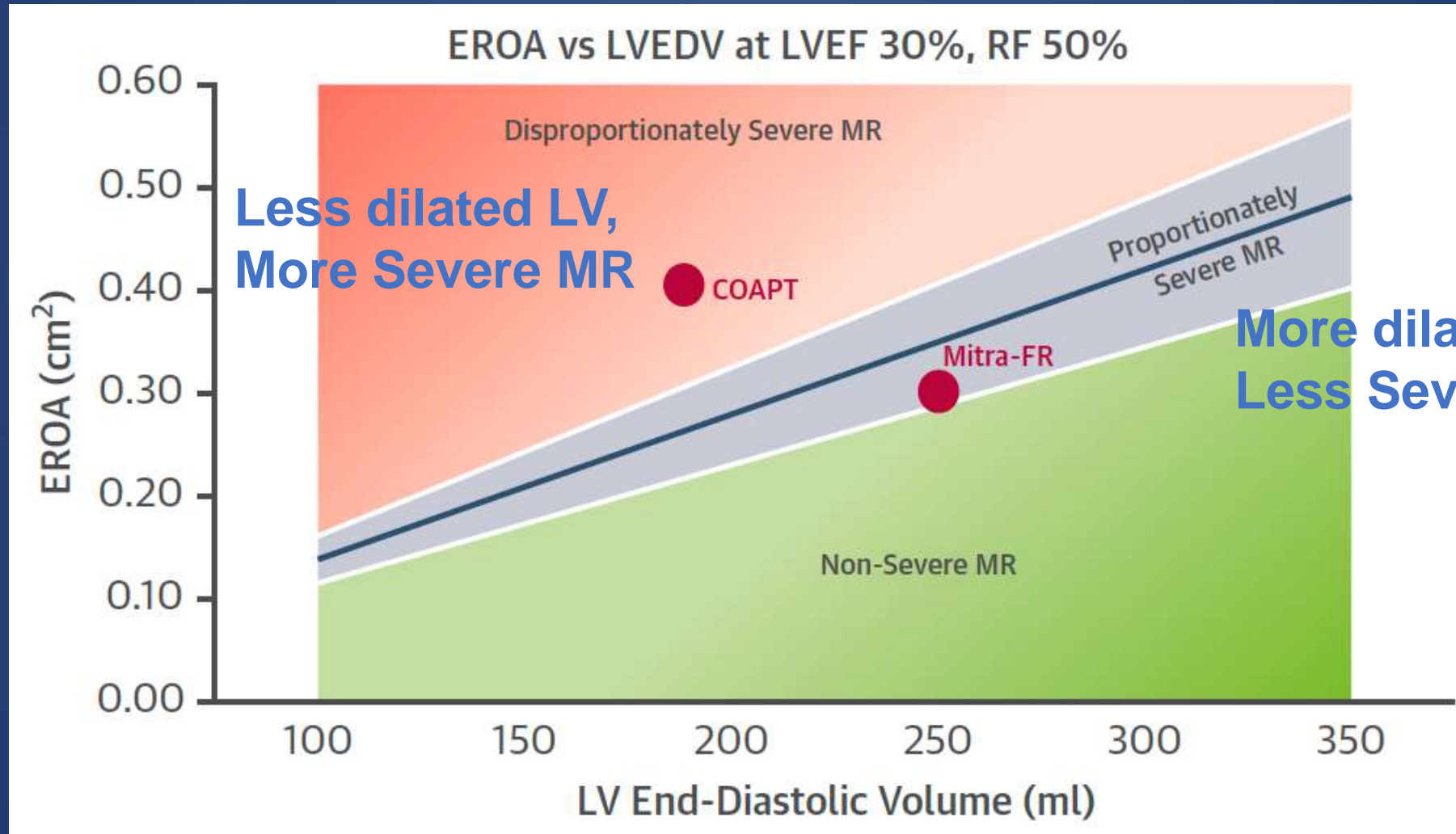
No. at Risk:

	0	3	6	9	12
Control Group	312	244	205	174	153
Device Group	302	264	238	215	194

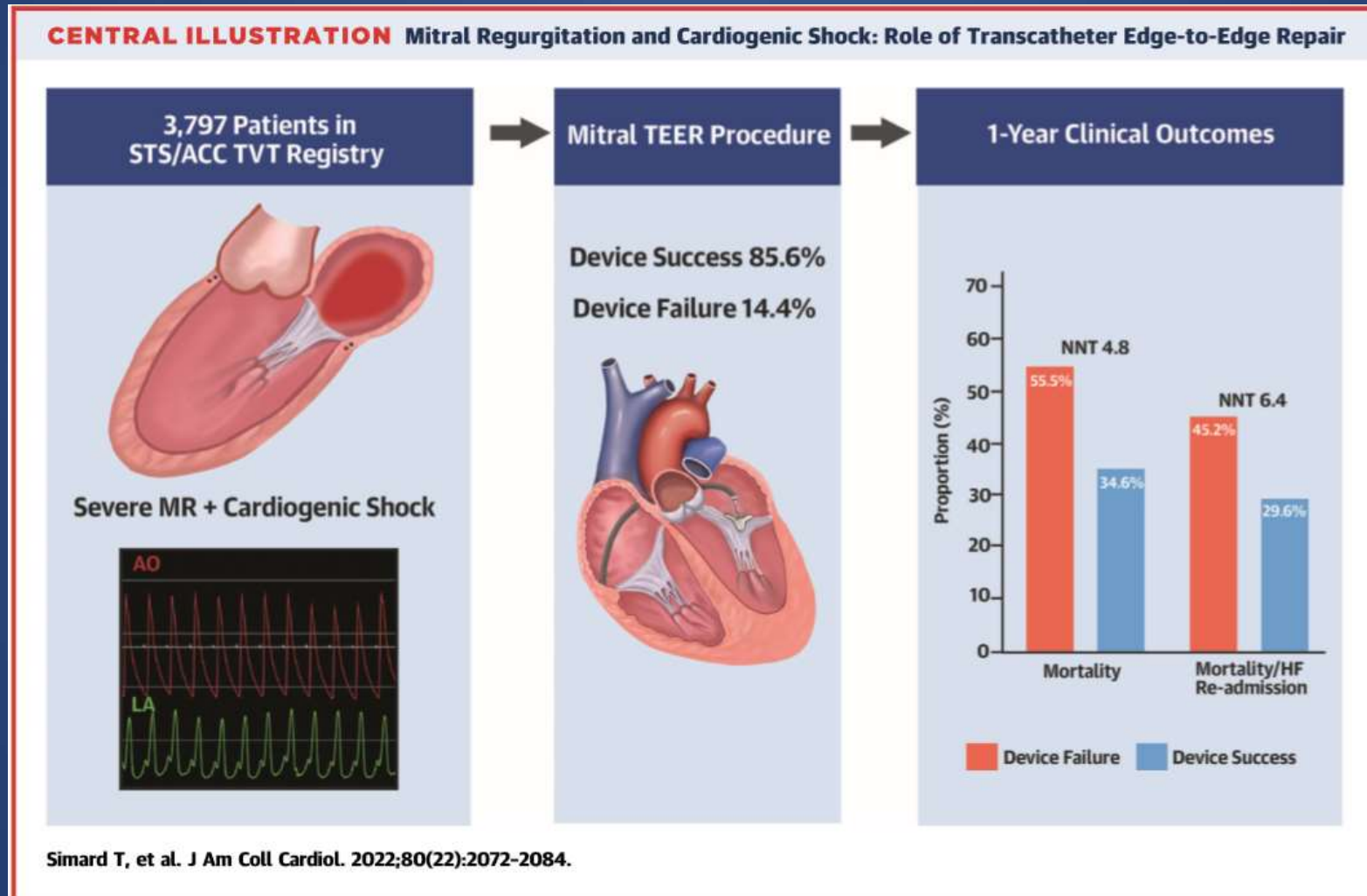
Obadia JF et al. N Engl J Med. 2018;379:2297-306

Stone GW et al. N Engl J Med. 2018;379:2307-18

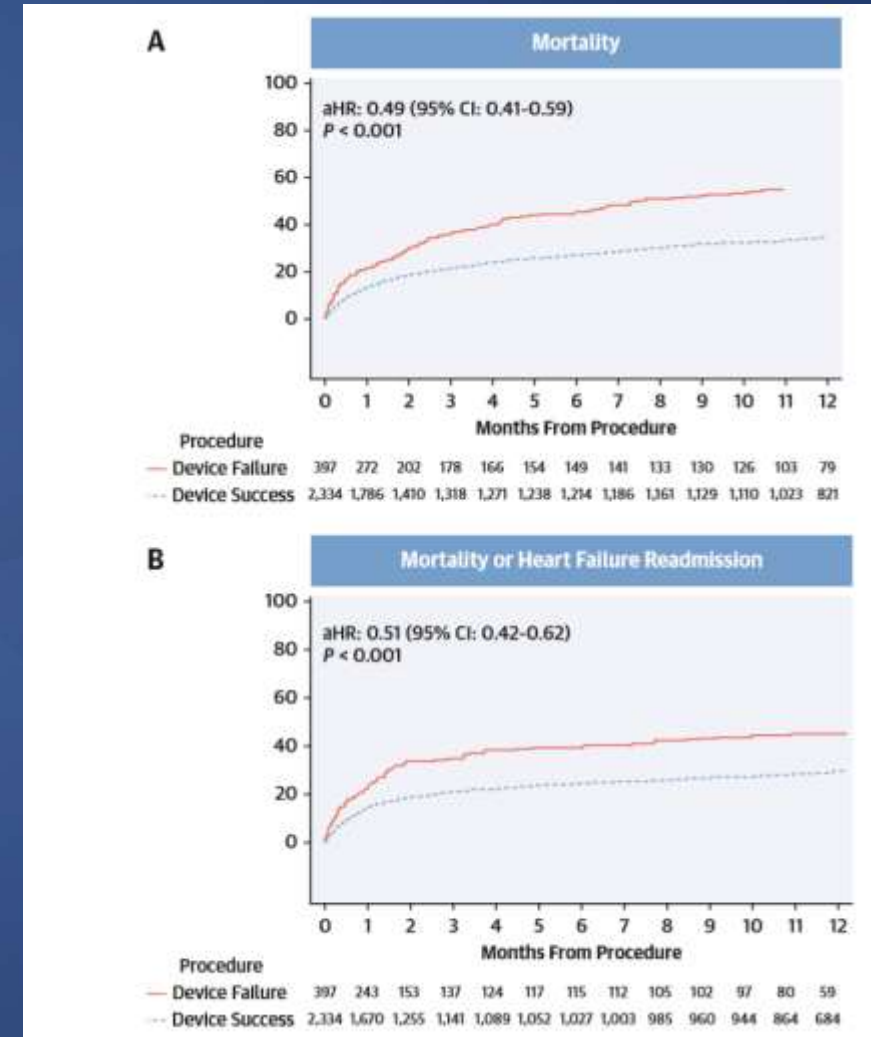
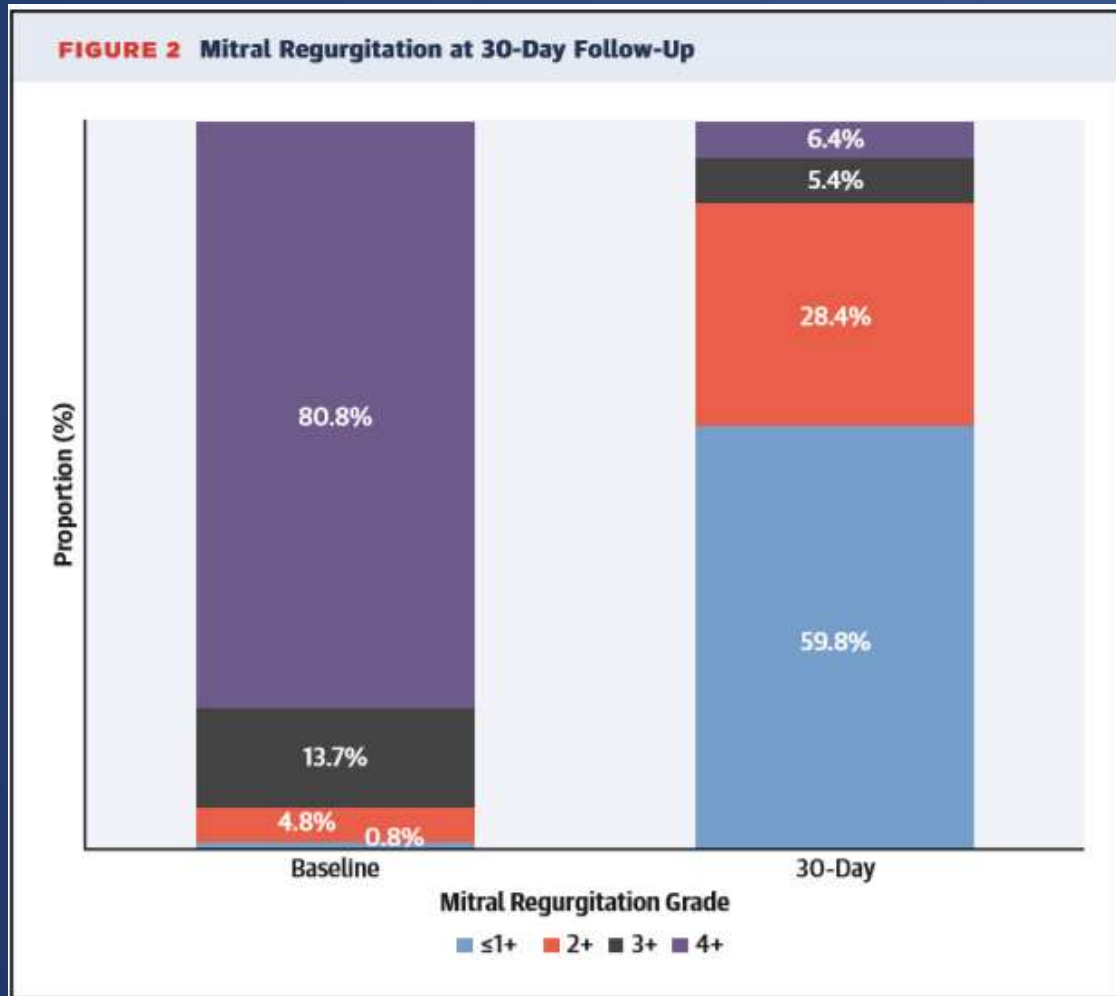
Concept of Disproportionate MR



TEER in Patient with Severe MR and Cardiogenic Shock

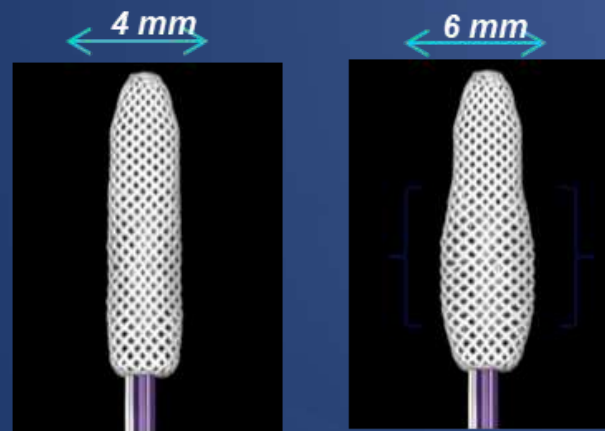
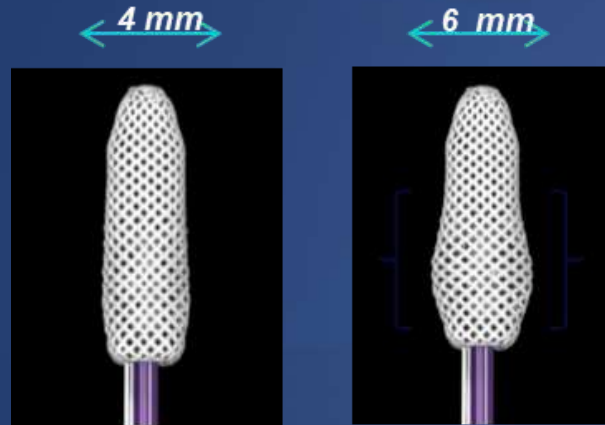


TEER in Patient with Severe MR and Cardiogenic Shock



Device Update to G4 Mitraclip

Mitraclip™ G4 : Various Length & Width of Clips



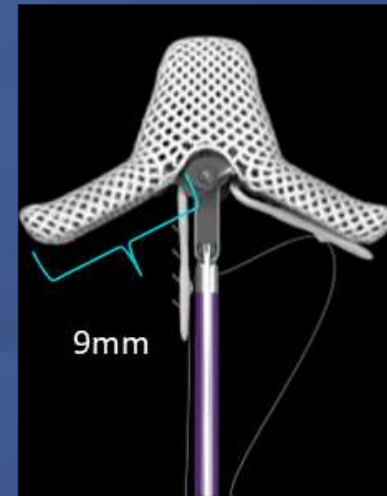
NT/XT

NTW/XTW

MitraClip™ G4 4 Clip sizes

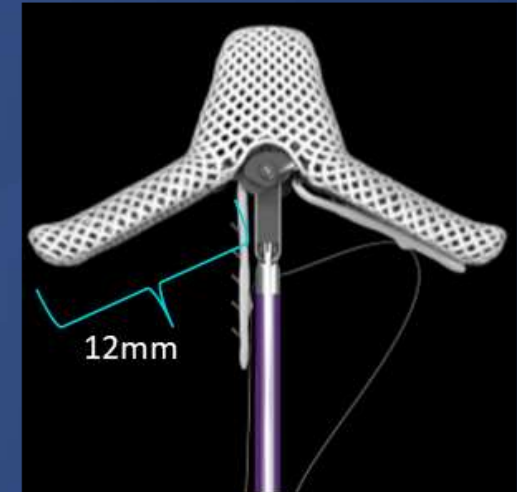
50% wider
in the grasping
area

50% wider
in the grasping
area



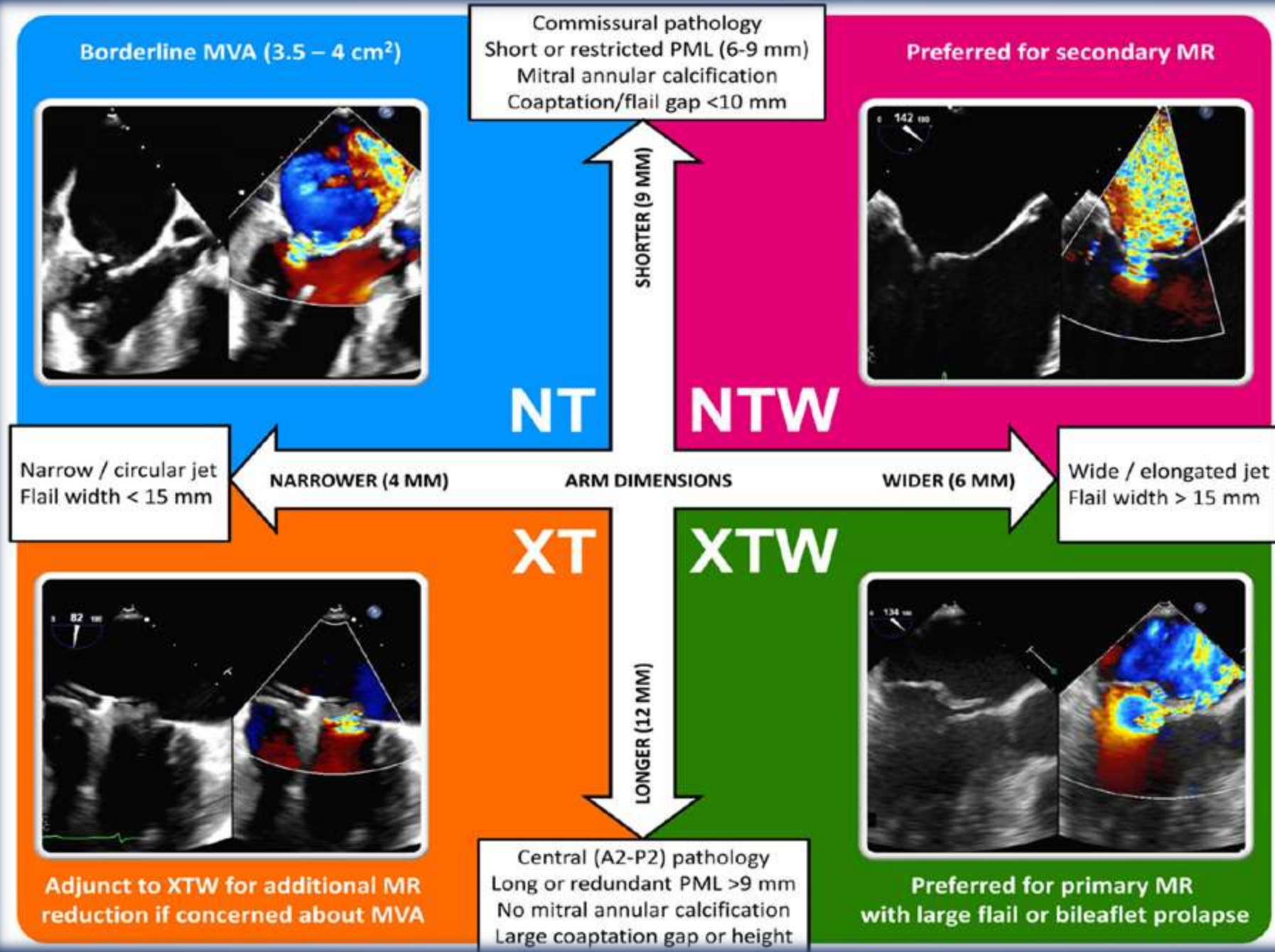
17 mm at 120 degrees
20 mm at 180 degrees

NT/NTW



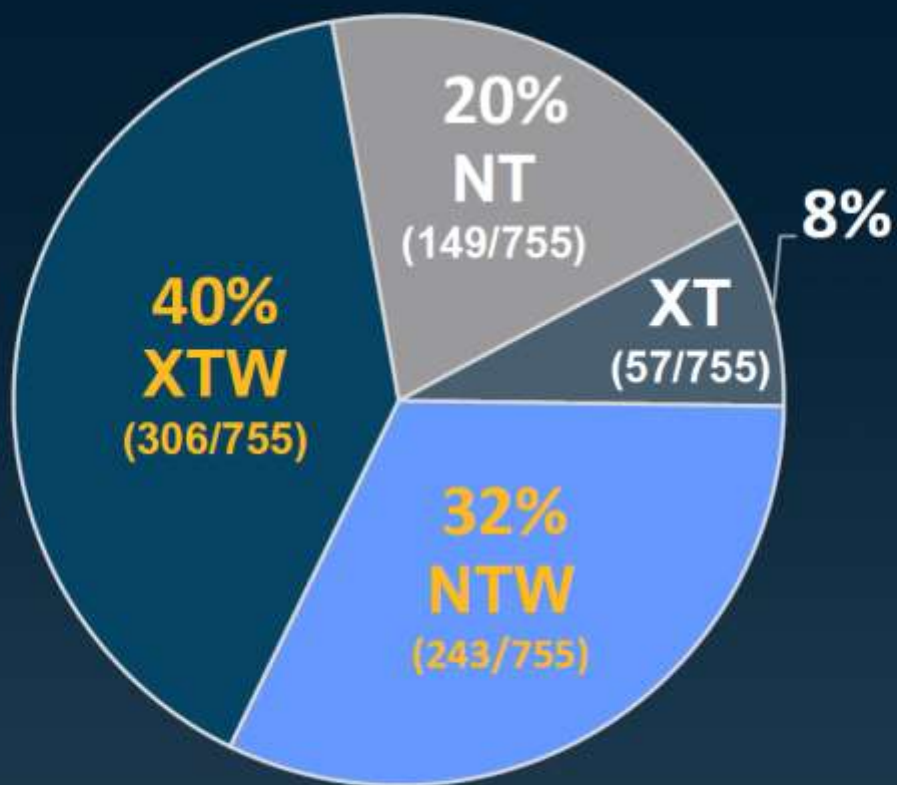
22 mm at 120 degrees
25 mm at 180 degrees

XT/XTW

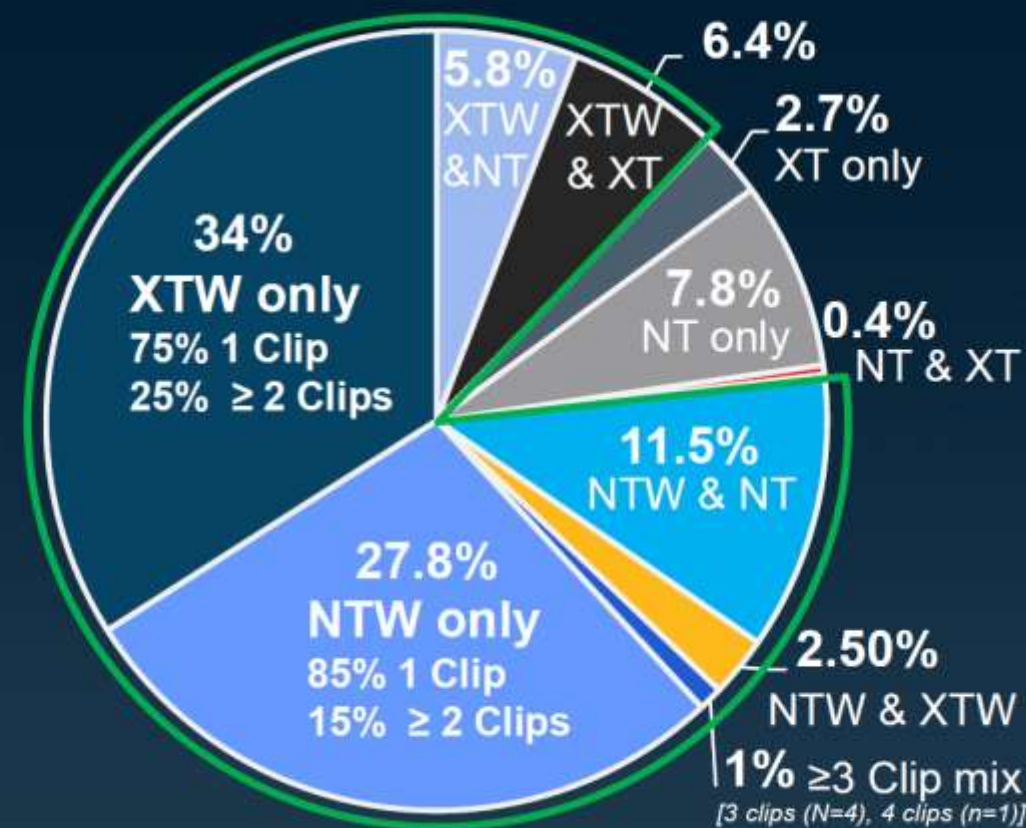


Clips Used in EXPAND G4 Registry (N=529)

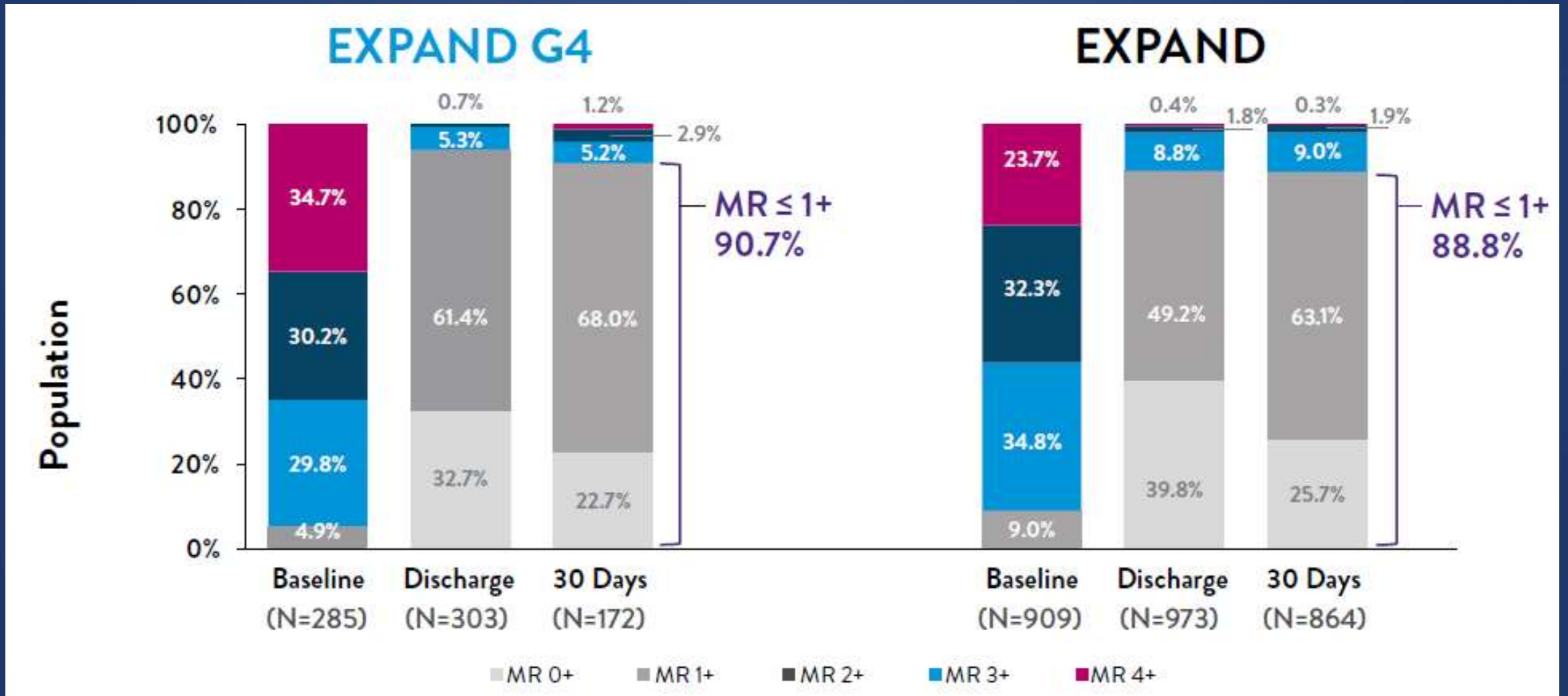
Clip Size Usage
(total clips implanted = 755)



Clip Mix
(N=514, 13 Clip combinations)



MR Severity in EXPAND G4 Registry

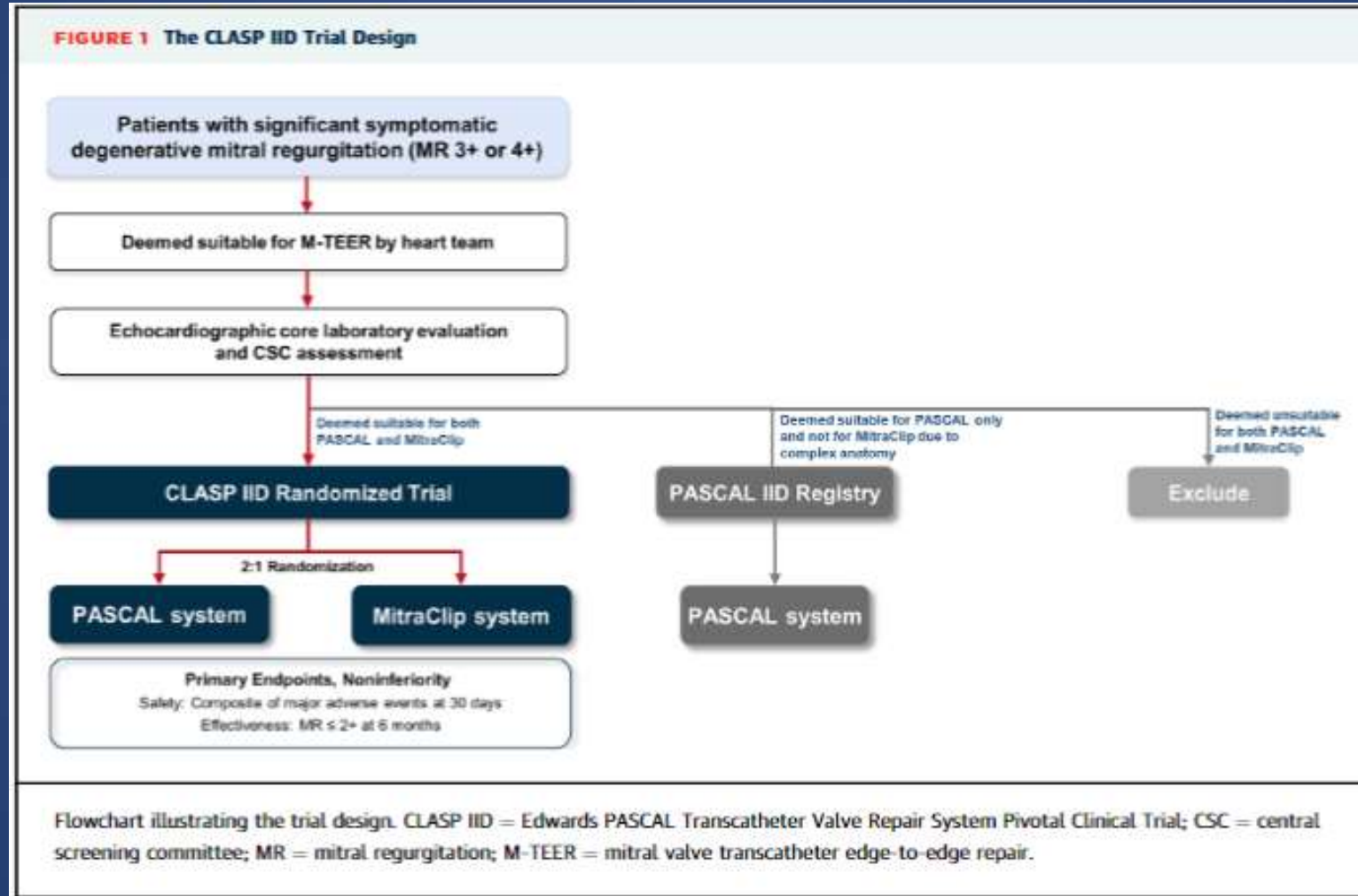


Real-World Safety & Durability of G4 Mitraclip

	TVT Registry 30-Day (N=2,952)	EXPAND 30-Day (N=1,041)	EXPAND 1-Year (N=1,041)	EXPAND G4 30-Day (N=529)
All-cause Death	5.2% (96)	2.3% (24)	14.9% (147)	1.5% (7)
MI	0.2% (3)	0.0% (0)	1.2% (12)	0.0% (0)
Stroke	1.0% (17)	1.2% (8)	1.7% (18)	0.0% (0)
Ischemic stroke	0.6% (11)	1.0% (6)	N/A	0.0% (0)
Non-elective CV surgery for device related complications	N/A	1.1% (11)	N/A	0.8% (4)
Leaflet Adverse Events	1.5% (17)	2.0% (20)	2% (20)	1.1% (6)
SLDA	1.5% (4)	1.7% (18)	1.7% (18)	1.1% (6)

CLASP IID Trial (PASCAL)

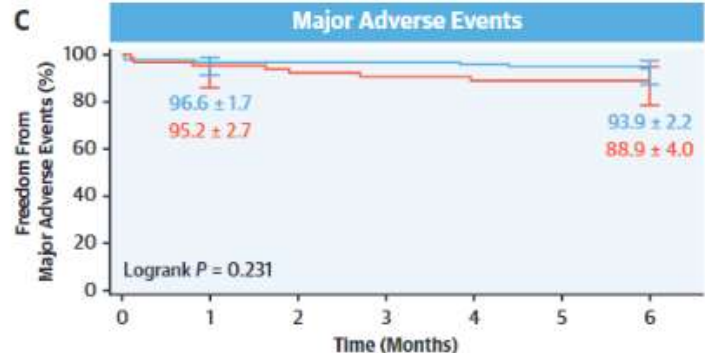
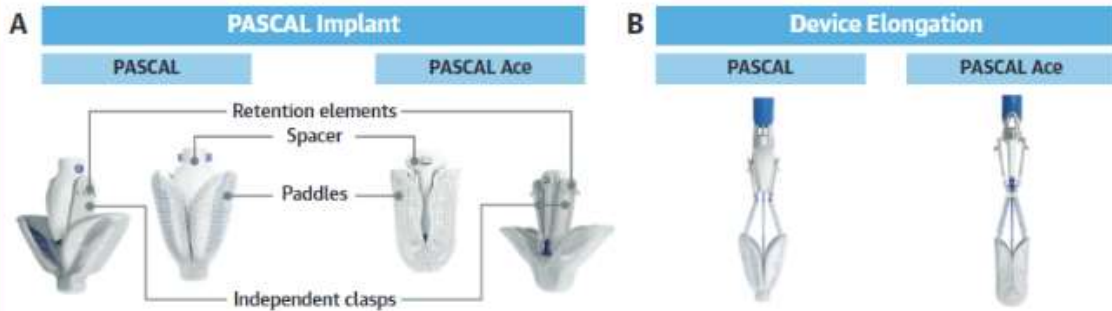
180 patients 2:1 Randomization to PASCAL : Mitraclip



CLASP IID Trial (PASCAL)

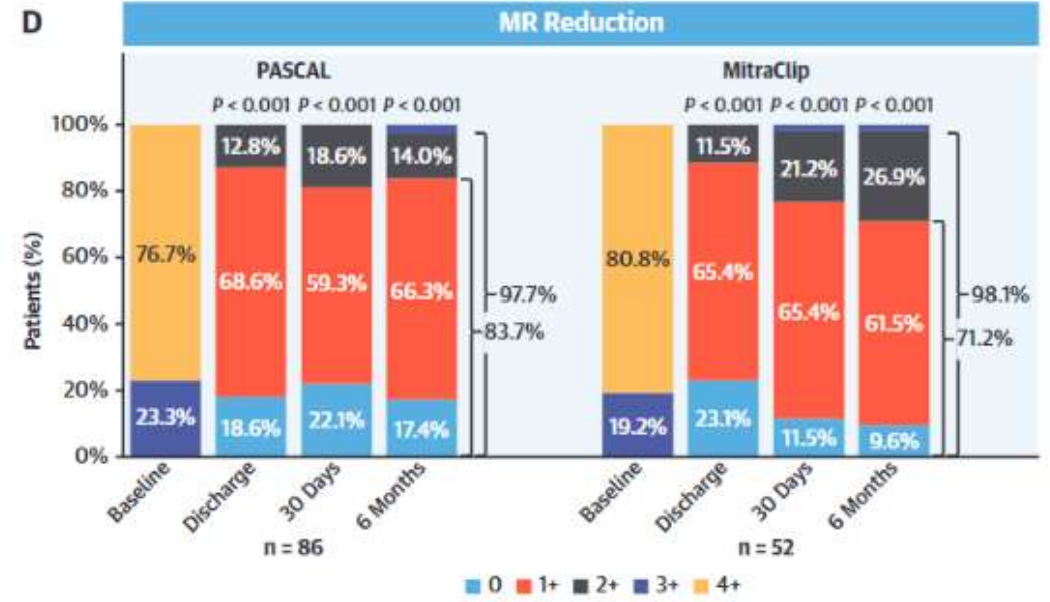
180 patients 2:1 Randomization to PASCAL : Mitraclip

CENTRAL ILLUSTRATION The CLASP IID Randomized Trial Key Outcomes at 6 Months



No. at risk:

	0	1	2	3	4	5	6
PASCAL	117	112	112	111	108	107	105
MitraClip	63	60	58	57	56	56	56

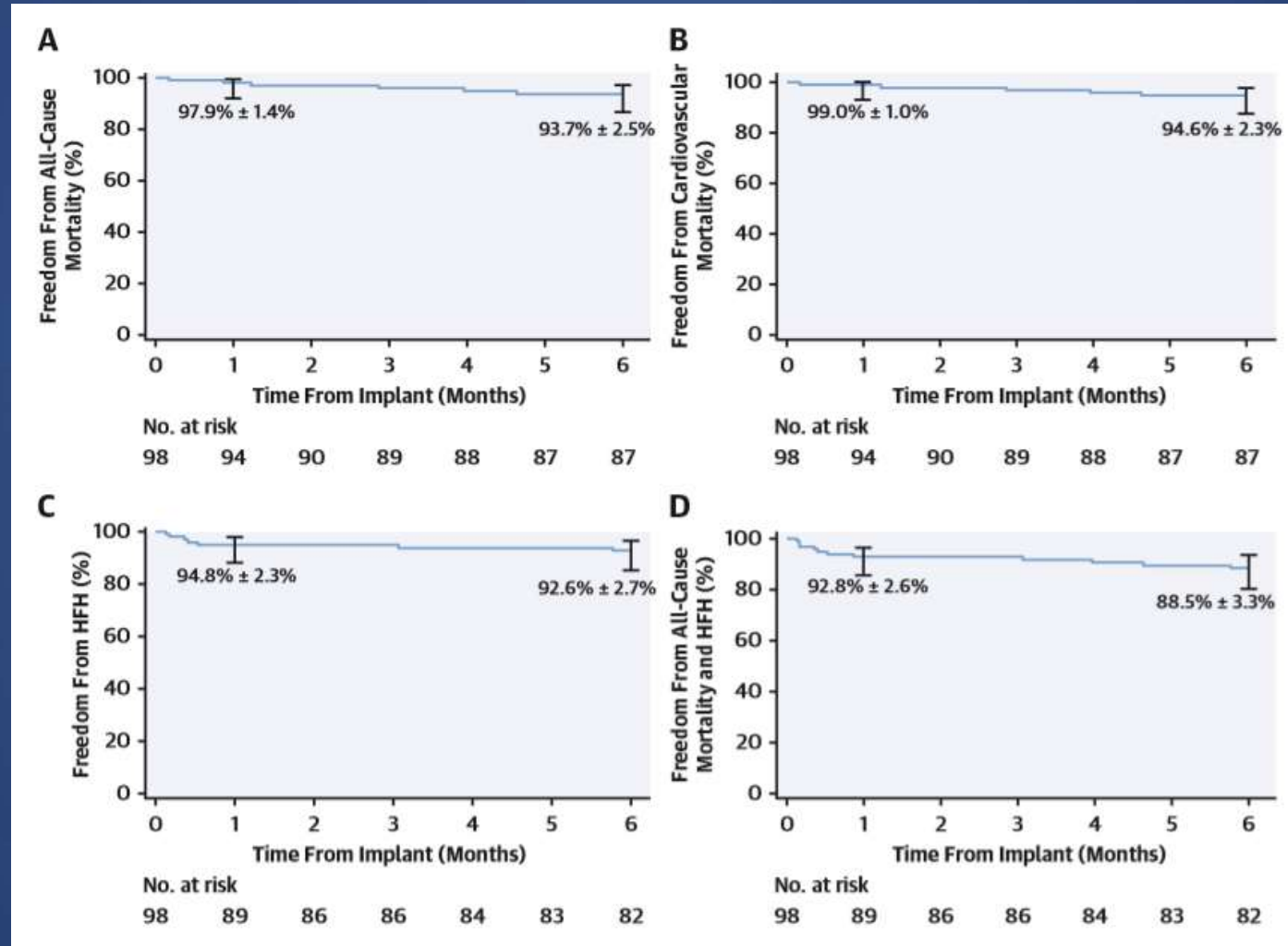


Lim DS, et al. J Am Coll Cardiol Interv. 2022;15(24):2523-2536.

(A) PASCAL implant design. (B) Elongation feature of the PASCAL implant. (C) Kaplan-Meier estimates for freedom from major adverse events (MAE) (Kaplan-Meier estimate ± SE). Error bars represent 95% CI. MAE include cardiovascular mortality, stroke, myocardial infarction, need for new renal replacement therapy, severe bleeding, and non elective mitral valve reintervention (either percutaneous or surgical). (D) Mitral regurgitation severity assessed by echocardiography core laboratory using transthoracic echocardiography. The graph shows paired analysis, and P values were calculated using the Wilcoxon signed rank test. CLASP IID – Edwards PASCAL Transcatheter Valve Repair System Pivotal Clinical Trial.

CLASP IID Trial (PASCAL)

180 patients 2:1 Randomization to PASCAL : Mitraclip



CLASP IID Trial (PASCAL)

TEER in Patient with Anatomically Complex Degenerative MR

CENTRAL ILLUSTRATION PASCAL IID Registry Outcomes at 6 Months

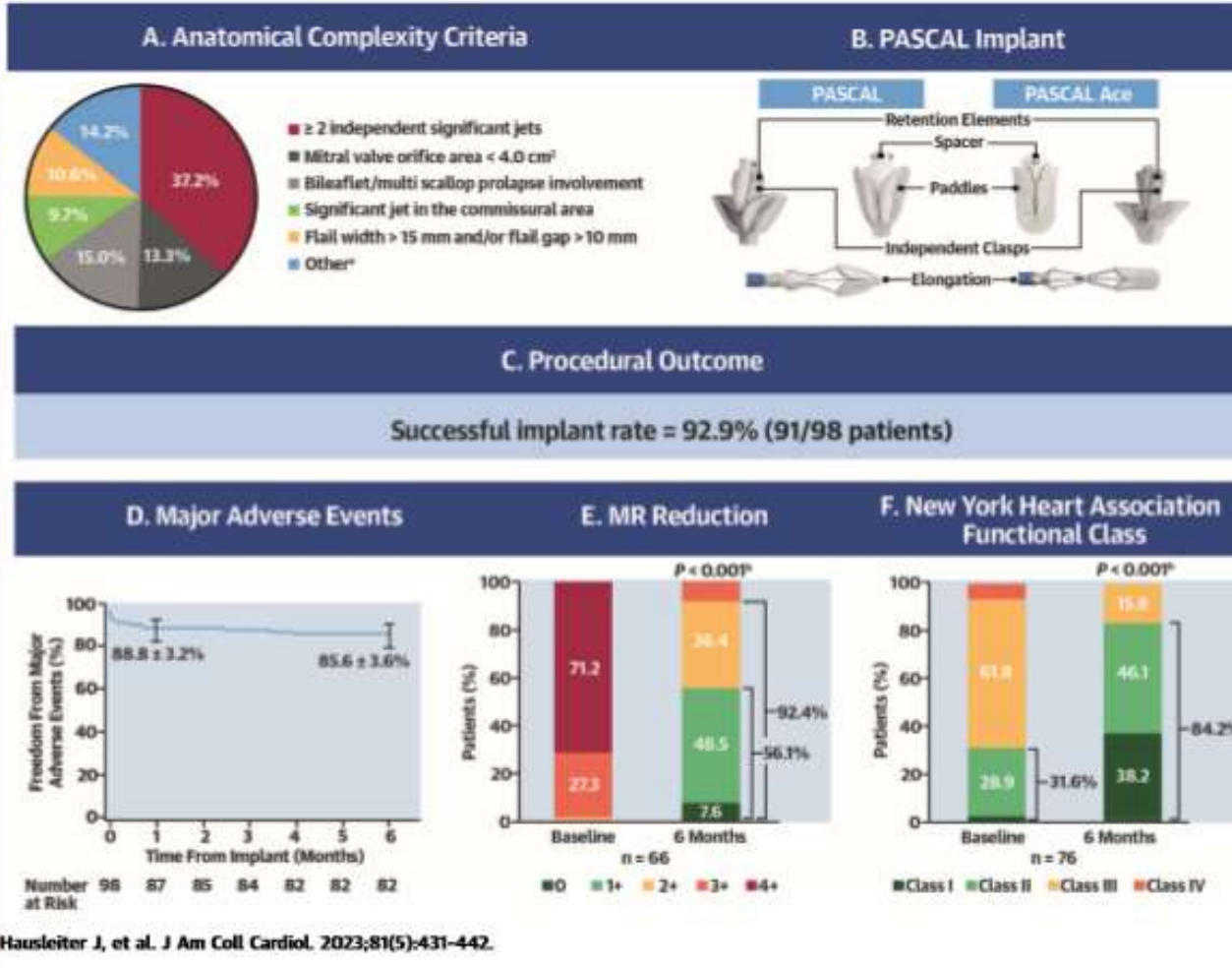


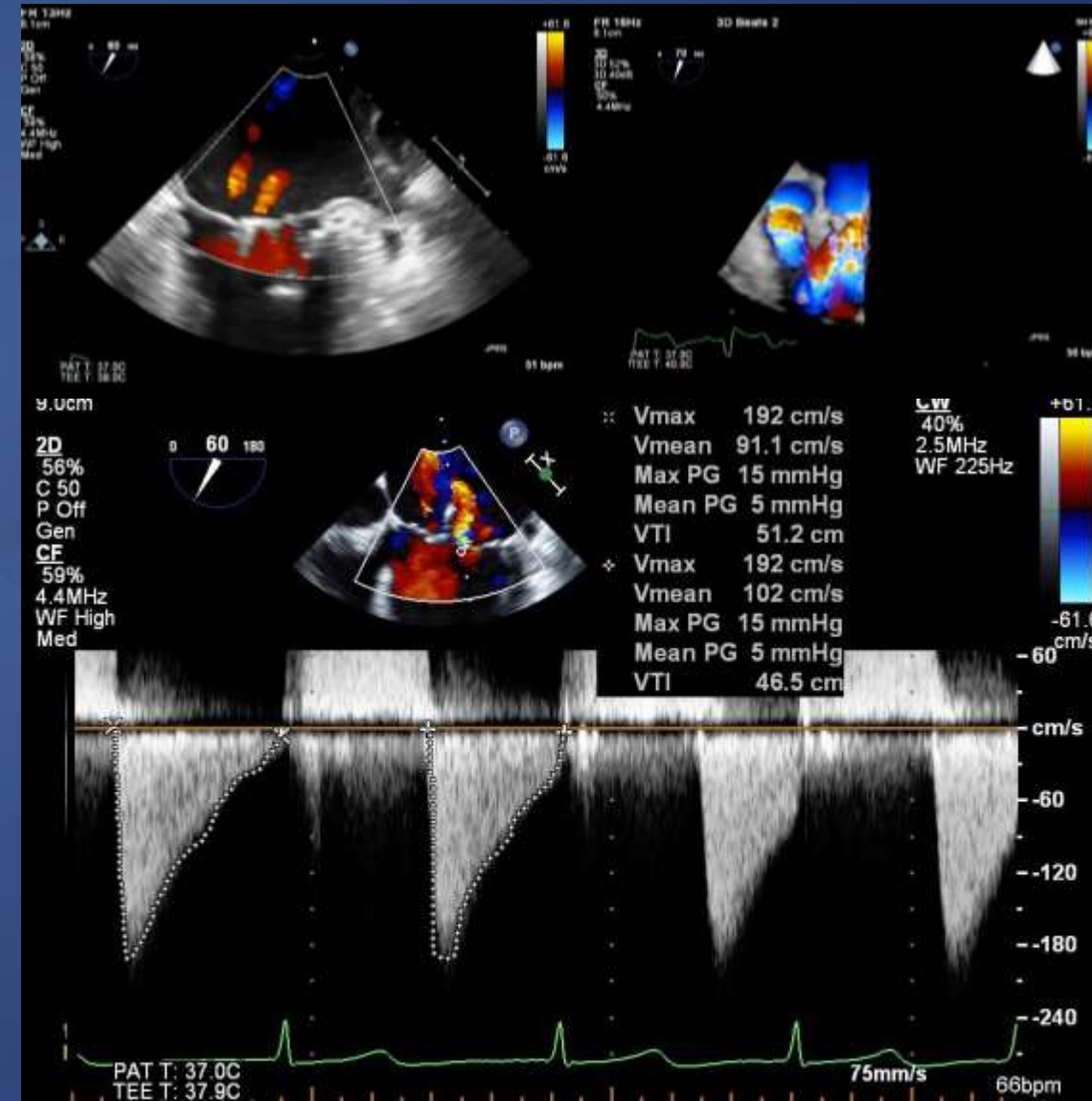
TABLE 2 Anatomical Complexity Criteria

Anatomic Criteria ^a	(N = 113)
Presence of ≥ 2 independent significant jets	42/113 (37.2)
Evidence of severe bileaflet/multi scallop prolapse involvement	17/113 (15.0)
Mitral valve orifice area $< 4.0 \text{ cm}^2$	15/113 (13.3)
Large flail gap and/or large flail width ^b	12/113 (10.6)
Presence of 1 significant jet in the commissural area	11/113 (9.7)
Presence of significant cleft or perforation in the grasping area	7/113 (6.2)
Leaflet mobility length $< 8 \text{ mm}$	4/113 (3.5)
Evidence of moderate to severe calcification in the grasping area	4/113 (3.5)
History of endocarditis and significant tissue defects in the leaflet	1/113 (0.9)
Total Number of Anatomic Criteria Met^c	(N = 98)
1	83/98 (84.7)
2	15/98 (15.3)

Optimal Procedural Outcomes

How to define TEER success?

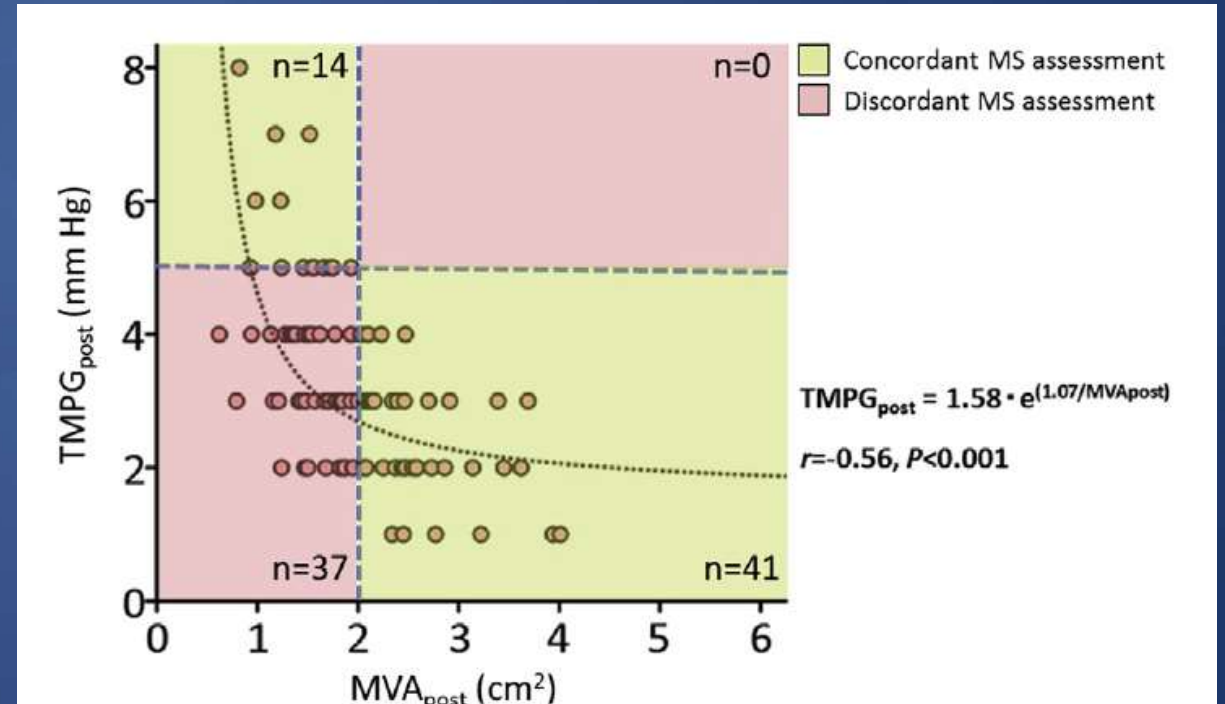
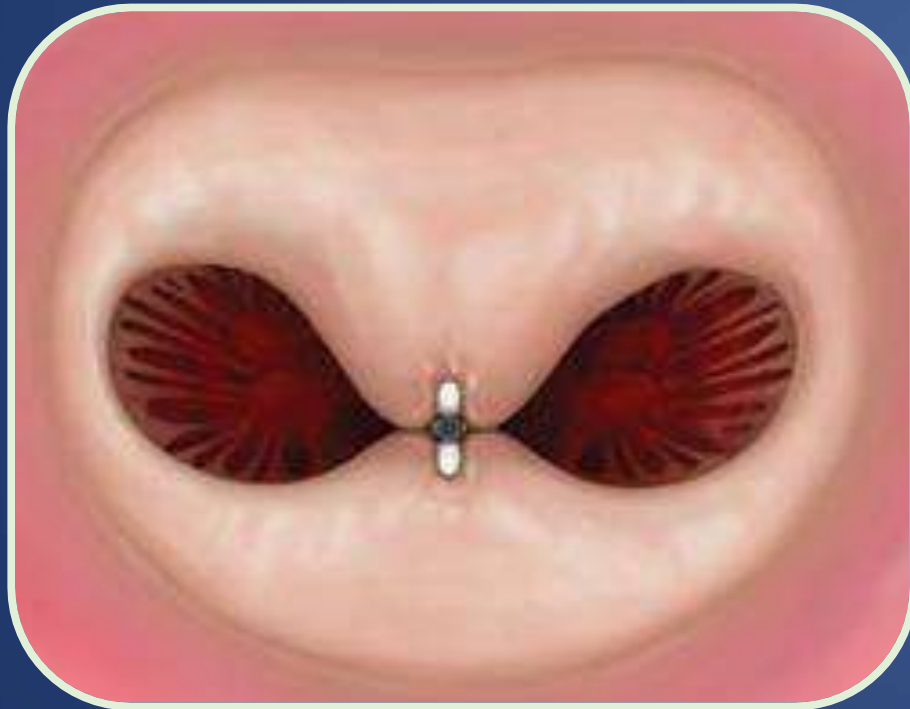
- MR reduction ($\leq 2+$)
 - “achievable” MR result will depend on starting MVA, baseline MR, etc
 - **Acceptable MR reduction (“success”) may vary among patients**
- Absence of significant MS
 - Mean gradient ≤ 5 mmHg
 - Increased gradients did OK in COAPT (MG +/- 7 mmHg), in secondary MR...



TEER Reduces MV Area, therefore Increase MV Gradient

Double-edged Sword of TEER

MVA & mean MV gradient after Mitraclip



Utsunomiya H et al. Am J Cardiol. 2017;120:662-669.

Predictor of Increased MV Gradient after TEER

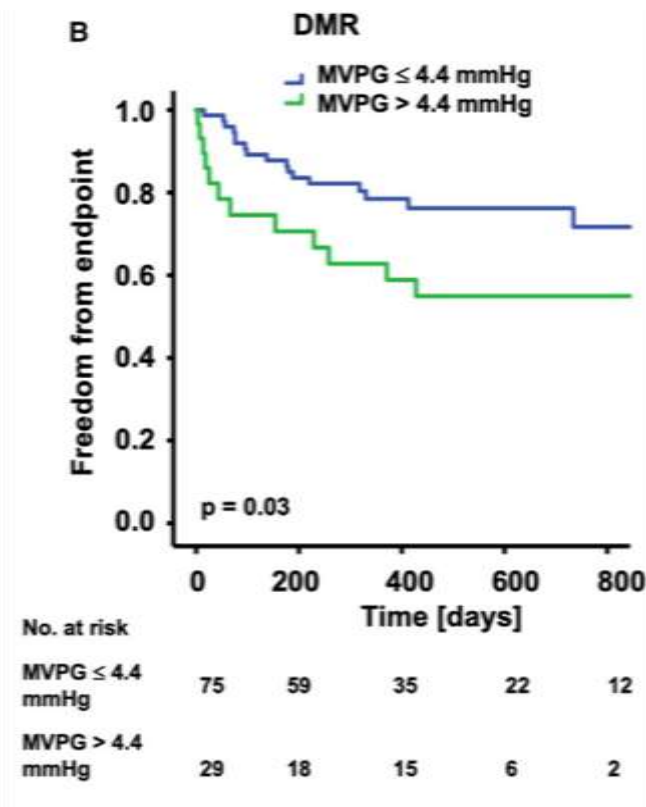
- MV Orifice Area $\leq 4.0 \text{ cm}^2$
- Baseline Mitral Gradient $\geq 4\text{mmHg}$
- Mitral Annular Calcification
- Hemodialysis
- More Clips used
- Higher Residual MR (Increased Blood Flow over MV)

Contrasting Results of Impact of High Transmitral Gradient after TEER for Primary MR

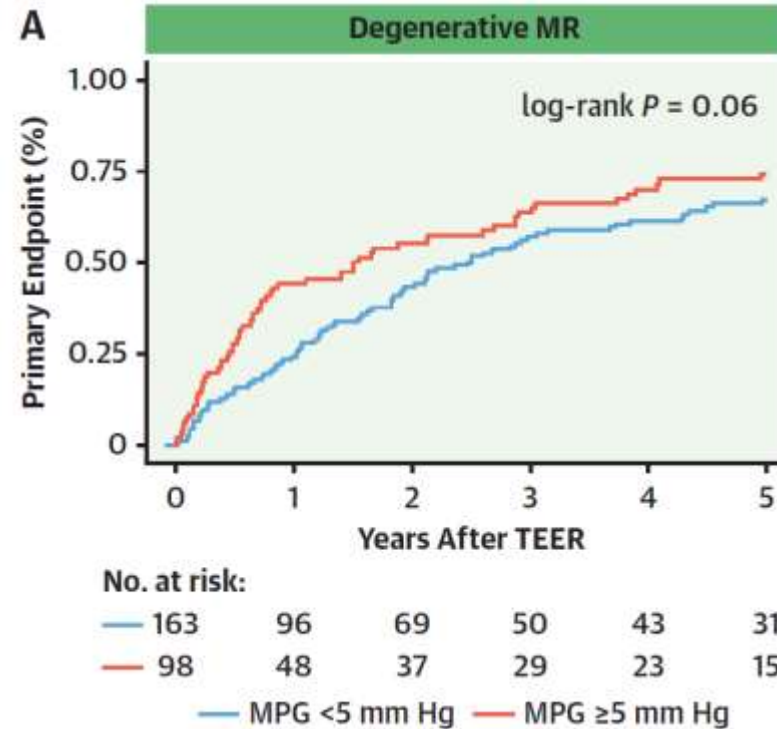
255 from German Single Center
Mortality, MV Surgery, Redo, LVAD

265 from German Single Center
Mortality, HF Hospitalization

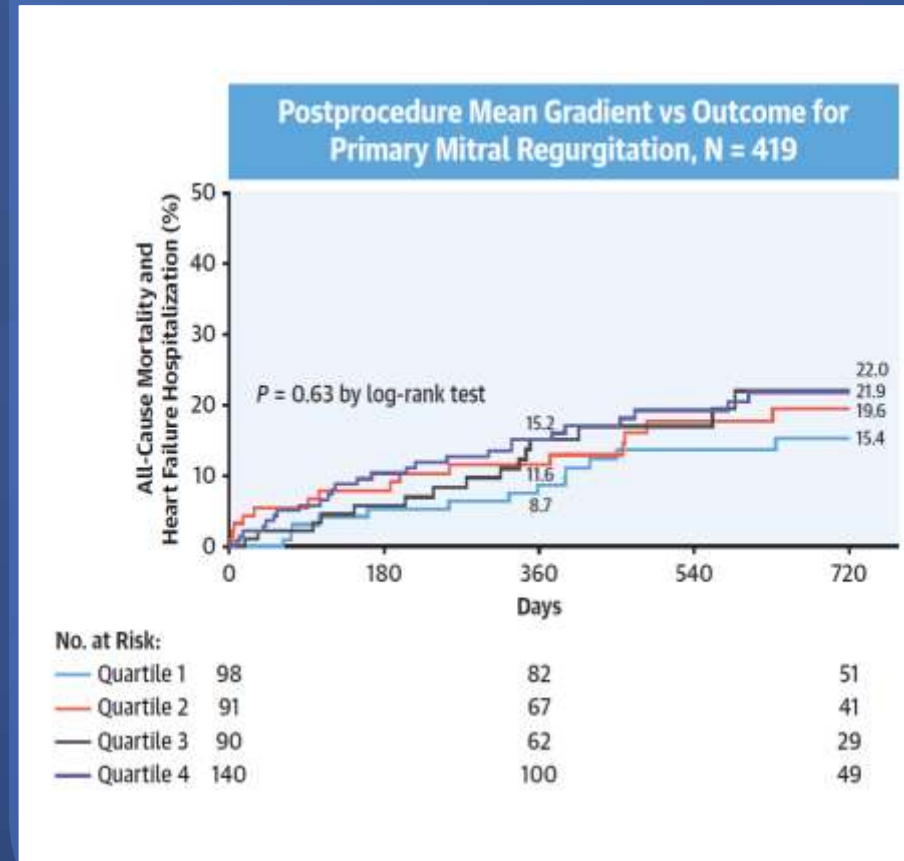
419 from US Single Center
Mortality



Patzelt J et al. JAHA. 2019;8:e011366.



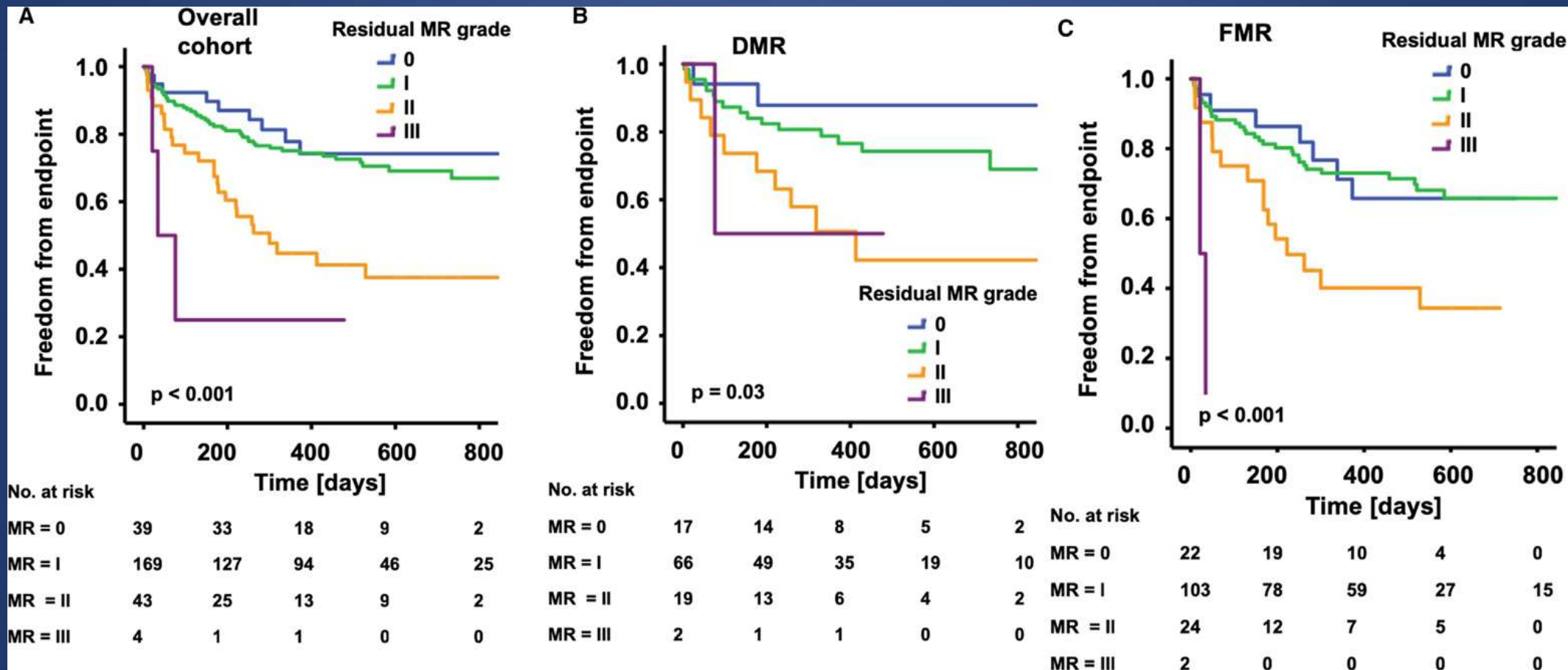
Koell B et al. JACC Interv. 2022;15:922-34.



Yoon S et al. JACC Interv. 2022;15:935-45.

Residual MR was Stronger Predictor than MV Gradient

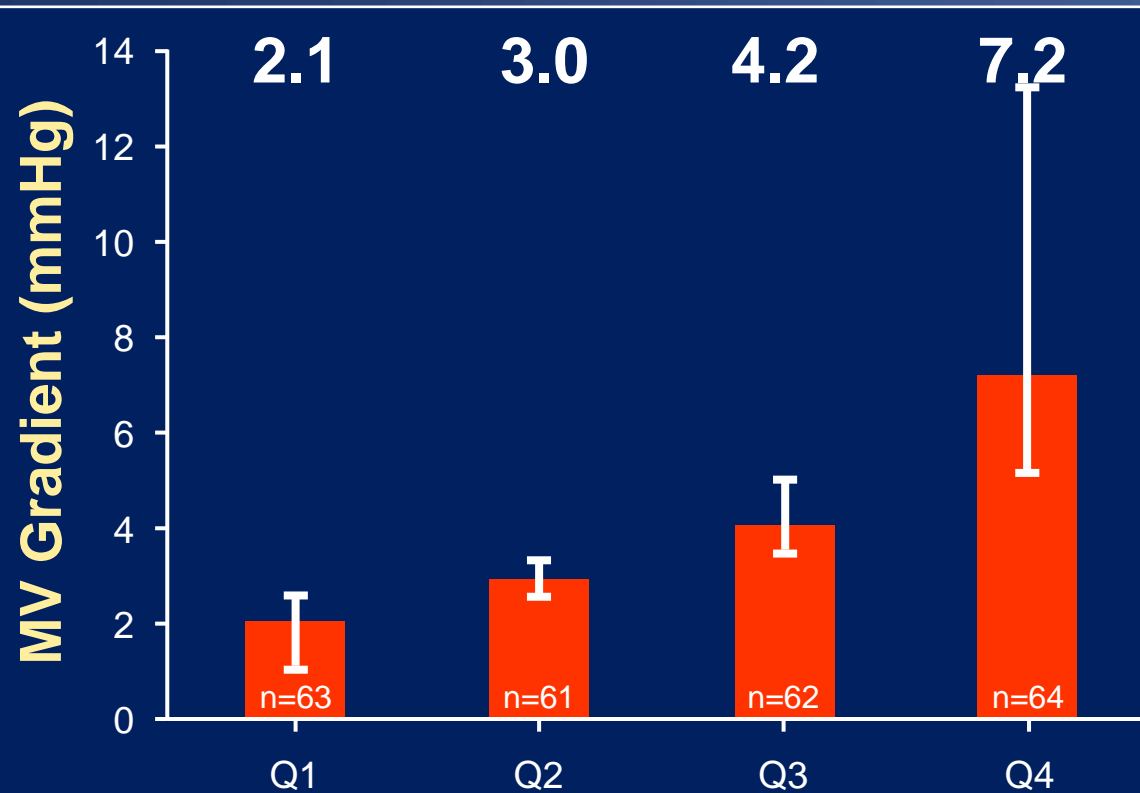
255 Patients from German Single Center from 2014 to 2017, Primary 41%, Secondary 59%
 Clinical Outcome: All-cause mortality, MV Surgery, LVAD, or Redo TEER



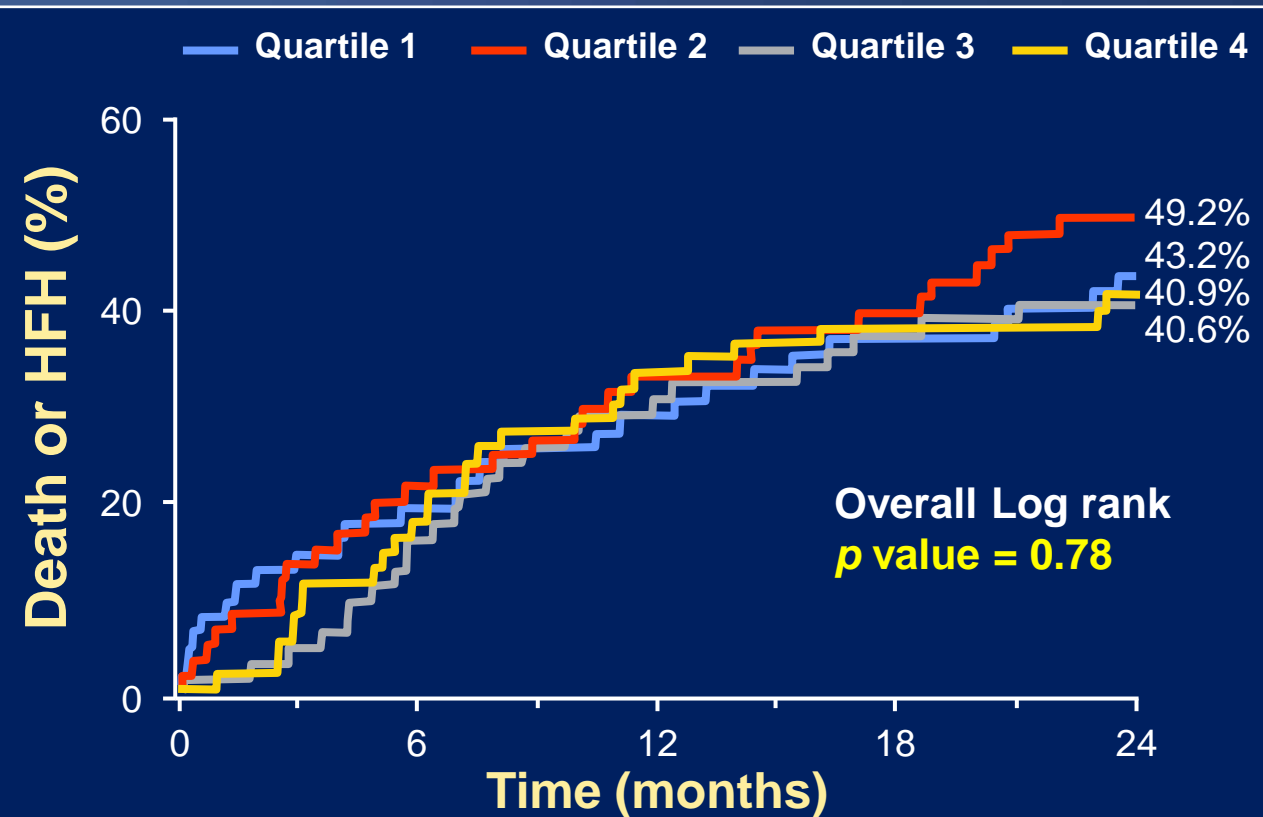
High Transmitral Gradient after TEER was NOT associated with Worse Outcome in COAPT Trial (Secondary MR)

Mean discharge TTE MVG after MitraClip was 4.2 ± 2.2 mmHg (range 1 to 13.2 mmHg)*

Mitral Valve Gradient by Quartile

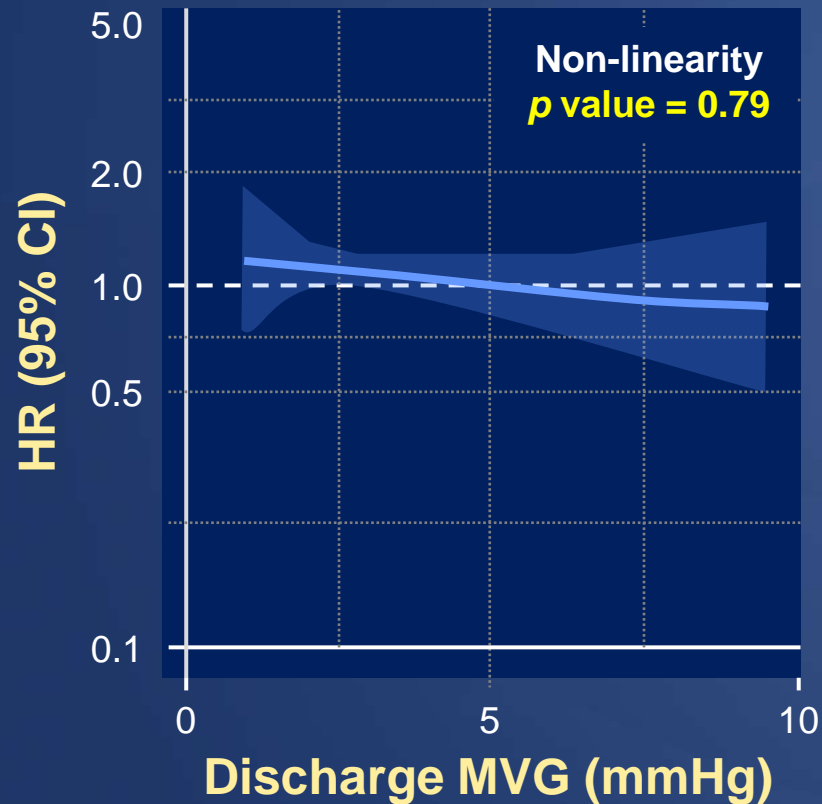


Death or HF Hospitalization

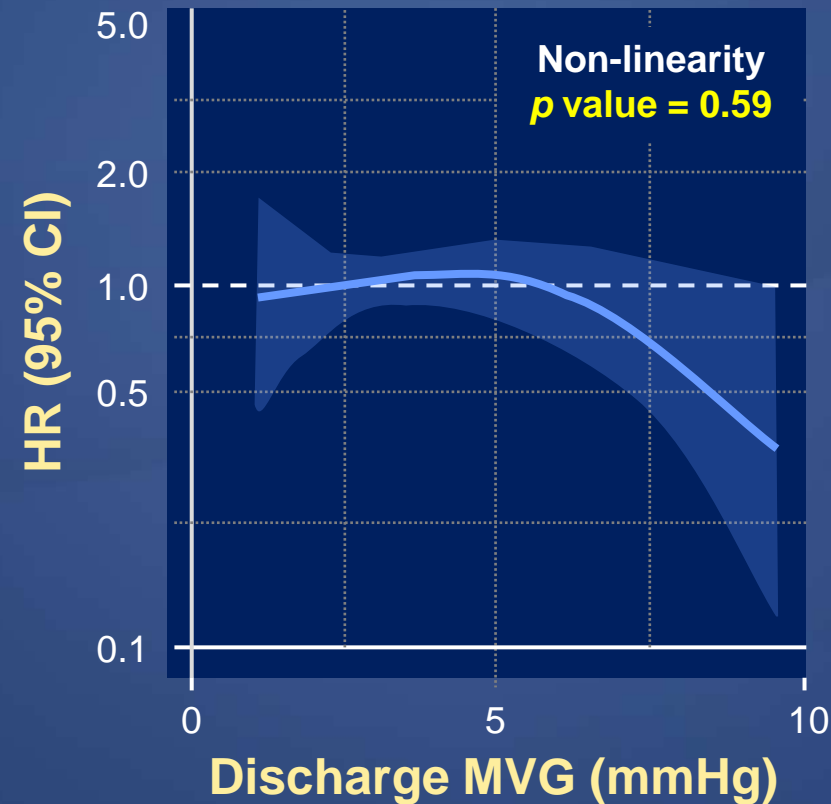


Impact of MV Gradient after TEER in COAPT Trial (Secondary MR)

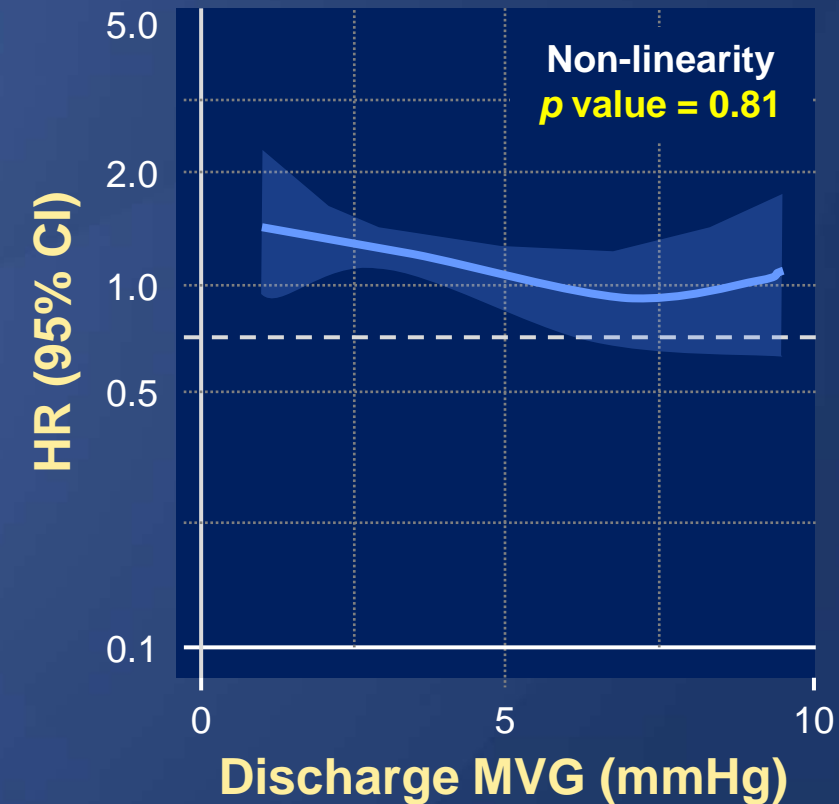
Death or HFH



Death



HFH

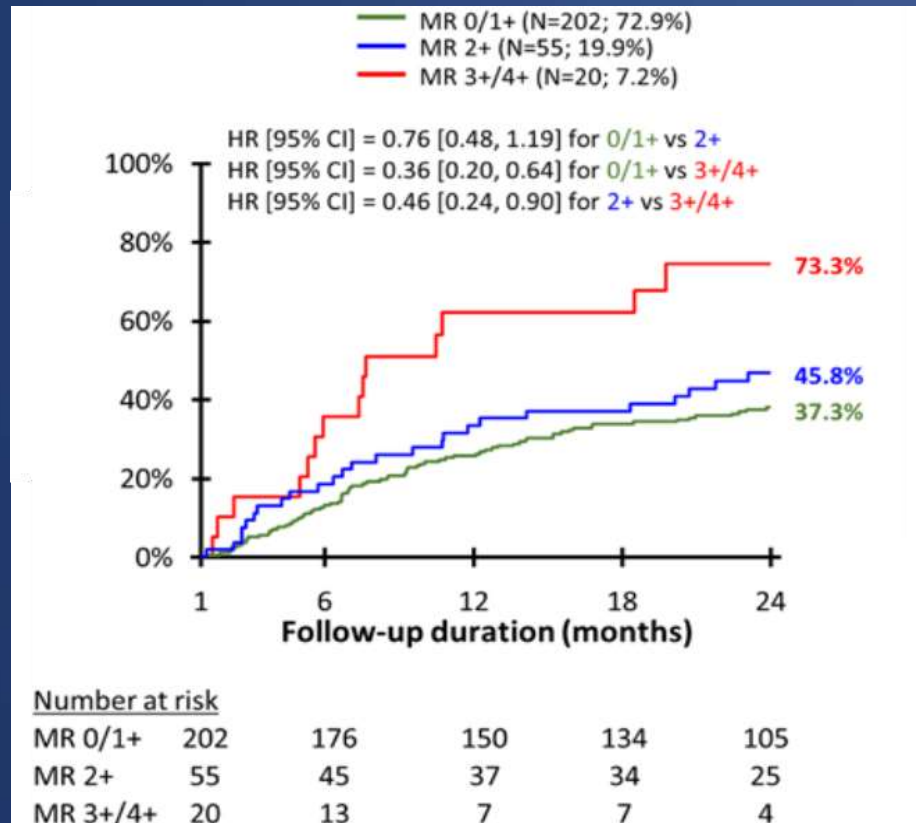


MR Reduction was Strong Predictor of Clinical Outcome

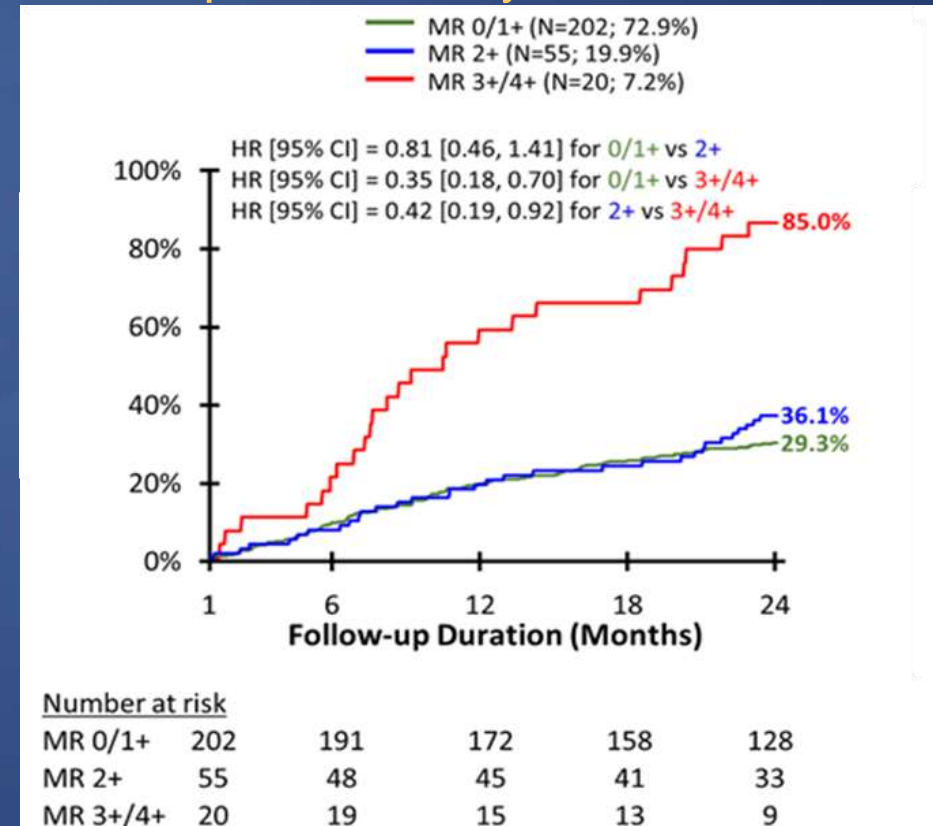
277 Secondary MR Patients after TEER from COAPT Trial

Benefits of MR Reduction Might Outweigh the Adverse Effects of Increased MV Gradient

Death or HFH by Residual MR

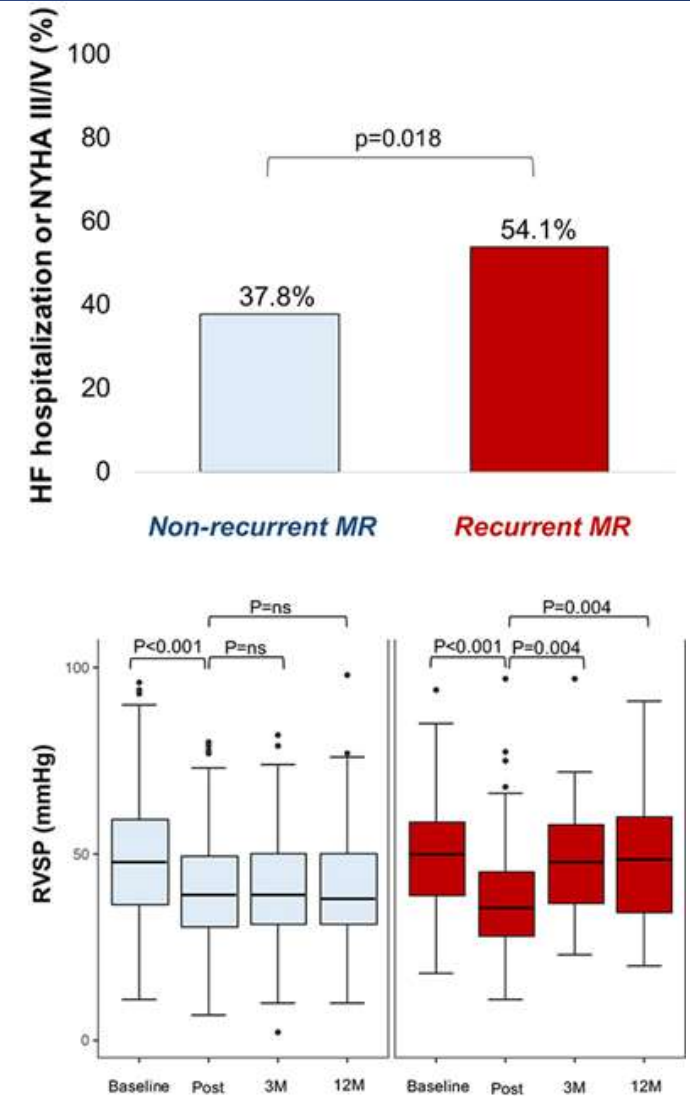
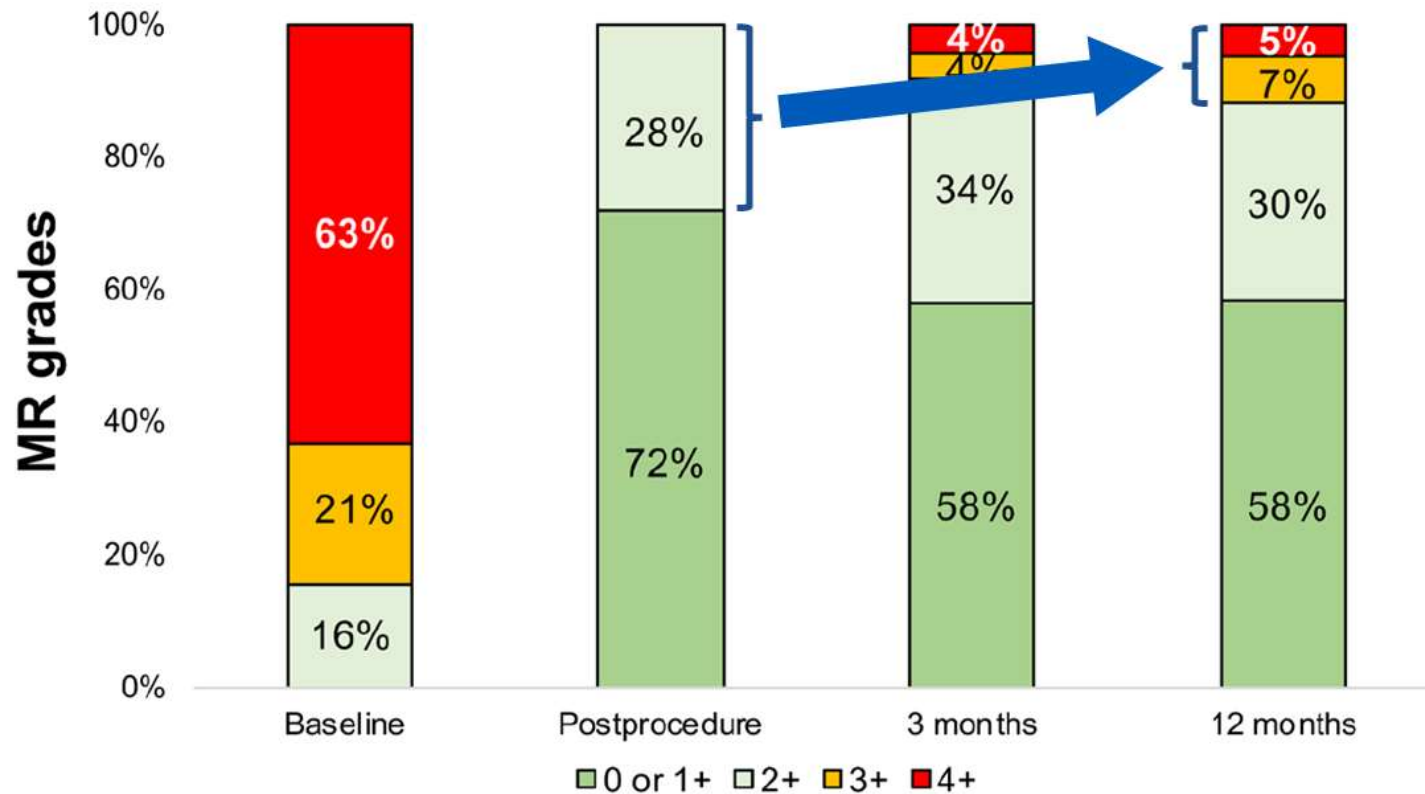


HF Hospitalization by Residual MR



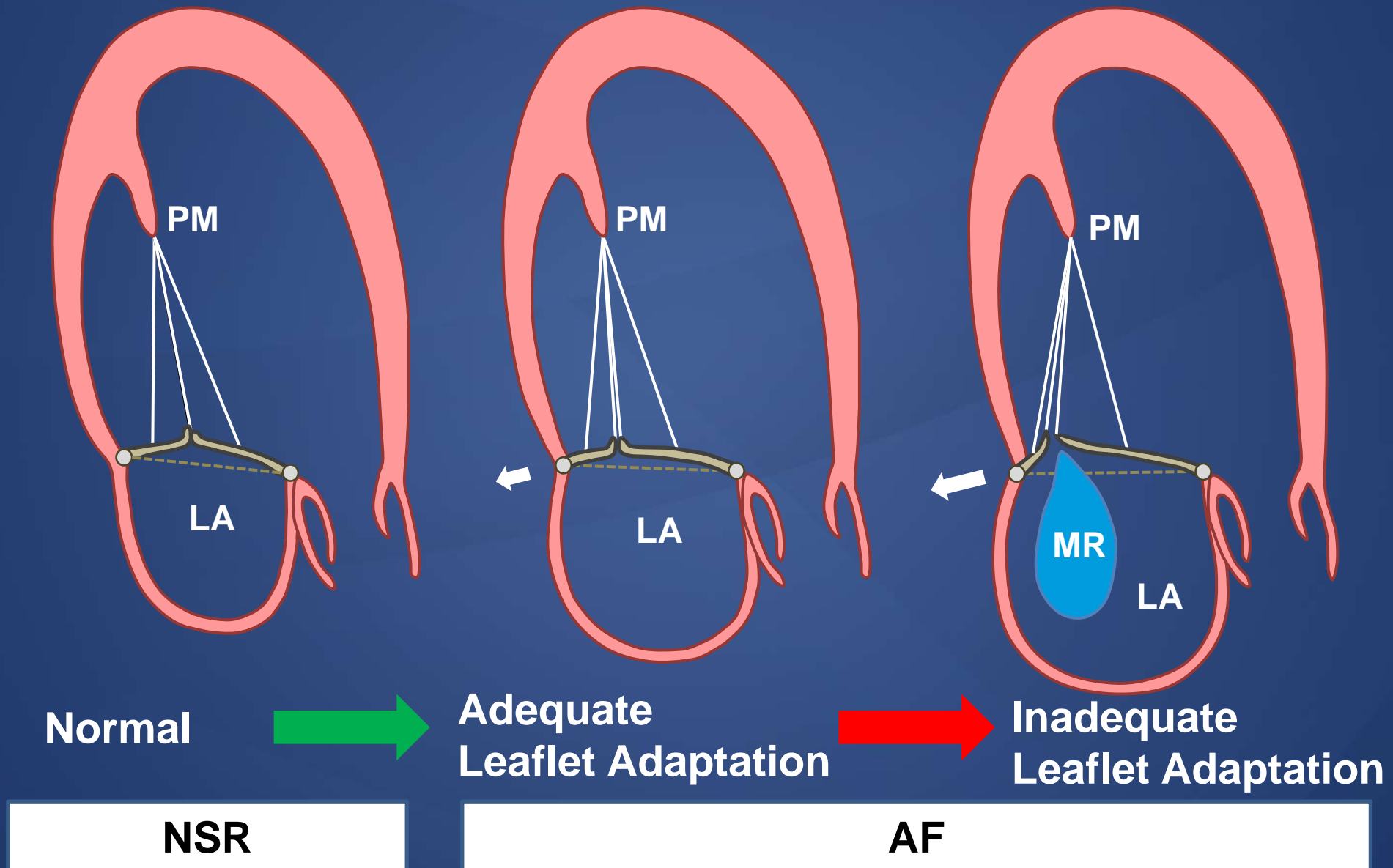
Deleterious Hemodynamic Effect of Recurrent MR

- German Single center, MR to $\leq 2+$ after Mitraclip (N=685)
- 61 (8.9%) patients developed recurrent MR within 12 months
- Predictor of Recurrent MR : MR 2+, Flail leaflet



TEER in Atrial Functional MR

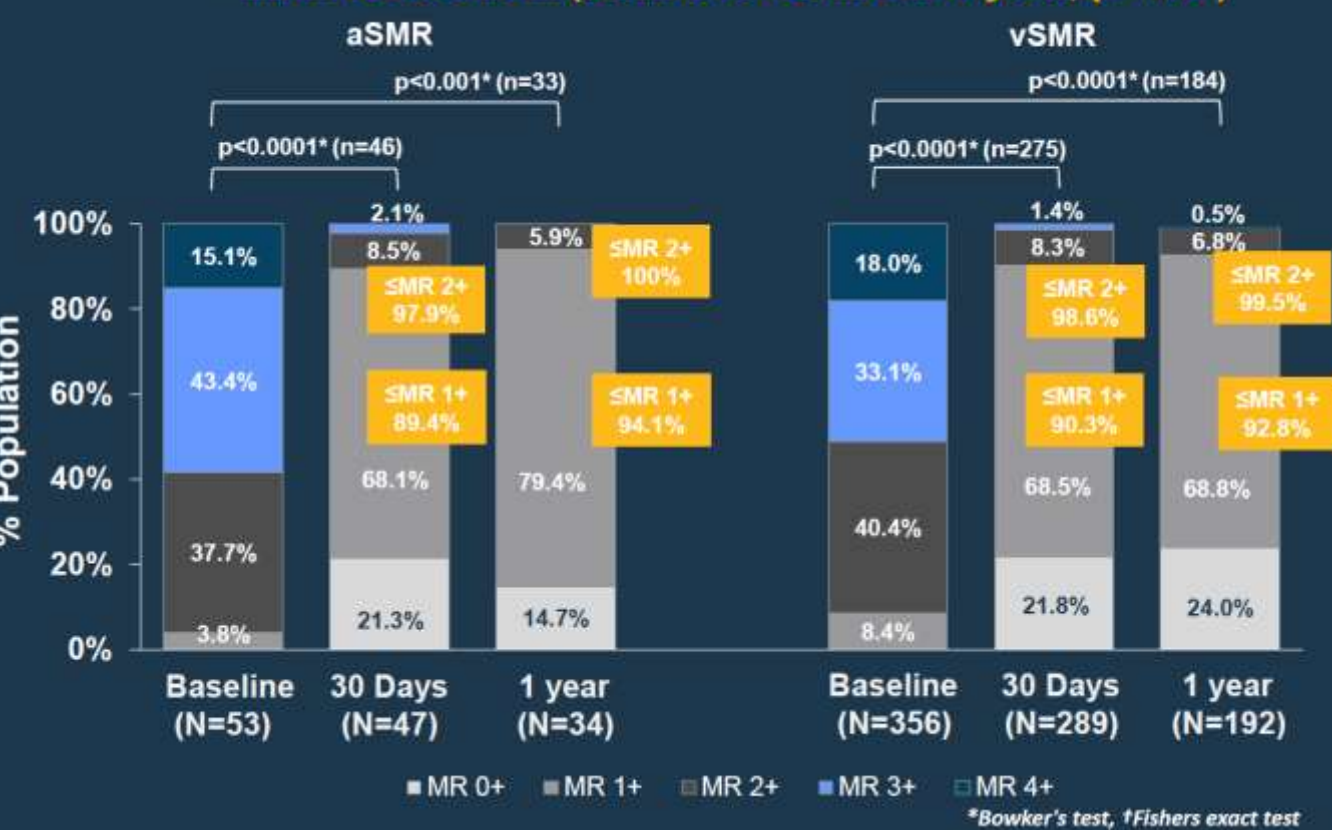
Isolated Annular Dilation Develops Atrial FMR in AF



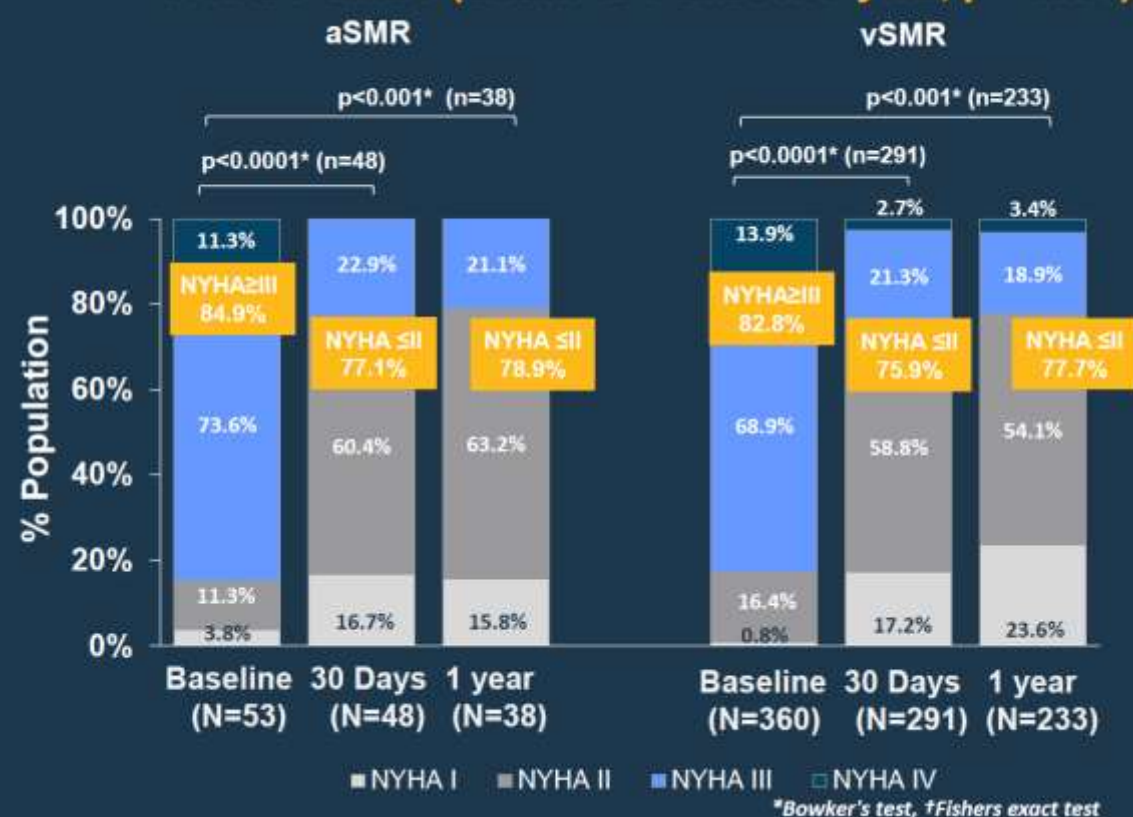
TEER in Atrial FMR : Global EXPAND study

N=53, LV EF ≥45% without RWMA, AF with Dilated LA

MR Reduction (aSMR vs vSMR at 1-year, p=1.0†)



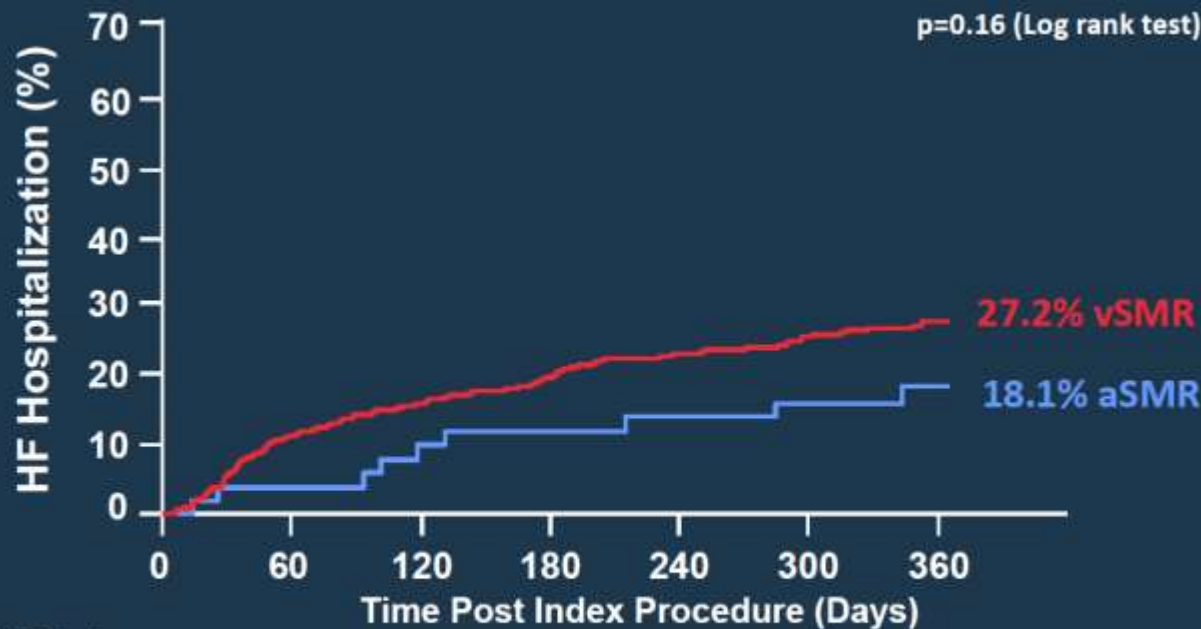
NYHA Class (aSMR vs vSMR at 1 year, p =0.86†)



TEER in Atrial FMR : Global EXPAND study

N=53, LV EF \geq 45% without RWMA, AF with Dilated LA

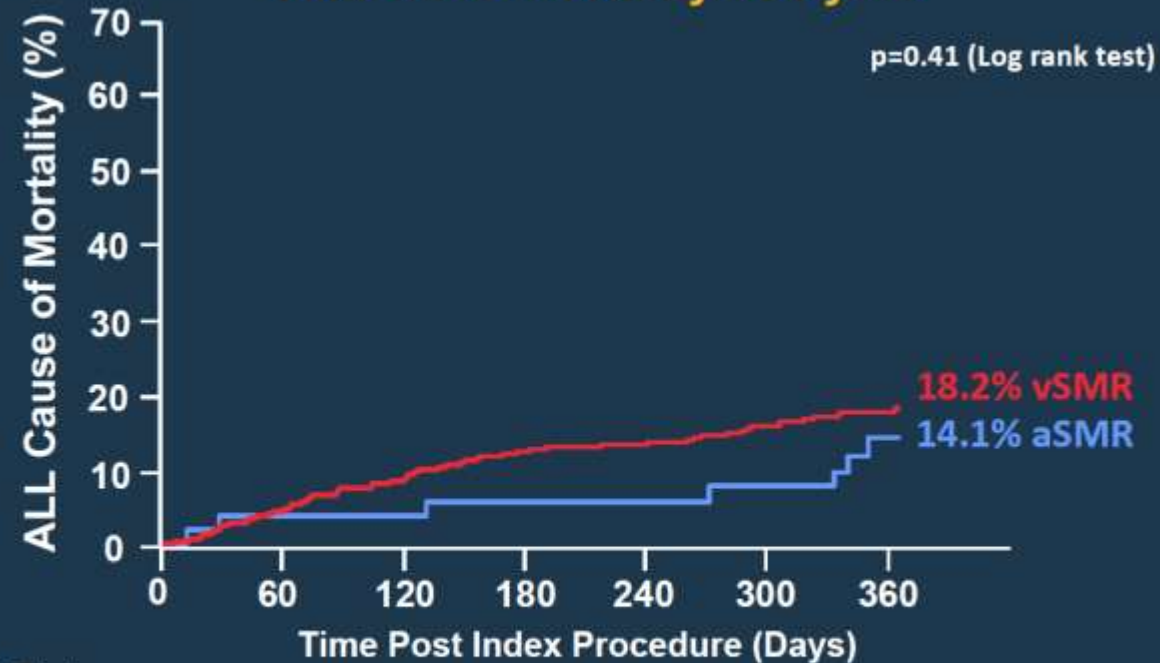
HF Hospitalization at 1 year



At Risk				
aSMR	53	49	44	24
vSMR	360	333	251	144

HFH, based on each patient's first occurrence of HF Hospitalization.

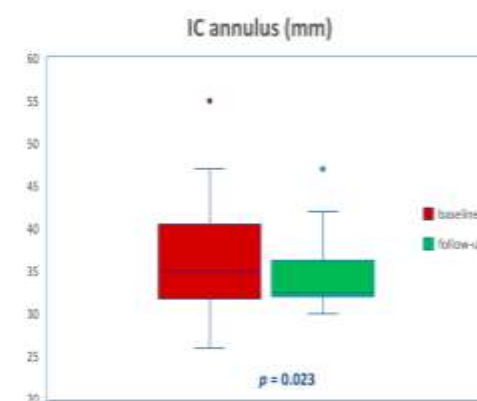
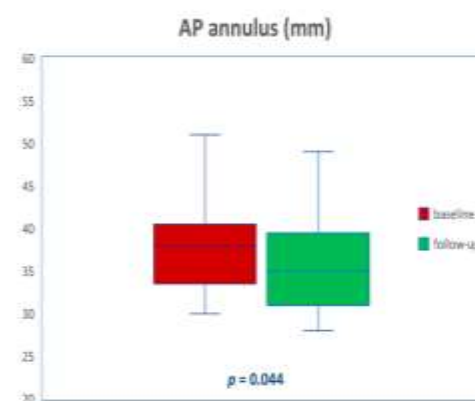
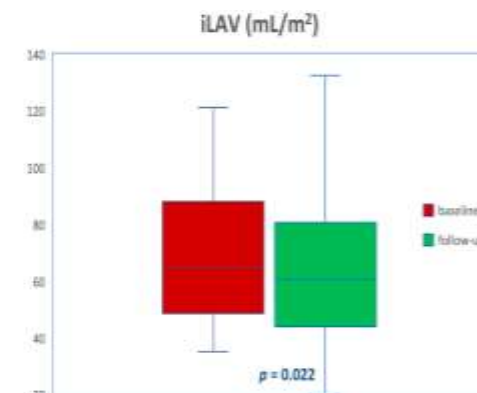
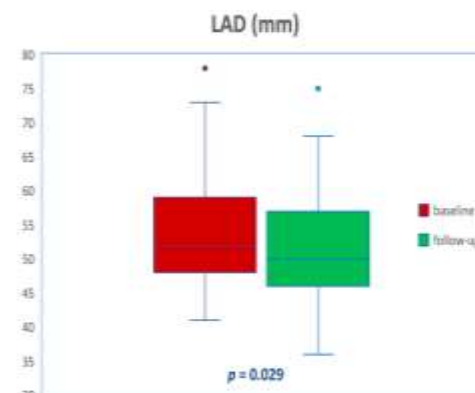
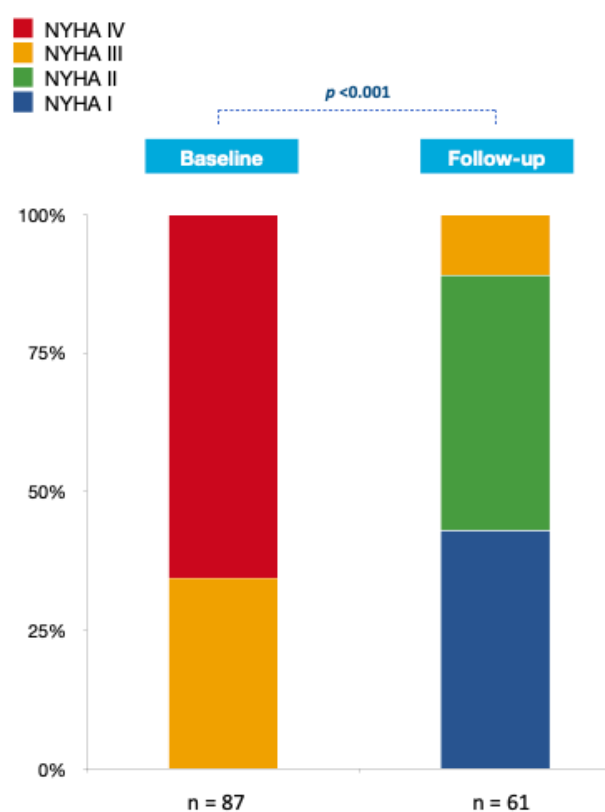
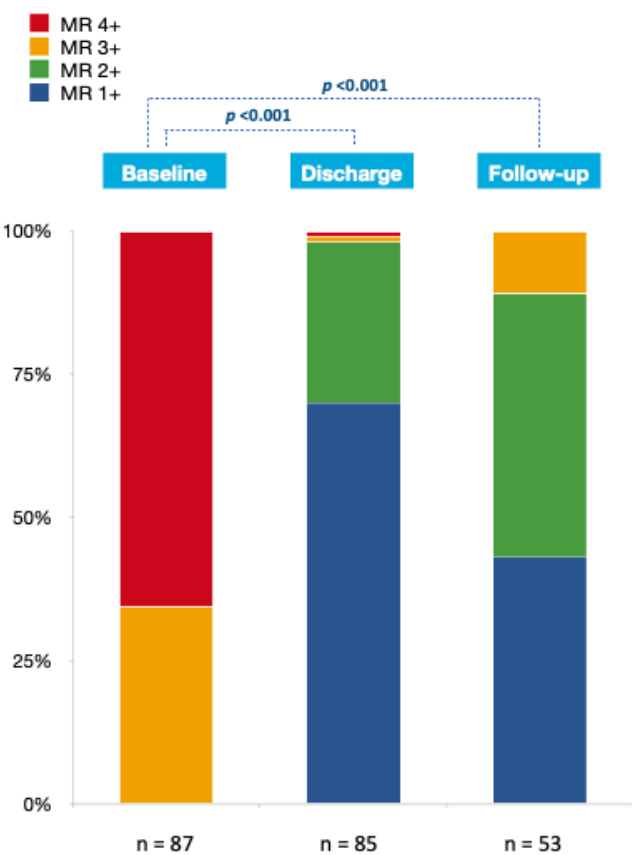
All-Cause mortality at 1 year



At Risk				
aSMR	53	50	49	29
vSMR	360	349	292	183

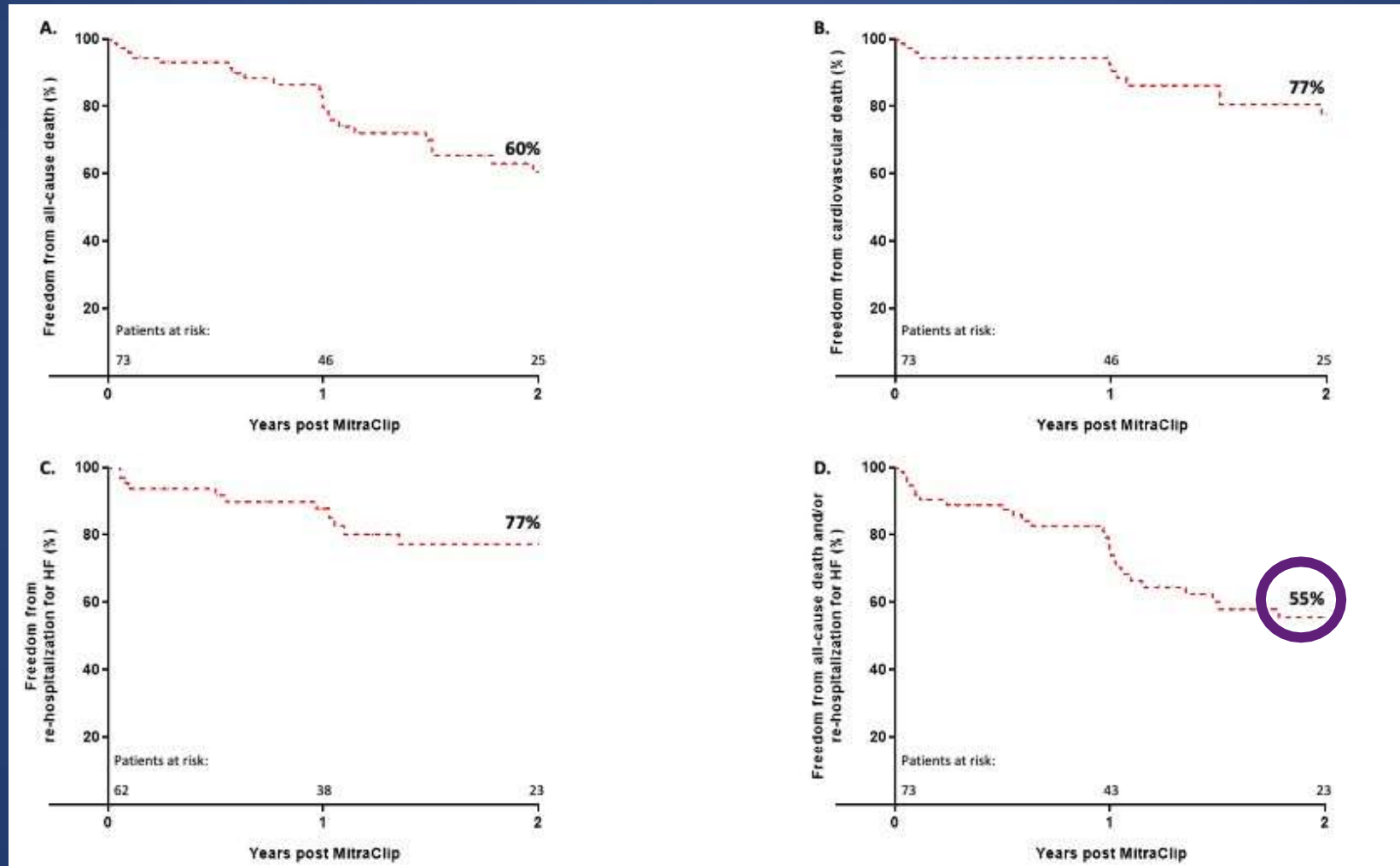
TEER in Atrial FMR : MITRA-TUNE

N=87 (7.6% of FMR), LV EF \geq 50%, LVEDD <55mm, AF
81 YO, 61% female, STS 4%



TEER in Atrial FMR : MITRA-TUNE

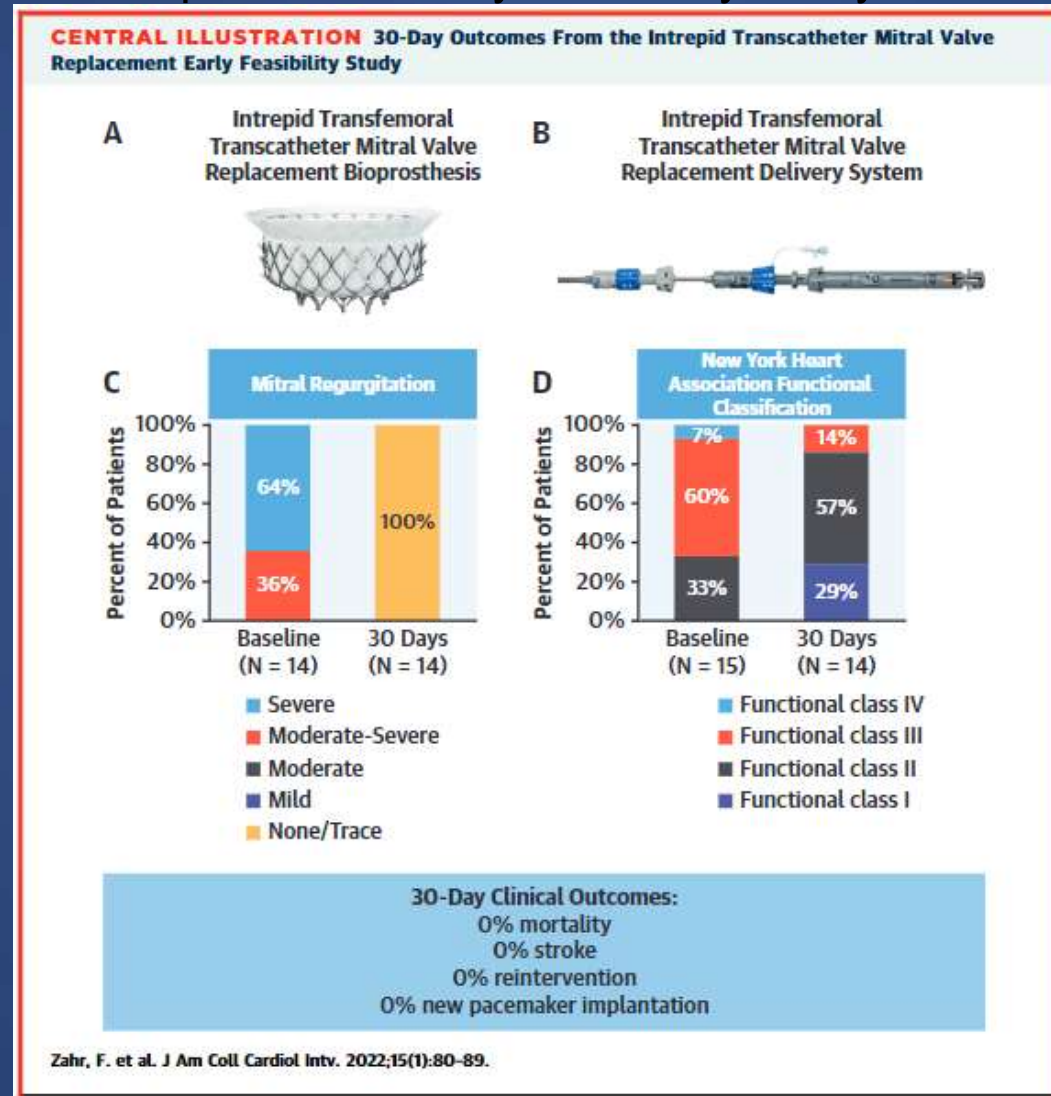
83% device success, 2% in-hospital death, 5% 30-day mortality



Transcatheter Mitral Valve Replacement (TMVR)

APOLLO Trial

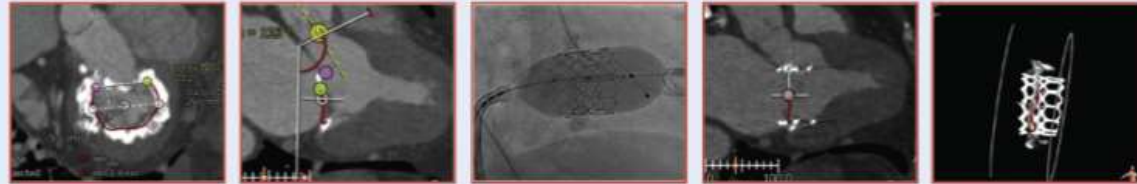
30-Day Outcomes Following Transfemoral TMVR Intrepid TMVR Early Feasibility Study Result



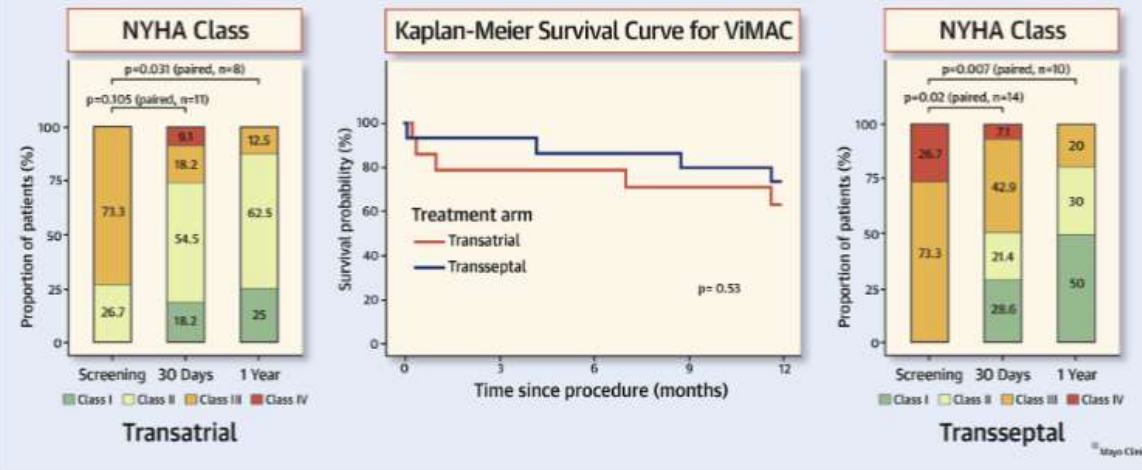
MITRAL Trial

Prospective Study of TMVR Using Balloon-Expandable Aortic Transcatheter Valves in MAC

CENTRAL ILLUSTRATION 30-Day and 1-Year Outcomes of Valve-in-Mitral Annular Calcification in the Mitral Implantation of Transcatheter Valves Trial



Transseptal ViMAC 30-day mortality=6.7%
 Transatrial ViMAC 30-day mortality=21.4%
 Similar all-cause mortality at 1 year
 Sustained improvement of symptoms at 1 year in both groups



Guerrero, M. et al. *J Am Coll Cardiol Interv.* 2021;14(8):830-45.

Early and late outcomes for functional capacity (New York Heart [NYHA] Association functional class) in the transatrial group (left) and transseptal group (right) and for survival (middle). ViMAC = valve-in-mitral annular calcification.

Ongoing Clinical Trials

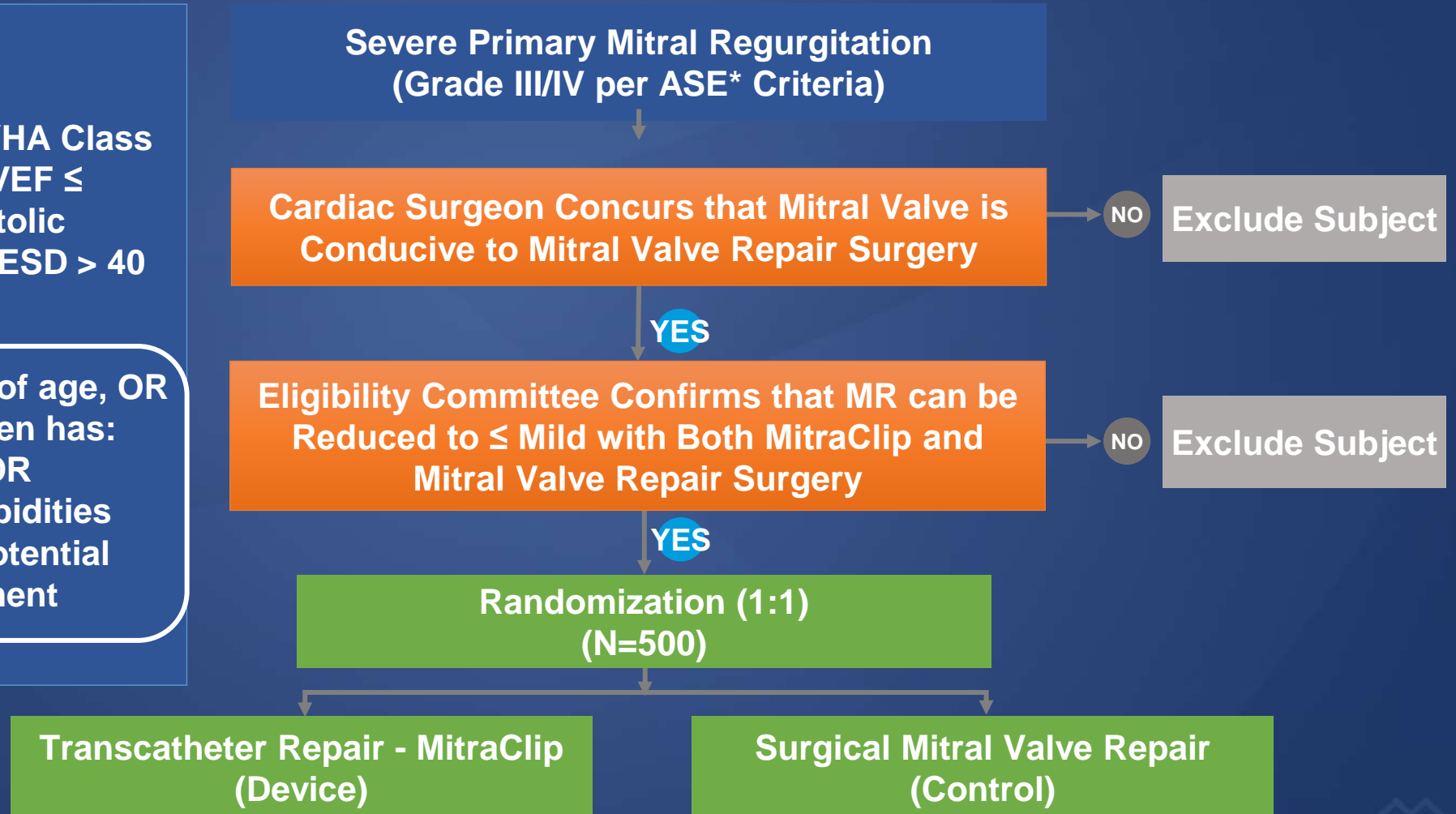
REPAIR MR

MitraClip vs. Surgery for Moderate Surgical Risk

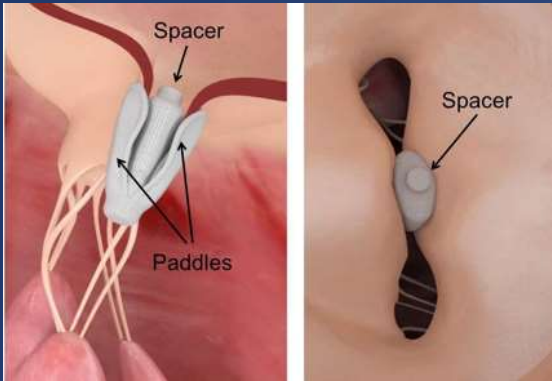
Primary Endpoint: Death, Stroke, Cardiac Hospitalization, AKI requiring RRT at 2 yrs

Patient Population

- Subject is symptomatic (NYHA Class II/III/IV) or asymptomatic (LVEF \leq 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 \geq 2%, OR
 - Presence of other comorbidities which may introduce a potential surgical specific impediment



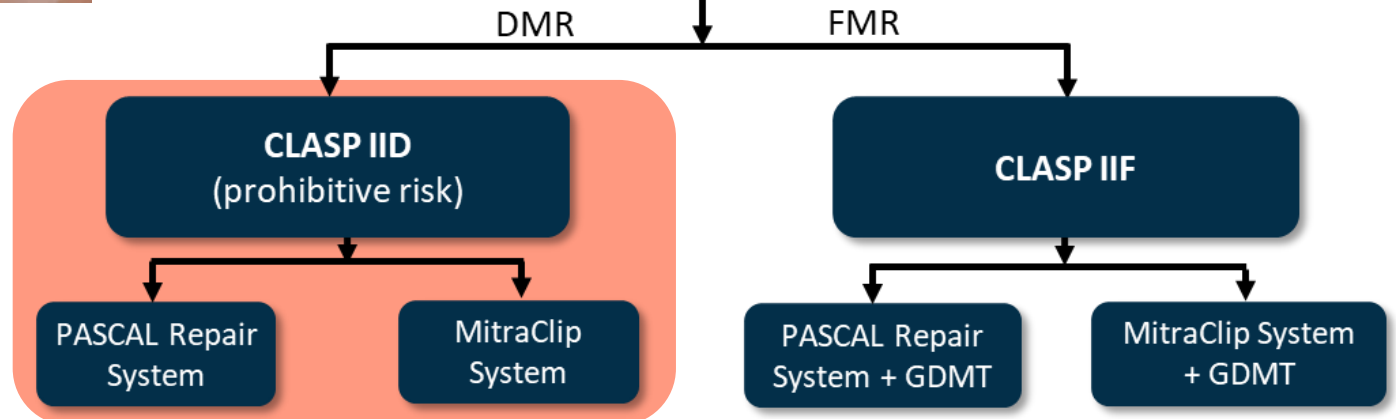
CLASP IID RCT (PASCAL)



Patients with Clinically Significant Mitral Regurgitation N=1275

Heart Team Assessment

- MR 3+ to 4+ as assessed by echo core lab
- Eligible for transcatheter mitral valve repair
- Patient suitable for both devices



Follow-up: 30 days, 6 months, 1 year and annually through 5 years

Primary Endpoints, Non-Inferiority

- MR severity reduction at 6 months
- Major adverse events (MAEs) at 30 days

Primary Endpoints, Non-Inferiority

- All-cause mortality and HF rehospitalization at 2 years
- Major adverse events (MAEs) at 30 days

Currently Enrolling | Approved and Enrolling Soon

NCT03706833

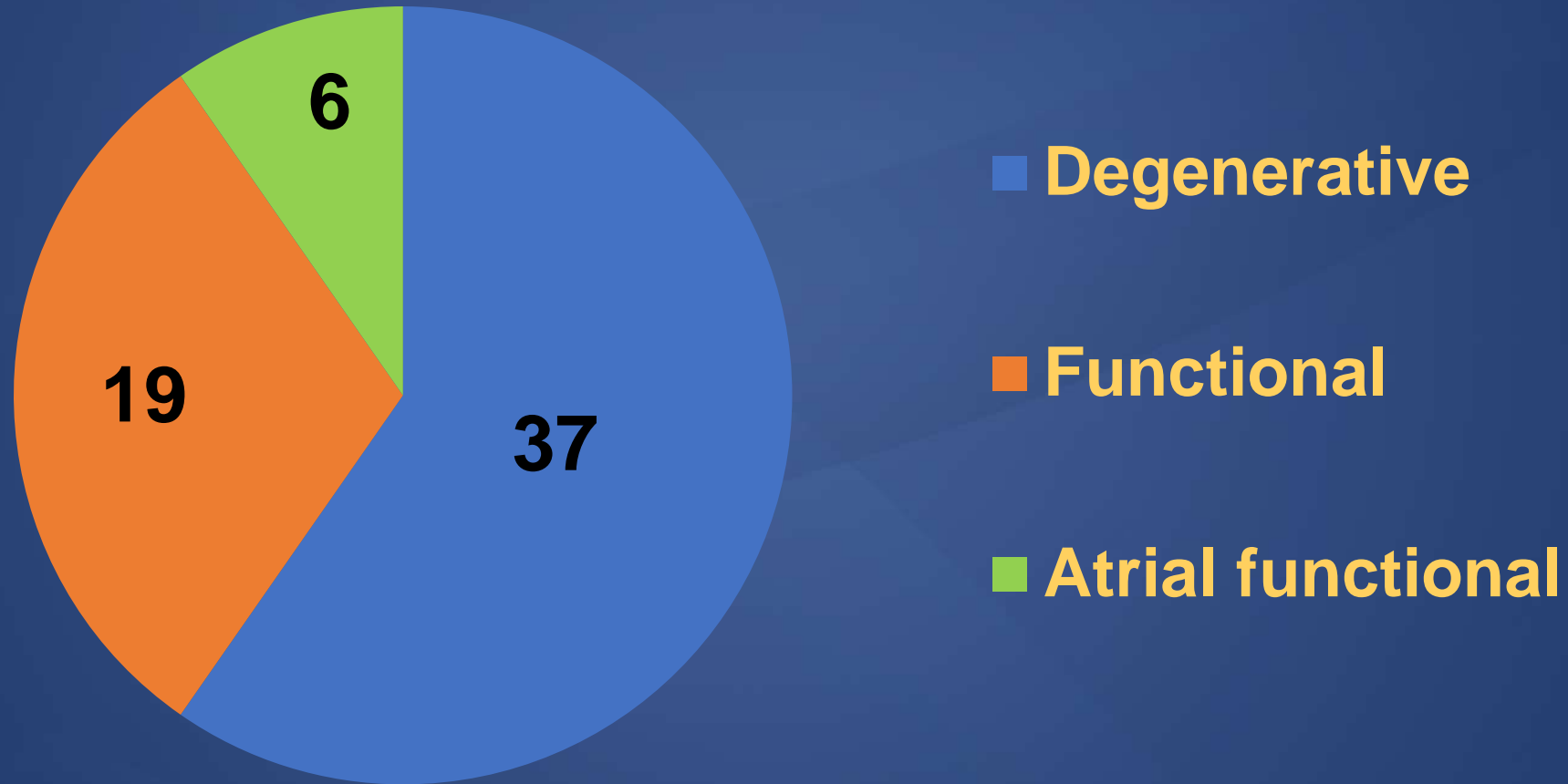
PI : Scott Lim, MD, Robert Smith MD., Linda Gillam, MD

Summary : Clinical Update of MitraClip

- Real-world registries showed higher efficacy, safety, and durability with contemporary MitraClip G4 devices.
- Obtaining optimal MR reduction was the key for better long-term clinical outcome.
- Reduction of MR seems more important than reducing transmitral gradient, especially in secondary MR patients.
- MitraClip is trying to widen its indication to moderate-risk primary MR or atrial functional MR.
- Another strong competitor (PASCAL) is coming.

Asan Medical Center Experience

MitraClip Indication in AMC (N=87)



10 among 15 patients with ischemic CMP had posterolateral wall akinesia

Mitraclips Used in AMC

	Primary MR N=37	Secondary MR N=25
Median number of clips	1.6	1.8
1 clip implanted	14 (38%)	6 (24%)
2 clips implanted	22 (59%)	16 (64%)
3 clips implanted	1 (3%)	1 (4%)
First clip used in G4 era		
Wide clips (NTW/XTW)	15	20
Narrow clips (NT/XT)	5	0

“G4” Clips Used in AMC

	Primary MR N=20	Secondary MR N=20
First Clip		
NTW	7 (35%)	3 (15%)
XTW	8 (40%)	17 (85%)
NT	1 (5%)	
XT	4 (20%)	
Second Clip	11	14
NTW	4 (36%)	7 (50%)
XTW	2 (18%)	2 (14%, Atrial)
NT	2 (18%)	4 (29%)
XT	3 (27%)	1 (7%)