Next Round of Transcatheter Mitral Trials

Are RCTs Between TEER and TMVR Necessary?

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Mount Sinai Heart

Relevant Disclosures

Consultant or equity/options: Valfix, Neovasc, Ancora, HighLife, Cardiac Success

Institutional grants: Abbott

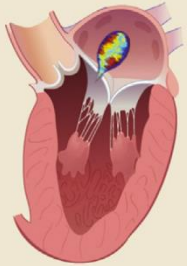
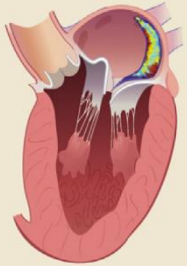
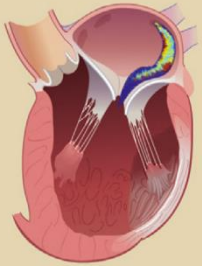
Classification of Mitral Regurgitation

Primary MR

AKA degenerative or organic

Secondary MR

AKA functional

Carpentier Type I	Carpentier Type II	Carpentier Type IIIa	Carpentier Type IIIb
(normal leaflet motion and position)	(excess leaflet motion)	(restricted leaflet motion in systole and diastole)	(restricted leaflet motion in systole)
 Leaflet Perforation Cleft	 Mitral Valve Prolapse	 Rheumatic Valve Disease Mitral Annular Calcification Drug Induced MR	
 Atrial MR  Nonischemic Cardiomyopathy			 Ischemic Cardiomyopathy

El Sabbagh A. et al. JACC Img. 2018;11:628-43

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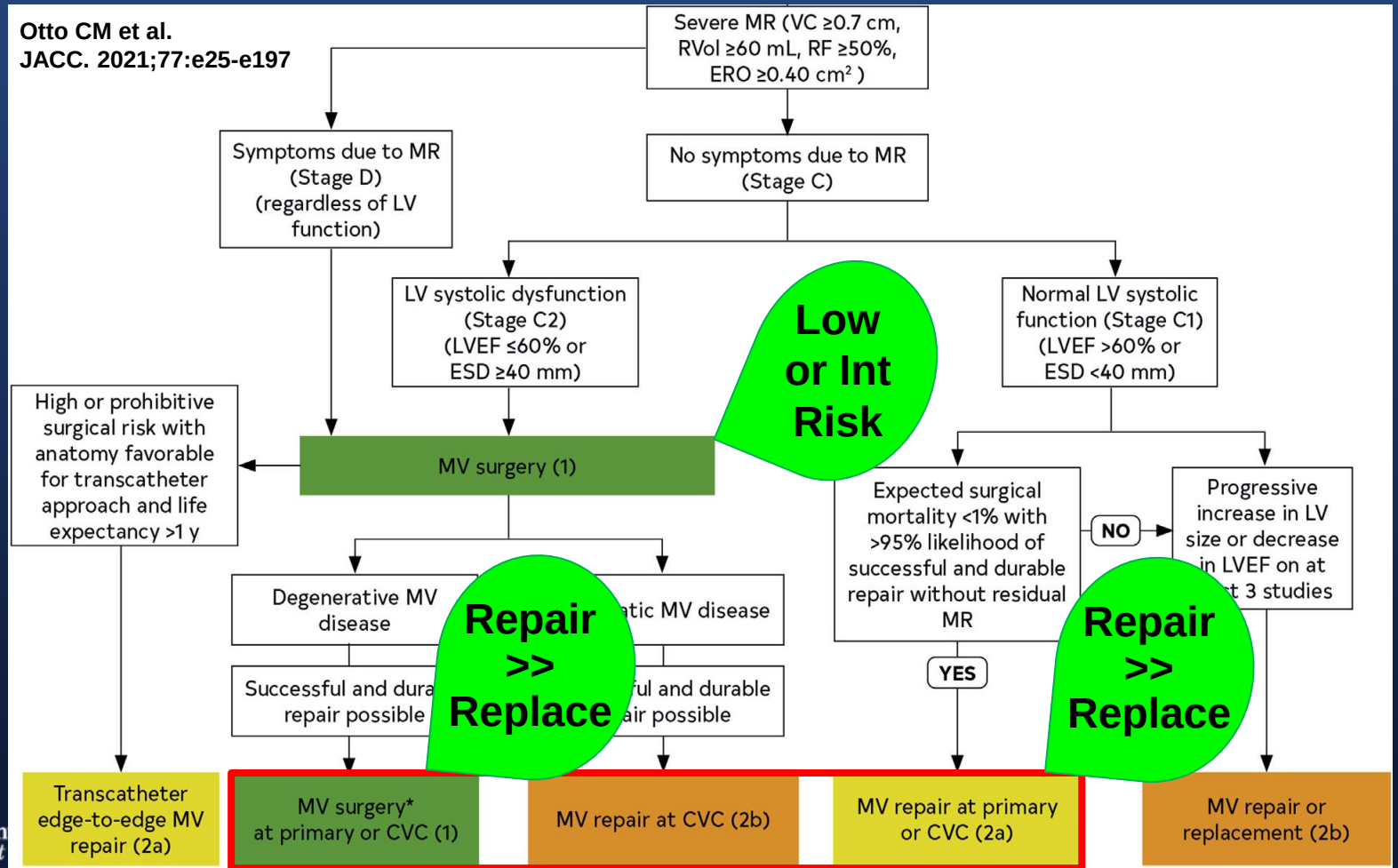
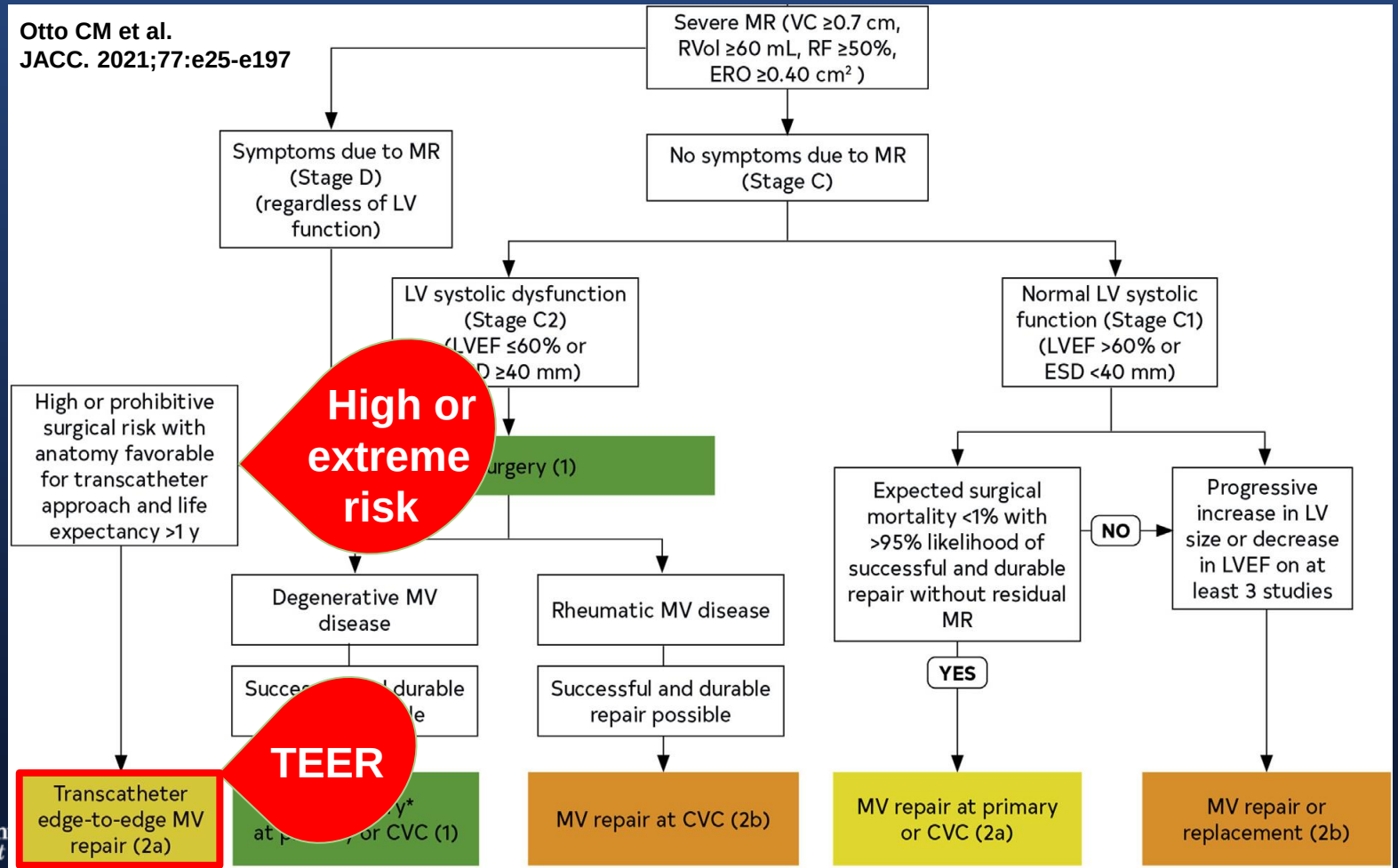
Primary MR: Surgical and TEER Treatment



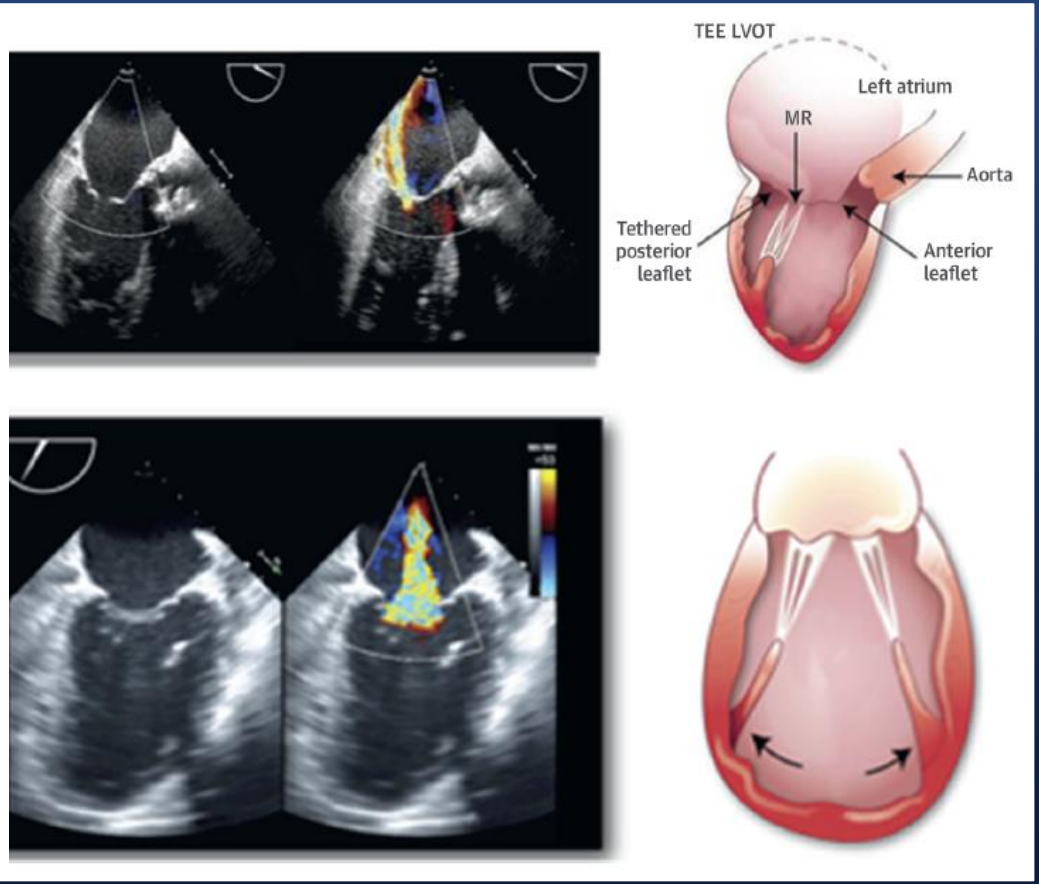
Primary MR: Surgical and TEER Treatment



Secondary (Functional) MR: The disease is the LV!

Ischemic cardiomyopathy

Idiopathic dilated cardiomyopathy



~10% atrial FMR
1˚ annular dilatation

Asgar, Mack, Stone. J Am Coll Cardiol 2015;65:1231–48

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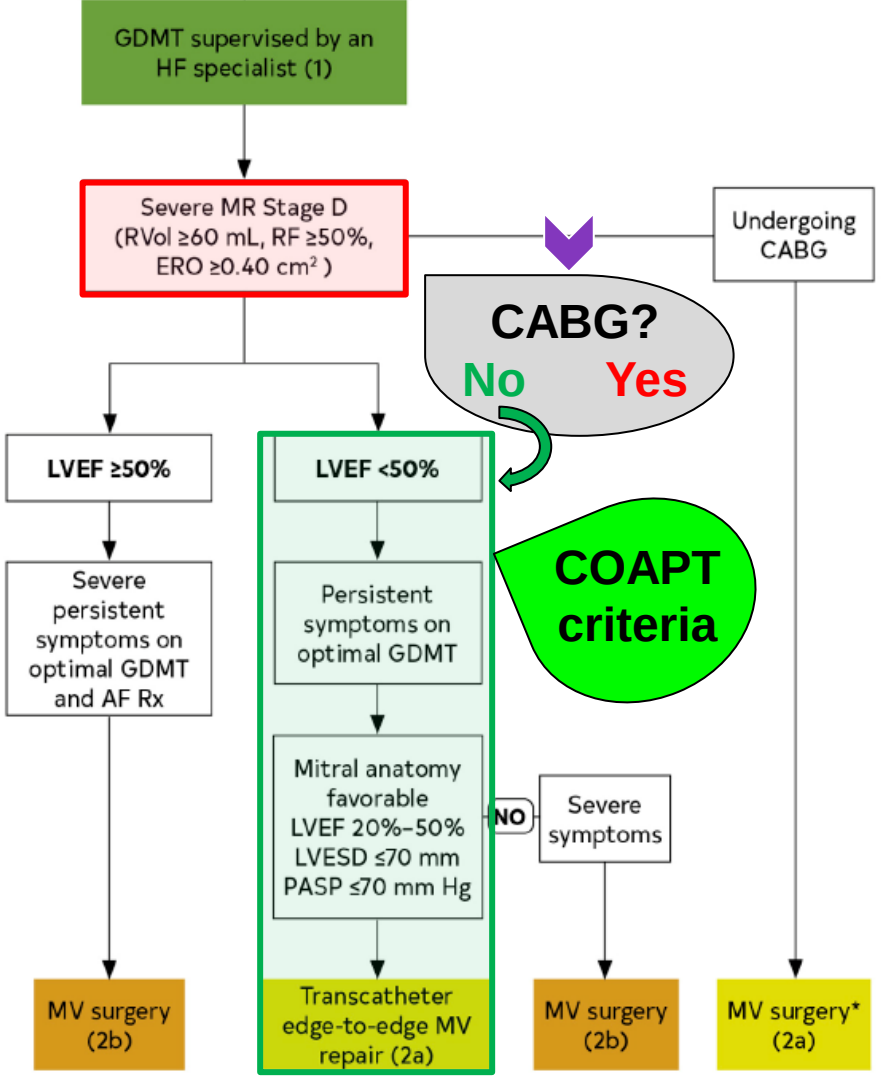
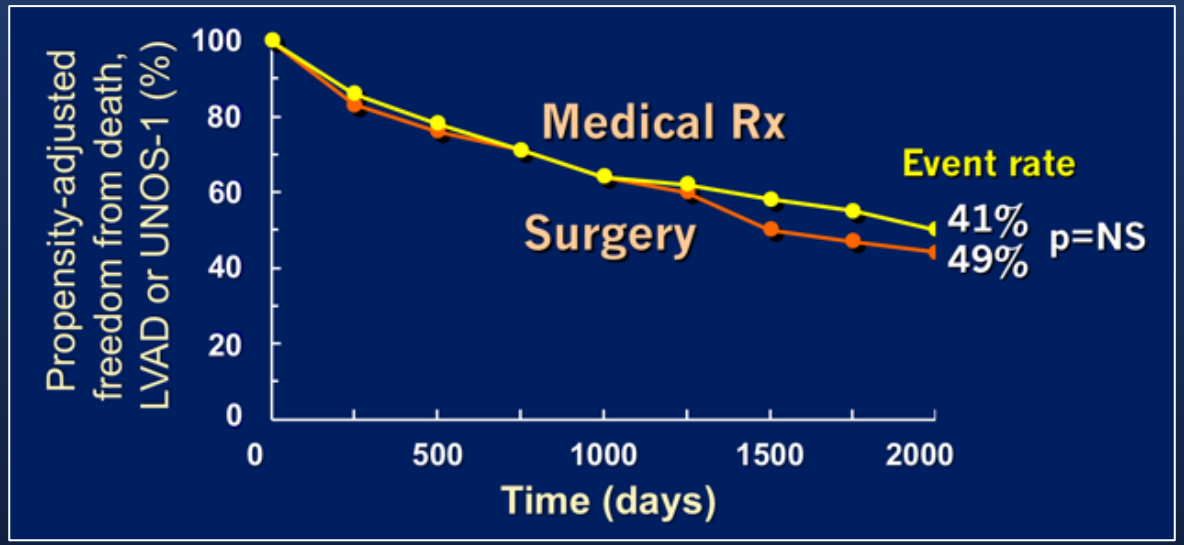
Secondary MR: Medical, TEER and Surgical Treatment



Otto CM et al. JACC 2021;77:e25-e197

Impact of Mitral Valve Annuloplasty for FMR

MV annuloplasty (with mostly flexible rings) was performed in 126 of 419 pts with 3+ - 4+ MR and LVEF ≤30% between 1995 and 2002 at the University of Michigan



Mortality was 38% vs. 48% in the medical vs. surgical groups respectively (p=NS) – including 4.8% 30-day surgical mortality

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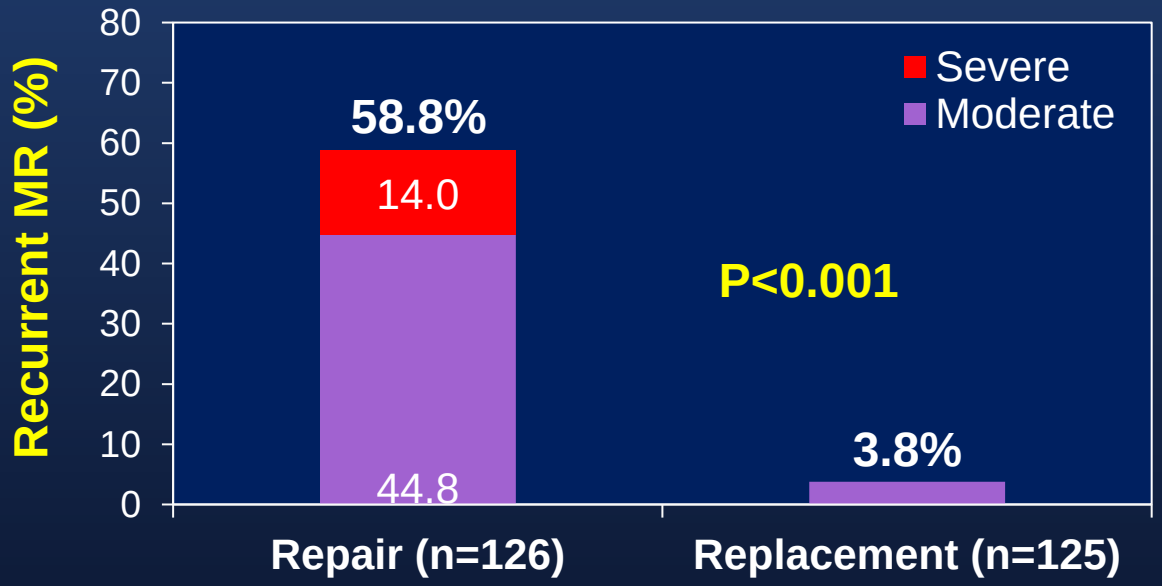
Wu AH et al. J Am Coll Cardiol 2005;45:381-387

CTSN Severe IMR Trial

251 pts with severe ischemic FMR were randomized to MV repair with rigid or semi-rigid complete downsized annuloplasty rings vs. chordal-sparing MV replacement; mean EROA ~0.40 cm^2, LVEF ~41%; 75% concomitant CABG. Primary endpoint = ΔLVESVI.



There were no significant 2-year differences in:

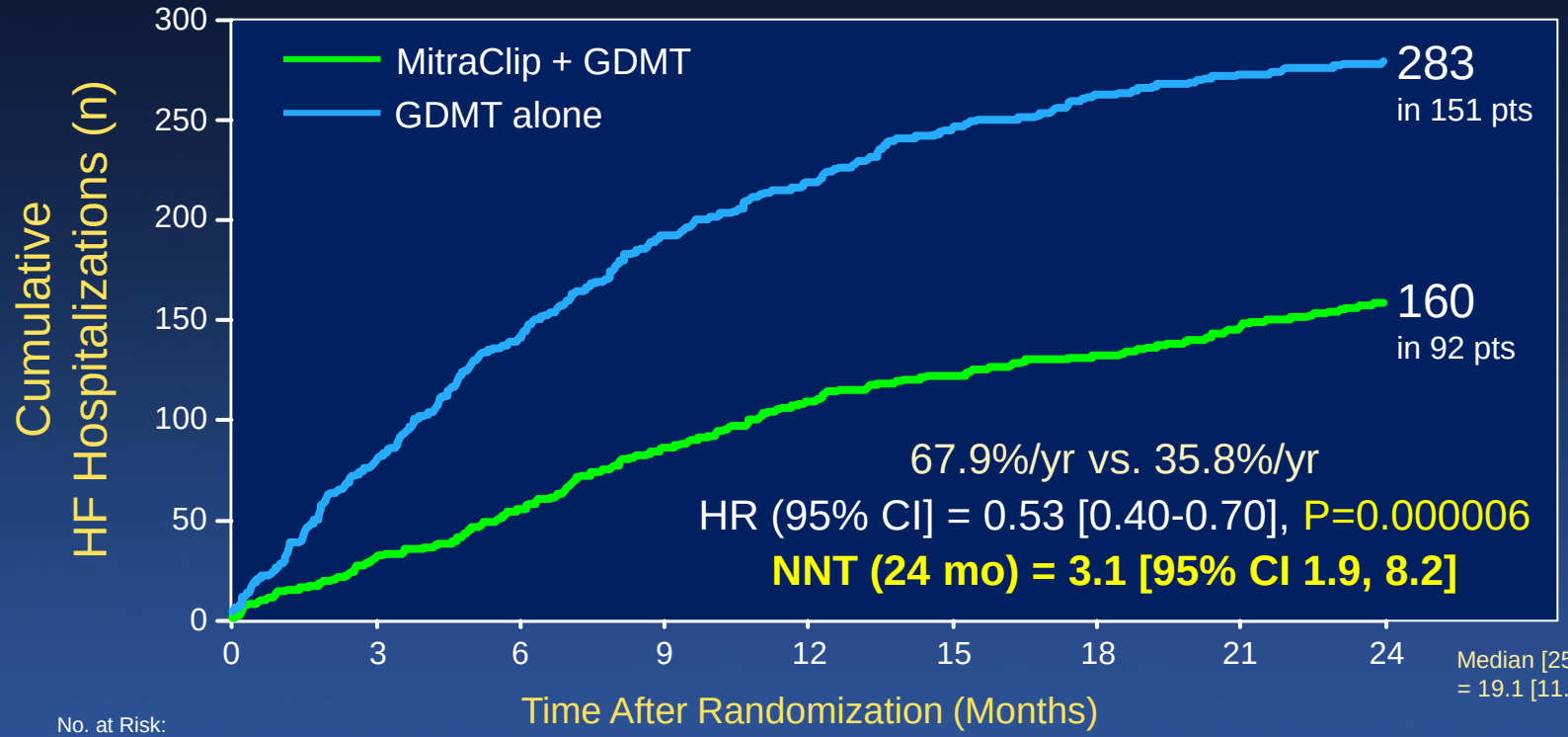
- LVESVI
- NYHA class
- SF-36 scores
- MLHF scores
- MV reoperation
- Death
- MACE

Goldstein D et al. NEJM 2016;374:344-353

COAPT TRIAL

Primary Effectiveness Endpoint

All Hospitalizations for HF within 24 months



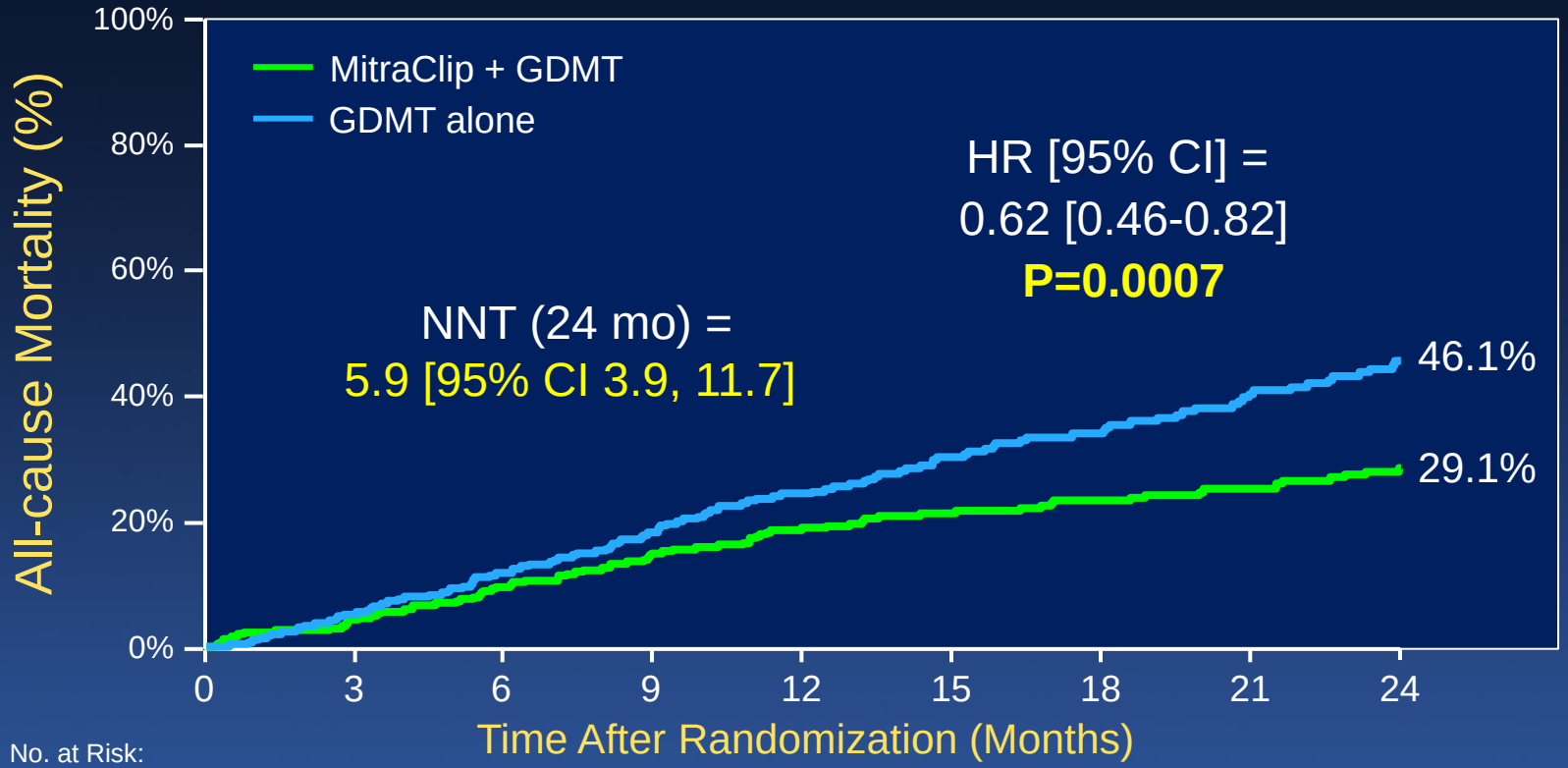
Median [25%, 75%] FU = 19.1 [11.9, 24.0] mos

No. at Risk:

MitraClip	302	286	269	253	236	191	178	161	124
GDMT	312	294	271	245	219	176	145	121	88

COAPT TRIAL

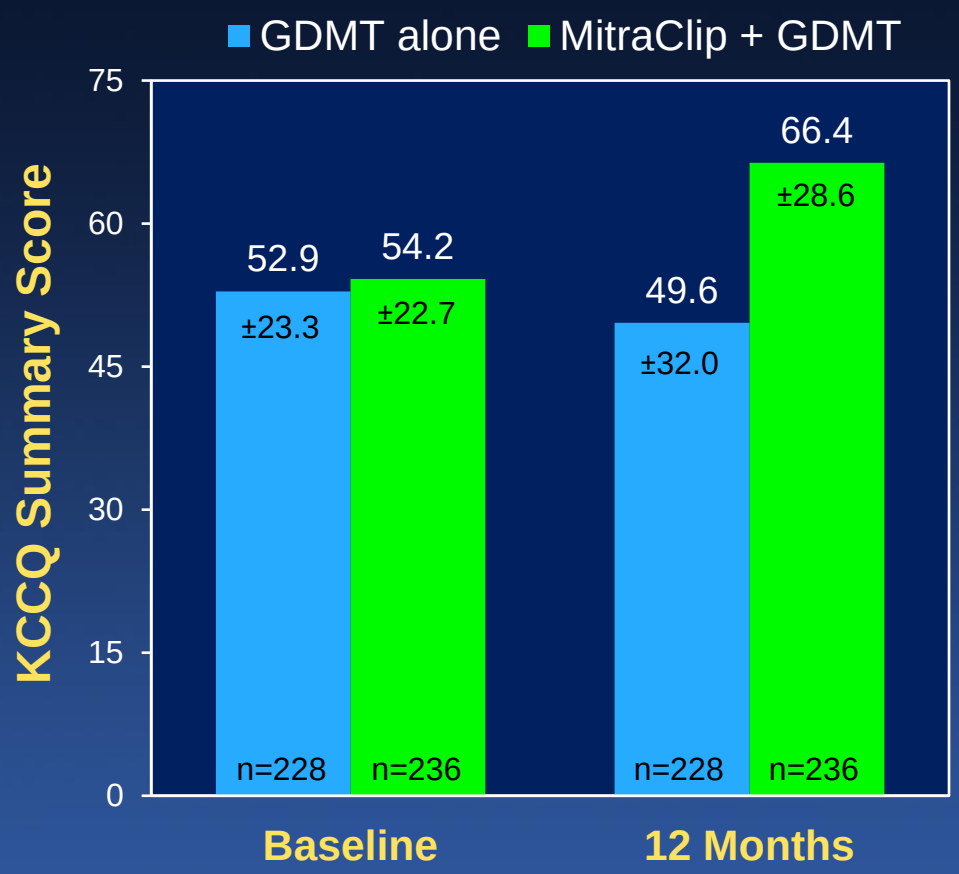
All-cause Mortality

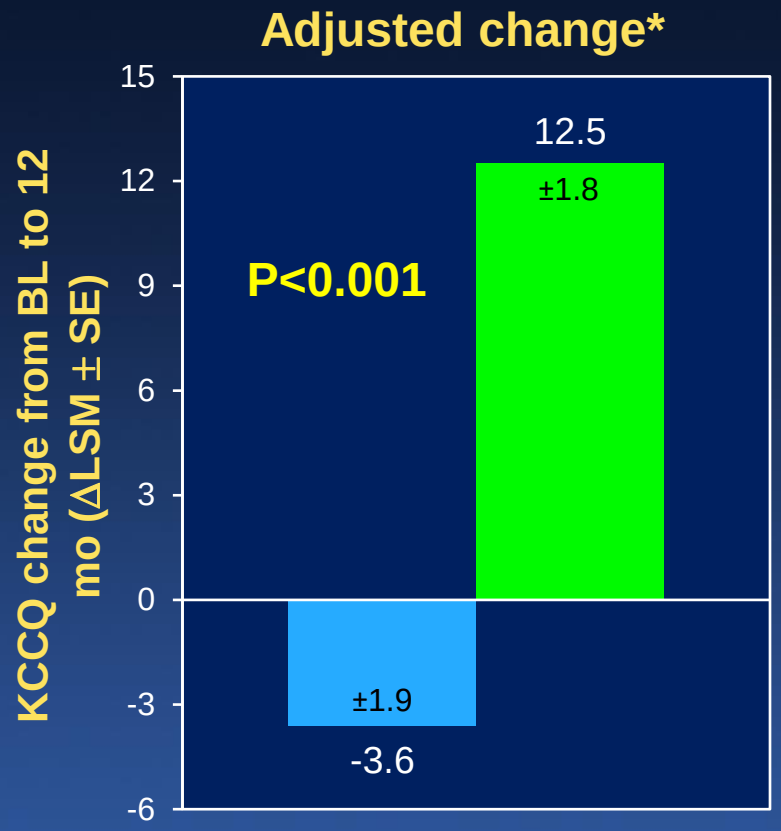


No. at Risk:									
MitraClip + GDMT	302	286	269	253	236	191	178	161	124
GDMT alone	312	294	271	245	219	176	145	121	88

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

Change in KCCQ from Baseline to 12 Months





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

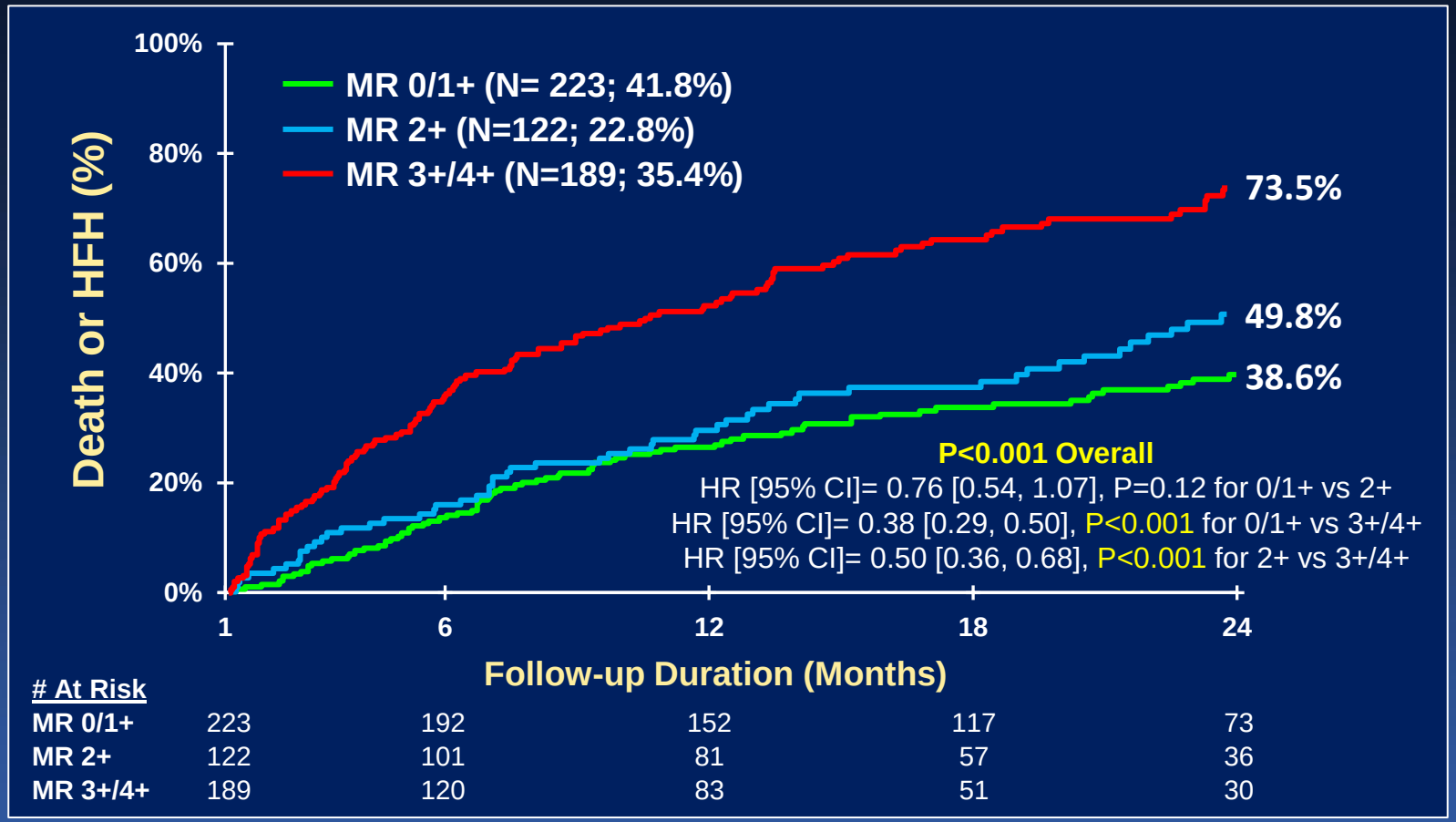
*Ancova

COAPT TRIAL

Time to Death or First HF Hosp

Pooled population, stratified by 30-day residual MR

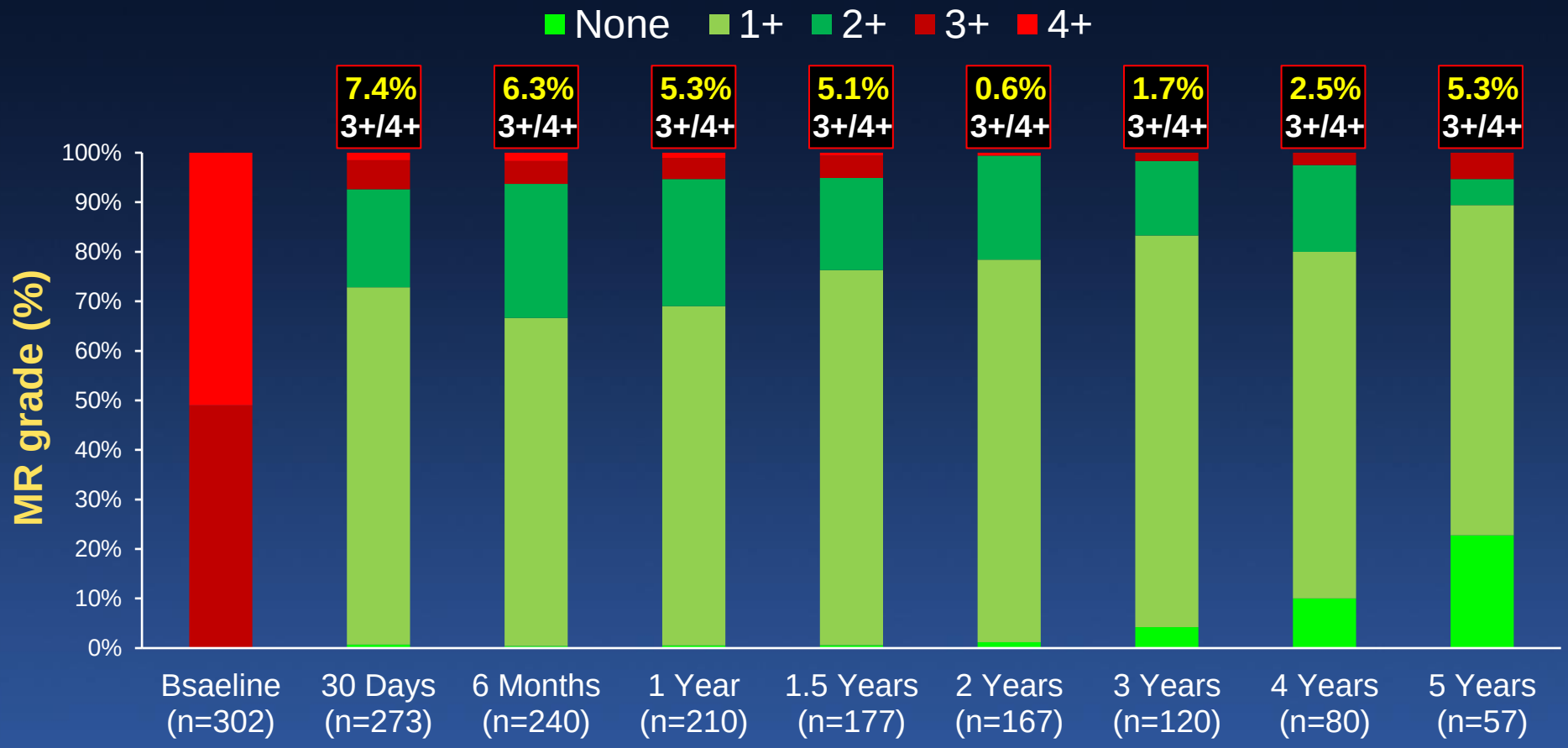
Kar S et al. Circulation. 2021;144:426-37



# At Risk					
MR 0/1+	223	192	152	117	73
MR 2+	122	101	81	57	36
MR 3+/4+	189	120	83	51	30

COAPT TRIAL

MR Severity (Core Lab) – MitraClip Group



Stone GW et al. NEJM 2023;388:2037-48

COAPT TRIAL

Primary Safety: Outcomes Through 5 Years

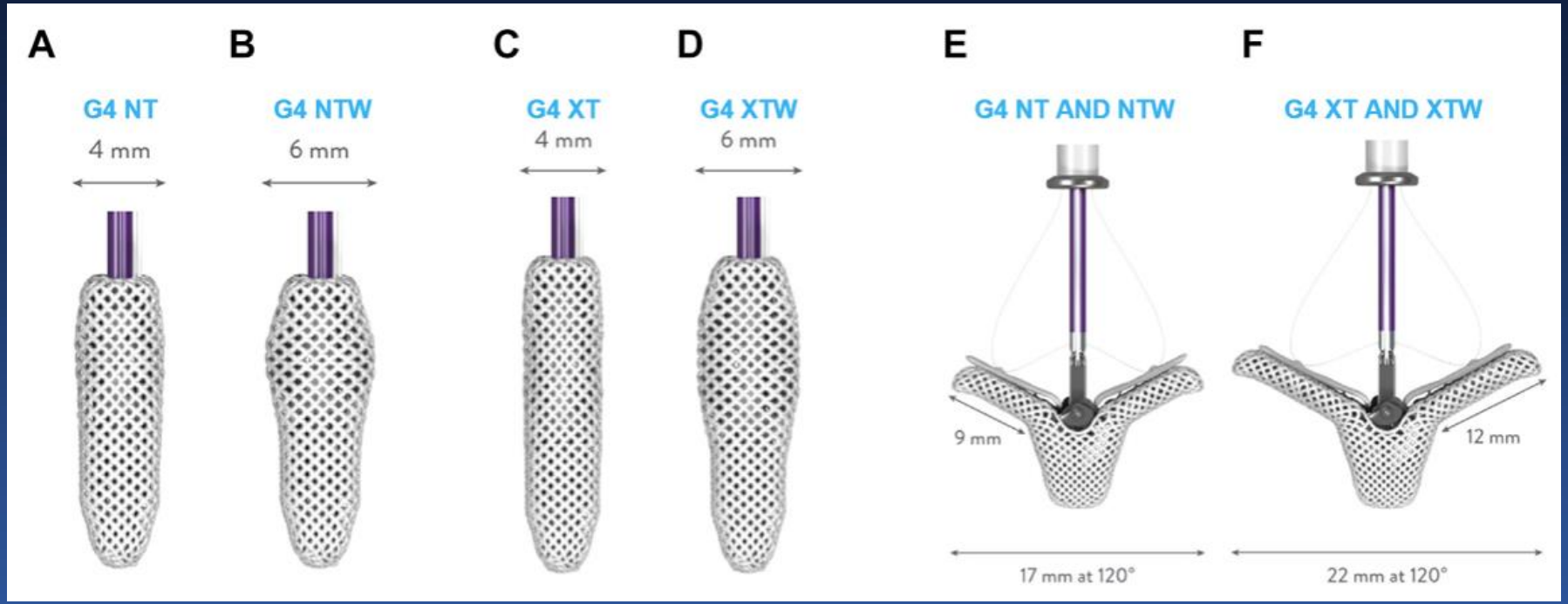
MitraClip implant attempts (n=293)	30 Days	12 Months	24 Months	36 Months	48 Months	60 Months
All safety events	4 (1.4)	9 (3.3)	13 (5.2)	20 (8.8)	22 (10.1)	23 (10.8)
Device-specific events	4 (1.4)	4 (1.4)	4 (1.4)	4 (1.4)	4 (1.4)	4 (1.4)
- SLDA	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)
- Device embolization	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
- Endocarditis requiring surgery	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Mitral stenosis* requiring surgery	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Any device-related complication requiring non-elective CV surgery	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Progressive HF unrelated to device complications	0 (0.0)	5 (2.0)	9 (3.8)	16 (7.5)	18 (8.8)	19 (9.5)
- LVAD	0 (0.0)	3 (1.2)	6 (2.6)	11 (5.1)	12 (5.8)	13 (6.5)
- Heart transplantation	0 (0.0)	2 (0.8)	3 (1.3)	7 (3.4)	9 (4.7)	9 (4.7)

SLDA = single leaflet device attachment. LVAD = left ventricular assist device. *Mitral valve area <1.5 cm^2 by echo core laboratory measurement.

1-Year Outcomes From the EXPAND G4 Registry

1,164 subjects underwent M-TEER with MitraClip G4 from 2020 to 2022

43% primary MR, 57% secondary MR; mean STS-PROM$_{MVR}$ = 7.6%



von Bardeleben RS et al. JACC CV Interv 2023;21:2600-10

1-Year Outcomes From the EXPAND G4 Registry

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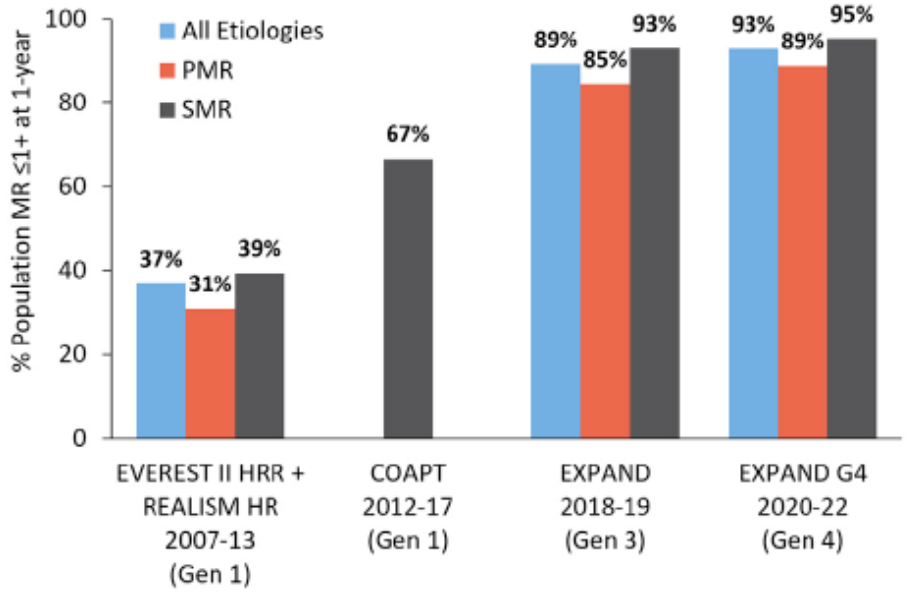
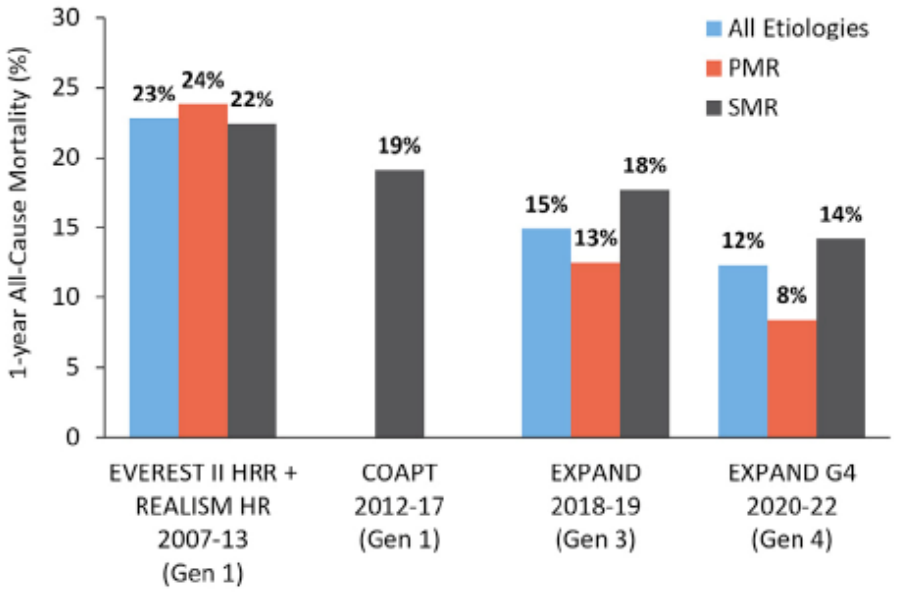
A 1-Year MR Reduction to ≤1+ Over Time with TEER



B 1-Year Mortality Rate Over Time with TEER



von Bardeleben RS et al. JACC CV Interv 2023;21:2600-10

One-Year Outcomes of Transfemoral TMVR: Intrepid EFS

33 subjects (from 234 screened) underwent TMVR with TF-Intrepid from 2020-2022

61% primary MR, 39% secondary MR; mean STS-PROM$_{MVR}$ = 5.3%

	In-hospital or 30 days	1 year
Delivery catheter insertion to removal	Median 42.5 min	-
Implant success	31/33 (93.9%) - (1 Surg MVR, 1 TEER)	-
ASD closure	74.5%	-
Mean post-TMVR LOS	5 days	-
MR ≤1+	100% (90% ≤ trace)	100% (96% ≤ trace)
PVL >trace	0%	0%
MVG	Mean 4.9 mmHg	Mean 4.6 mmHg
KCCQ↑ (paired)	10.2 points	11.4 points

Firas F et al. JACC CV Interv 2023 Oct 10:S1936-8798(23)01357-2.

One-Year Outcomes of Transfemoral TMVR: Intrepid EFS

33 subjects (from 234 screened) underwent TMVR with TF-Intrepid from 2020-2022

61% primary MR, 39% secondary MR; mean STS-PROM$_{MVR}$ = 5.3%

	30 days	1 year
Death	0%	6.7%
Stroke	0%	0%
MI	3.0%	6.4%
Major vasc compls	24.2%	24.2%
LVOT	12.1% (1 MV surgery)	0%
Surgical MVR	6.1% (1 other valve emboliz)	6.1%
TEER	3.0%	3.0%
Hemolysis	3.0%	3.0%
Device thrombosis	0%	3.4%
Endocarditis	0%	6.8%
DVT/PE	12.1%	12.1%
Major bleeding	27.3%	30.9%
New PM/CRT/ICD	3.0%	14.7%
CV rehospitalization	6.1%	22.3%

6 mo OAC

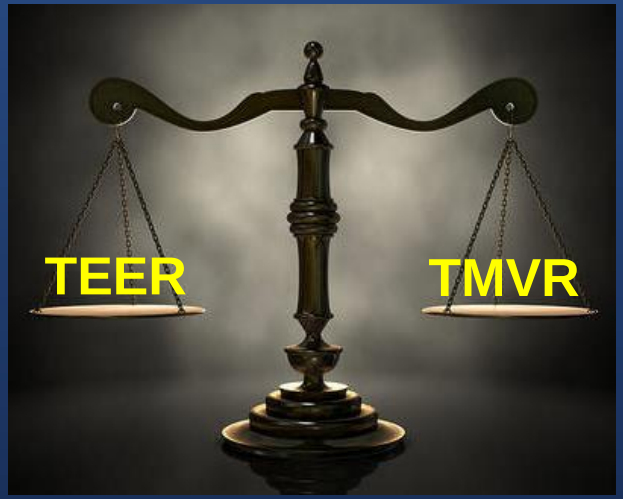
Firas F et al. JACC CV Interv 2023 Oct 10:S1936-8798(23)01357-2.

PRO

- Very safe
- Excellent clinical outomes

CON

- Procedure can be complex
- MR ≥2+ in ~10-20%
- Deforms MV



PRO

- Procedure can be quick
- Reliably eliminates MR

CON

- More exclusion criteria
- More procedural (and ? late) complications
- Need for chronic anticoagulation

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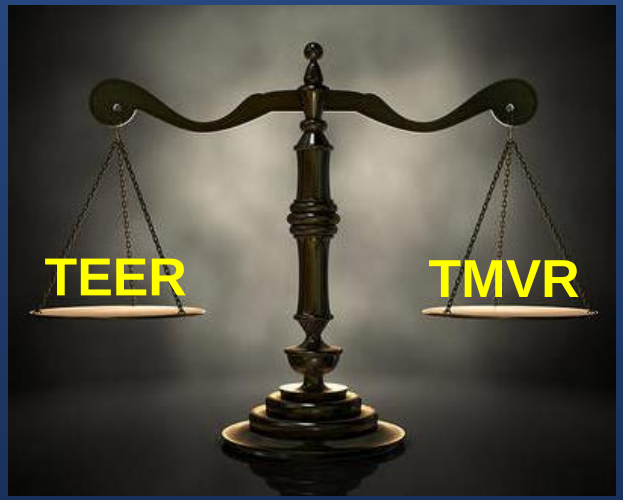


Are RCTs Between TEER and TMVR Necessary?

OF COURSE THEY ARE!

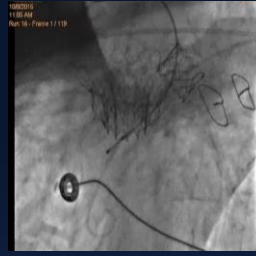
(what did you think I was going to say?)

Implications of COAPT for TMVR to Treat Secondary MR in Heart Failure

Given the likelihood of greater procedural complications and the need for chronic oral anticoagulation with TMVR compared with M-TEER, TMVR must be shown to be more effective than M-TEER in COAPT-eligible pts, and/or more effective than GDMT alone in COAPT-ineligible pts

But are RCTs of TMVR vs TEER feasible?

APOLLO Trial (NCT03242642)



Evaluate the safety and efficacy of Medtronic Intrepid™ TMVR System in patients with severe symptomatic mitral regurgitation (primary or secondary)

RCT Version 1

Assessment by Multidisciplinary Heart Team
STS PROM ≥3%, EF ≥25% (n=1200)

Roll-ins
120-180

Eligible for surgical procedure
(candidate for MVR – not repair)

Ineligible for surgical procedure

1:1 Randomization
n=300, 400, 500 (adaptive)
(stratified by DMR vs. FMR)

Single-arm Cohort
n=200, 300, 400, 500 (adaptive)
(DMR and FMR)

TMVR

SMVR

Non-inferiority (Bayesian adaptive design)

Non-inferiority (performance goal)

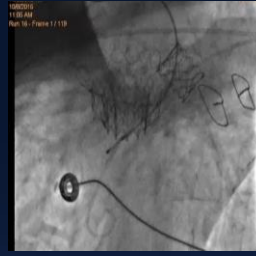
TMVR analysis cohort

TMVR MAC registry

Primary Composite Endpoint:
All-cause mortality, stroke, reoperation (or reintervention) and cardiovascular hospitalization at 1 year

PIs: M. Leon and D. Adams. Chairman: M. Mack. Sponsor: Medtronic

APOLLO Trial (NCT03242642)



Evaluate the safety and efficacy of Medtronic Intrepid™ TMVR System in patients with severe symptomatic mitral regurgitation (primary or secondary)

RCT Version 2

Assessment by Multidisciplinary Heart Team
STS PROM ≥3%, EF ≥25% (n=1200+)

Roll-ins
120-180

Eligible for surgical procedure
(candidate for MVR – not repair)

Ineligible for surgical procedure

1:1 Randomization
n=650
(stratified by DMR vs. FMR)

Single-arm Cohort
n=550+
(DMR and FMR)

TMVR

SMVR or TEER

Non-inferiority (Bayesian adaptive design)

Non-inferiority (performance goal)

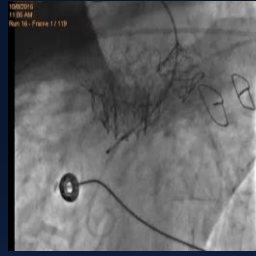
TMVR analysis cohort

TMVR MAC registry

Primary Composite Endpoint:
All-cause mortality, stroke, reoperation (or reintervention) and cardiovascular hospitalization at 1 year

PIs: M. Leon and D. Adams. Chairman: M. Mack. Sponsor: Medtronic

APOLLO Trial (NCT03242642)



Evaluate the safety and effectiveness of the Medtronic Intrepid TMVR system in pts with 3+ or 4+ symptomatic primary or secondary MR

Assessment by multidisciplinary heart team → Not suitable candidates for either surgery or FDA-approved transcatheter MV repair (TEER); LVEF ≥30%

N = 1156

Roll-in cases

TMVR Primary cohort

TMVR MAC cohort

Version 3

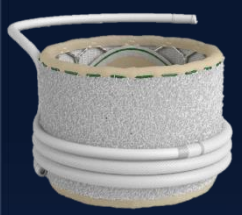
Non-randomized!

Primary 1-year endpoints (objective performance goals)

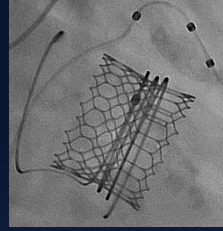
Primary cohort: Composite of all-cause mortality or HF hospitalization (post-30 days) or KCCQ improvement <10 pts

MAC cohort: All-cause mortality

PIs: M. Leon and D. Adams. Chairman: M. Mack. Sponsor: Medtronic



ENCIRCLE Trial (NCT04153292)



Evaluate the safety and effectiveness of the Edwards M3 transseptal TMVR system in pts with 3+ or 4+ symptomatic primary or secondary MR

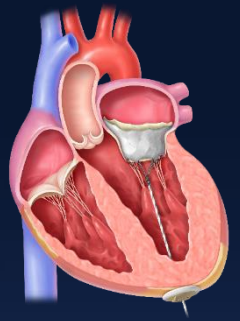
Assessment by multidisciplinary heart team →
Not suitable candidates for either surgery or FDA-approved transcatheter MV repair (TEER)
LVEF ≥30%
N=500

TMVR Primary cohort	TMVR Attempted but failed TEER	TMVR MAC cohort

Primary endpoint (objective performance goal)
All-cause mortality or HF hospitalization at 1 year

PIs: J. Webb, M. Guerrero, D. Daniels. Sponsor: Edwards

SUMMIT Trial (NCT03433274)



Symptomatic 3+ or 4+ primary or secondary MR, or severe mitral annular calcification (MAC)

↓

Heart team deems transcatheter Rx more appropriate than surgery, and anatomy amenable to Tendyne TMVI?

NO → Exclude subject

↓ YES (n=958)

Heart Team deems valve anatomy amenable to transcatheter repair, and meets MitraClip indications?

YES → Randomization (1:1) (N=382)

- Tendyne
- MitraClip

Primary endpoint: Death or HF hosp at 12 mo (non-inferiority)

NO → Severe MAC?

NO → Tendyne (non-randomized cohort) N=313

Primary endpoint: Death or HF hosp at 12 mo

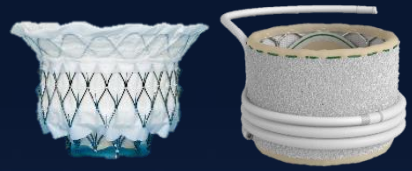
YES → Tendyne (MAC cohort) N=103

Primary endpoint: Death or HF hosp at 12 mo

→ Tendyne (MAC CAP cohort) N=160

PIs: G. Ailawadi, J. Rogers. Sponsor: Abbott

Issues Arising from the TMVR IDE Trial Designs



1. How rigorous will heart teams be in identifying patients that are truly ineligible for M-TEER (or MV surgery)?
   - → Risk of including pts who might benefit from M-TEER (or MV surg)
2. Outside of the trial, patients truly ineligible for M-TEER and MV surgery would be treated with best medical therapy. Why are the single arm groups not randomizing to GDMT? The PARTNER 1B opportunity
3. Given the complexities of TMVR (and TMVr) devices and their complications, can a single-arm study truly gauge their safety and effectiveness compared with standard of care (GDMT)?
   - Are registries with OPC 1˚ endpoints sufficiently precise to support approvals or guide appropriate clinical utilization of class III devices?