Transcatheter Mitral Valve Repair:

Guideline Changes, Evidence Gaps and Future Directions

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and the Cardiovascular Research Foundation

Mount Sinai Heart

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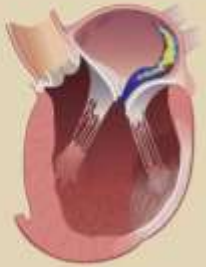
Disclosure Statement

Equity or consulting fees from Neovasc, Ancora, Valfix, Cardiac Success

Classification of Mitral Regurgitation

Primary MR

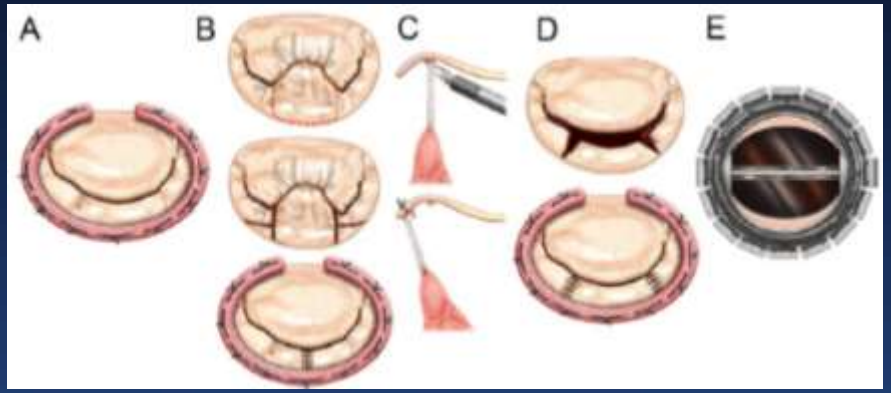
Secondary MR

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

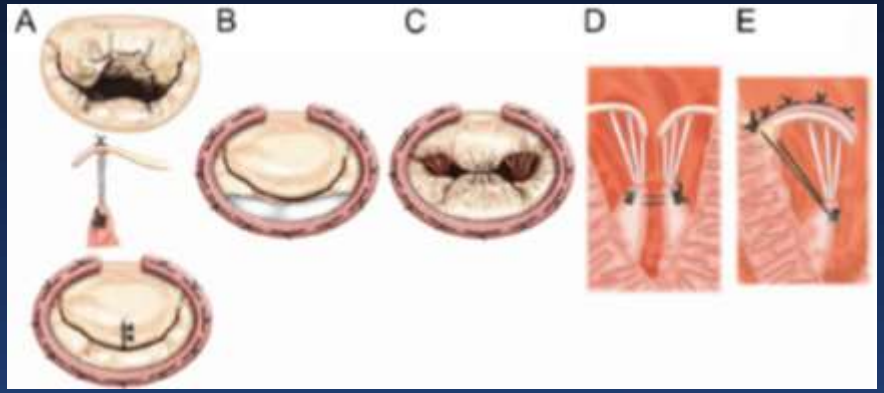
Surgical Techniques for MR

Established techniques



(A) Ring annuloplasty
(B) Quadrangular resection and sliding leaflet plasty
(C) Chordal transfer
(D) Cleft closure
(E) Mitral replacement

Newer techniques

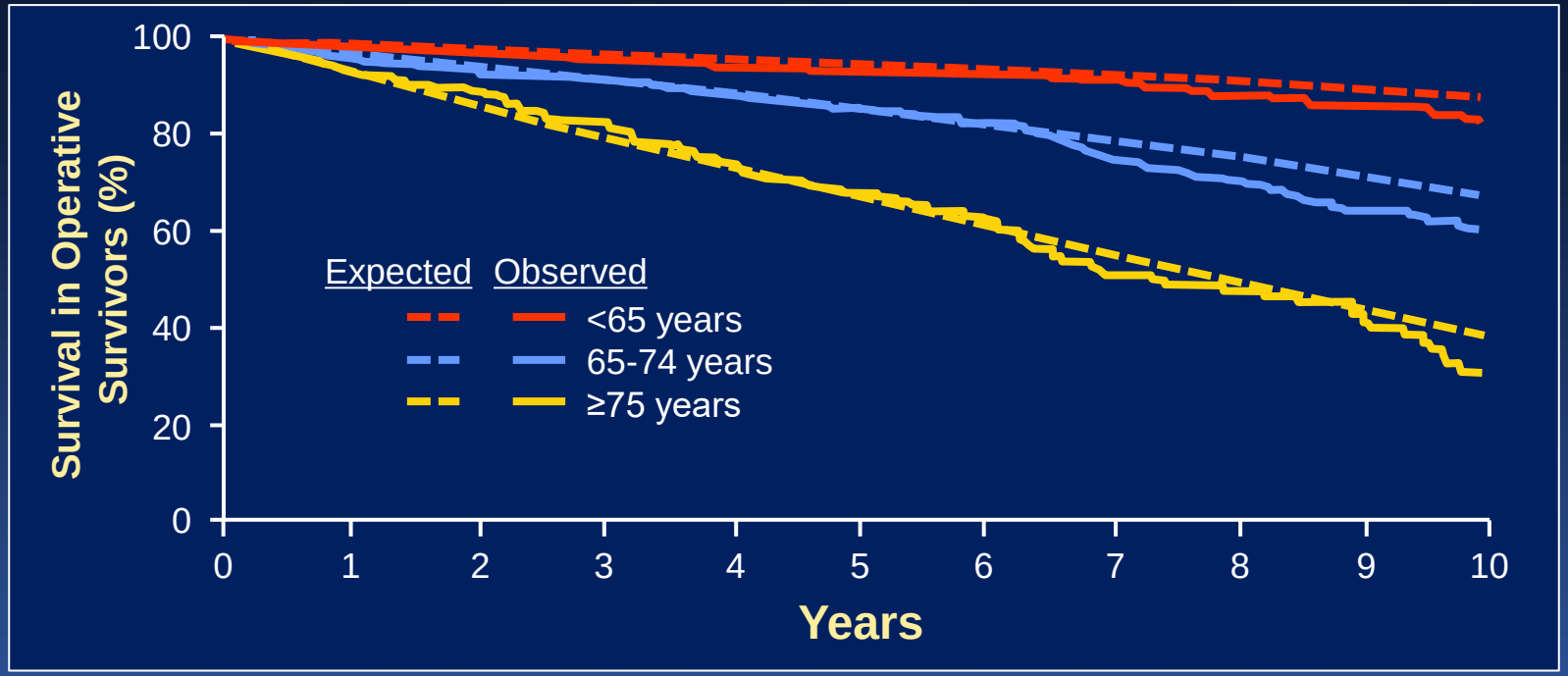


(A) Chordal replacement (PTFE)
(B) Posterior leaflet augmentation
(C) Edge-to-edge Alfieri stitch
(D) Papillary muscle approximation
(E) Posterior wall reduction

Glower DD. JACC 2012;60:1315–22

MV Surgery in Degenerative (Primary) MR

Mayo Clinic 1980-1995, N=856 pts (350 <65 yo, 313 65-74 yo, 193 ≥75 yo)

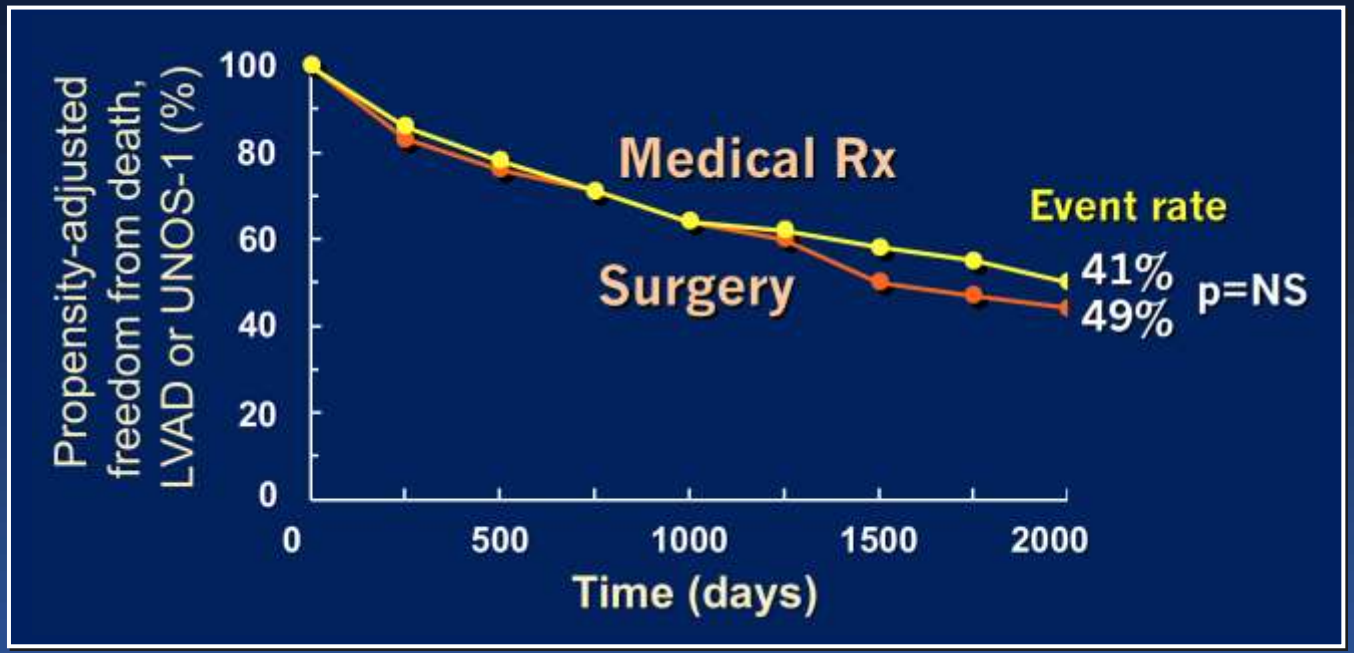


Survival is restored to that expected in pts without DMR

Detaint D et al. *Circulation*. 2006;114:265-72

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 UM

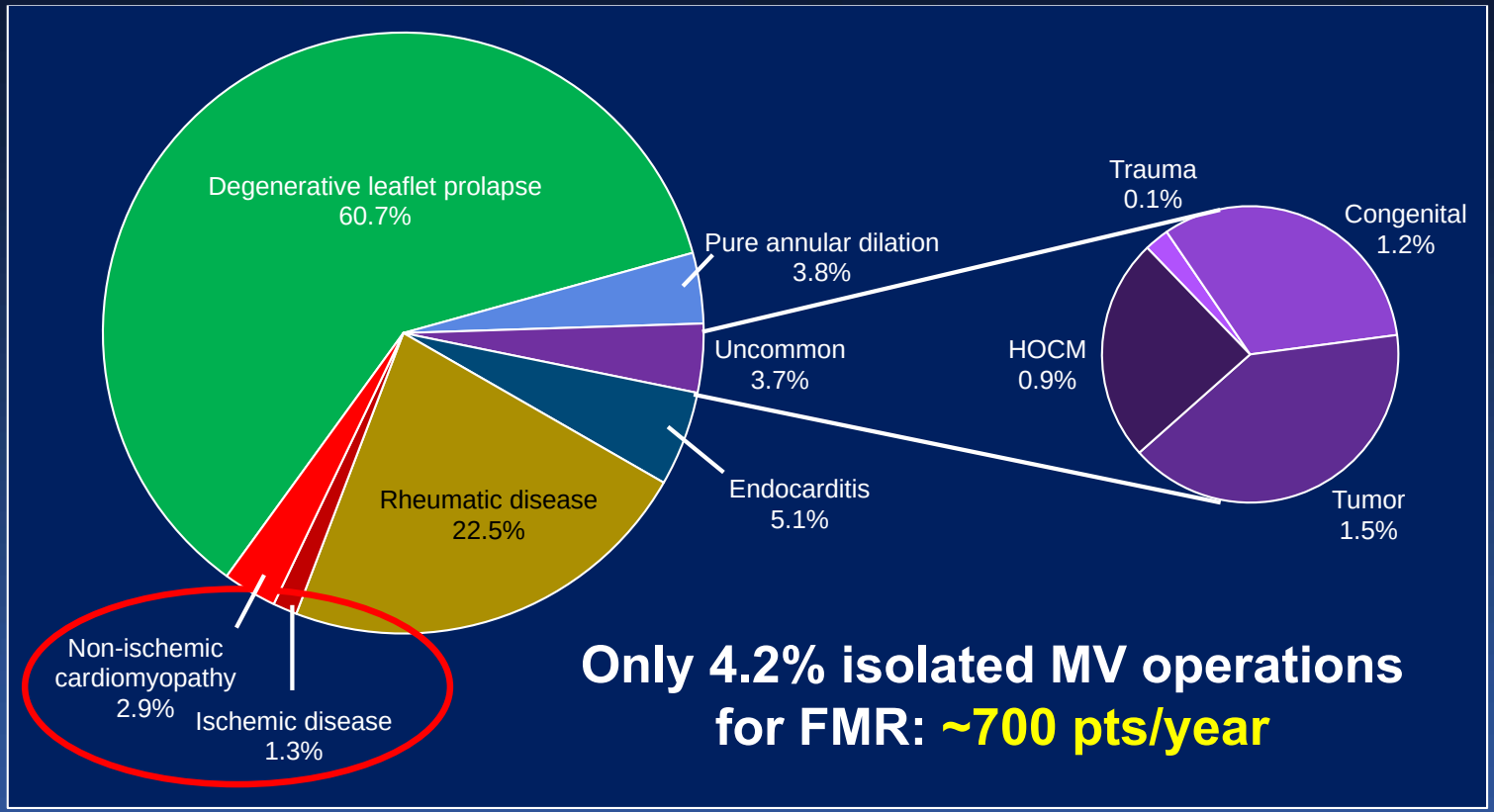


Mortality was 38% vs. 48% in the medical vs. surgical groups respectively (p=NS) – including 4.8% 30-day surgical mortality

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

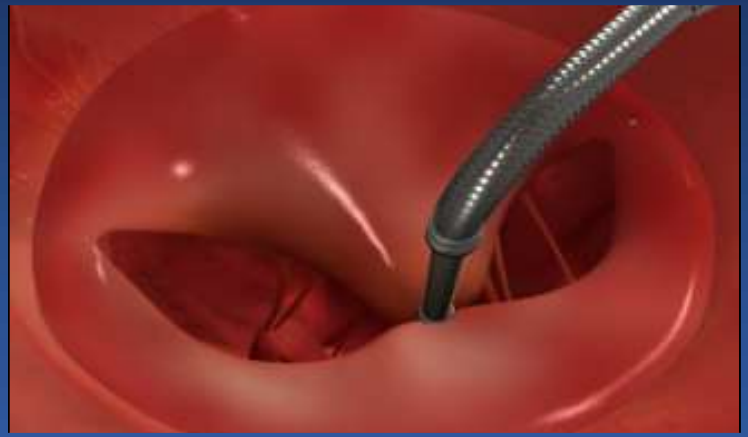
Isolated Mitral Valve Operations

STS Registry - N=87,214 from 2011-2016



Gammie JS et al. Ann Thorac Surg. 2018;106:716–27

MitraClip System and Implant



EVEREST II Randomized Trial

279 patients enrolled at 37 sites

Significant MR (3+ - 4+)

73% DMR, **27% FMR**

Specific anatomical criteria

Randomized 2:1

Device group	Control group
MitraClip system	Surgical repair or replacement
N=184	N=95

Echocardiographic core lab and clinical follow-up

Baseline, 30 days, 6 months, 1 year, 18 months, and annually through 5 years

Feldman T et al. NEJM 2011;364:1395-406

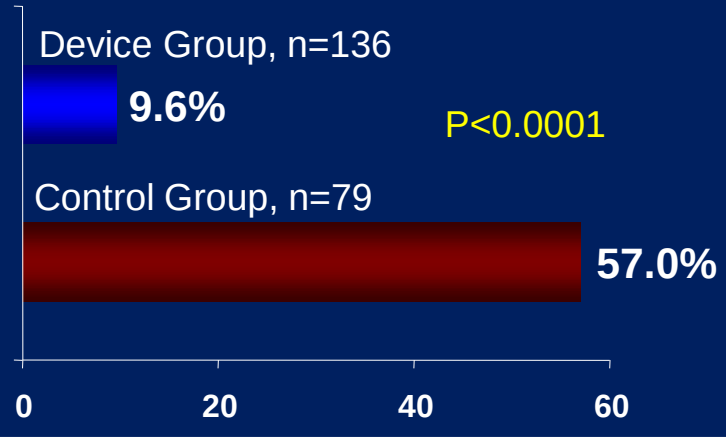
EVEREST II

279 pts with 3+/4+ MR randomized 2:1 to MitraClip vs. Surgical Repair

Primary Endpoints (per protocol cohort)

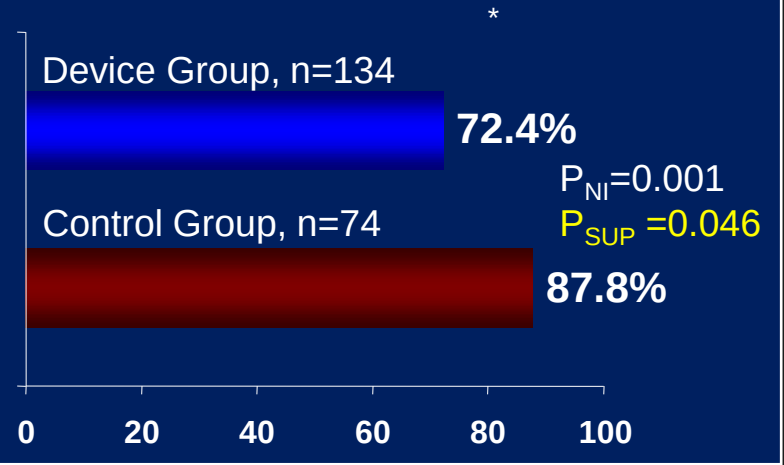
Safety†

Major adverse events (30 days)



Effectiveness‡

Clinical success rate (12 months)



†Death, major stroke, reop of MV, urg/emerg CV surgery, MI, renal failure, deep wound infection, sepsis, ventilation >48 hrs, new permanent AF, GI complication requiring surgery, transfusion ≥2U

‡Freedom from death, MV surgery or reoperation for MV dysfunction, or MR >2+ at 12 months

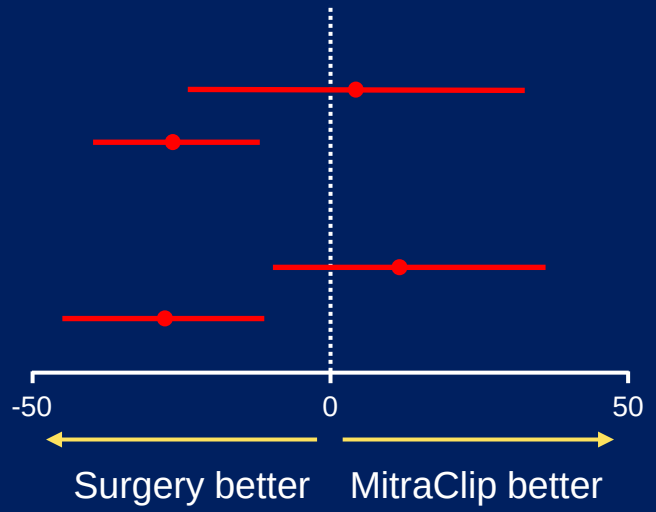
Feldman T et al. NEJM 2011;364:1395-406

EVEREST II: Primary EP at 1 and 5 Years

- DMR (73%) vs. FMR (27%) -

Freedom from Death, MV Surgery, or 3+ or 4+ MR: ITT

Etiology	MitraClip	Surgery
1 year		
Functional	26/48 (54.2%)	12/24 (50.0%)
Degenerative	74/133 (55.6%)	53/65 (81.5%)
5 years		
Functional	17/42 (40.5%)	4/14 (28.6 %)
Degenerative	51/112 (45.5%)	32/42 (76.2%)



Feldman T et al. NEJM 2011;364:1395-406; Feldman T et al. JACC 2015;66:2844–54

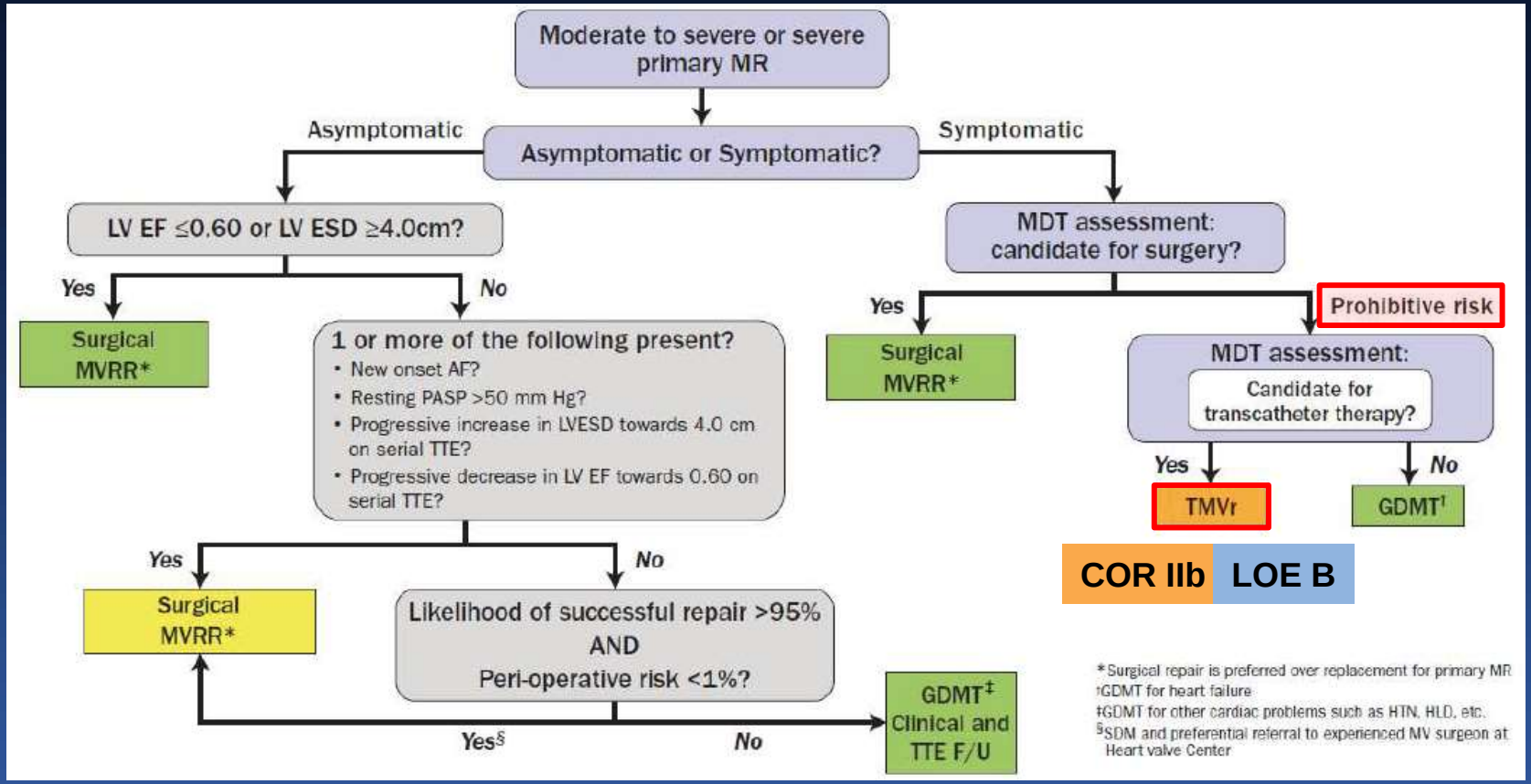
FDA MitraClip Approval

October 24th, 2013

The MitraClip is approved for treatment of patients with 3+-4+ primary (degenerative) MR who are at “prohibitive risk” for mitral valve surgery and are likely to benefit from MR reduction

Intervention for Primary MR

2020 Focused Update of the 2017 ACC Expert Consensus Decision Pathway for MR



Bonow RO et al. JACC 2020, doi: https://doi.org/10.1016/j.jacc.2020.02.005

REPAIR MR Trial

MitraClip vs. Surgical MV Repair in Moderate Surgical Risk Pts

500 pts with 3+ or 4+ degenerative MR

- NYHA class II-IV or asx (NYHA class I) with LVEF ≤60%, PASP >50 mmHg, or LVESD >40 mm
- Moderate surgical risk = ≥75 yo, or if <75 years: (1) STS PROM Repair Score ≥2%, or (2) other comorbidities which may introduce a potential surgery-specific impediment

Appropriate anatomy for both MitraClip and mitral surgical repair

MitraClip

Mitral Surgery

10-year FU

Primary endpoint: All-cause mortality, stroke, cardiac hosp >30 days post-Rx, or AKI requiring RRT at 2 years (powered for non-inferiority)

Primary endpoint: Proportion of pts with ≤2+ MR, w/o MV replacement, and w/o recurrent surgical or transcatheter MV intervention w/i 2 years (powered for non-inferiority)

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PIs: S. Kar and P. McCarthy. Clinicaltrials.gov NCT04198870

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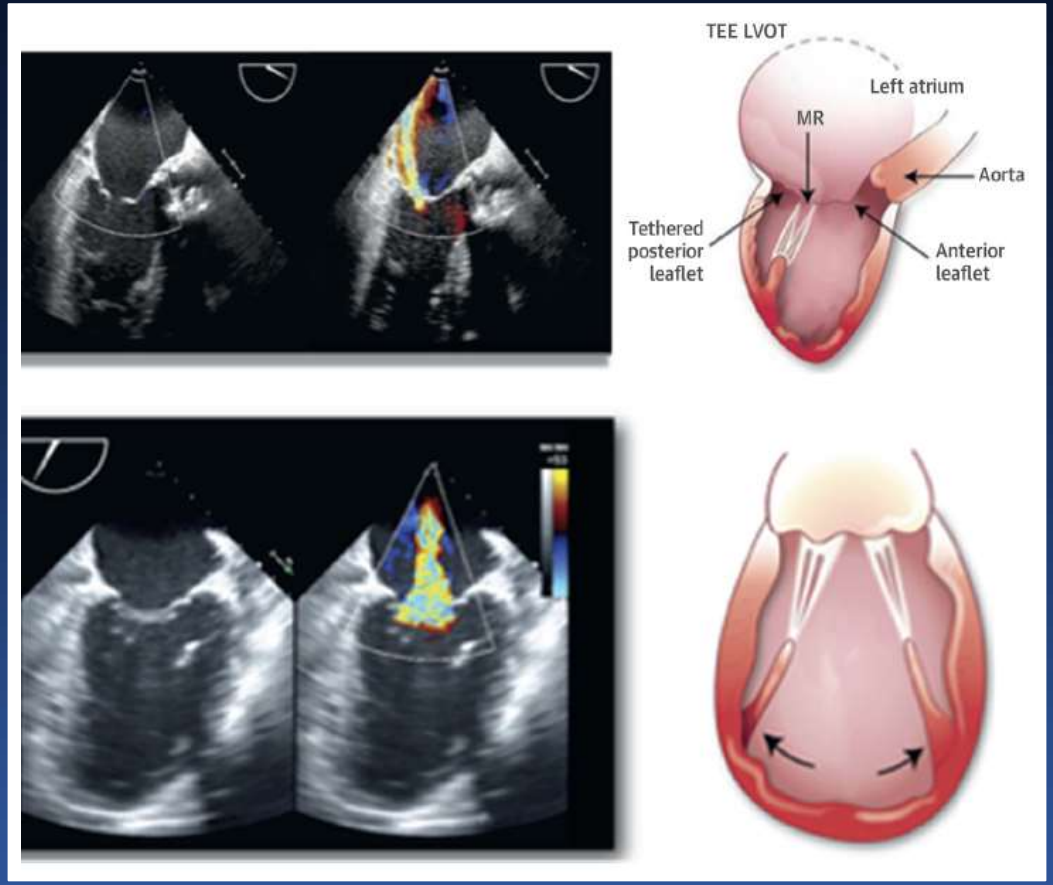
Secondary (Functional) MR: The disease is the LV!

Ischemic cardiomyopathy

Idiopathic dilated cardiomyopathy



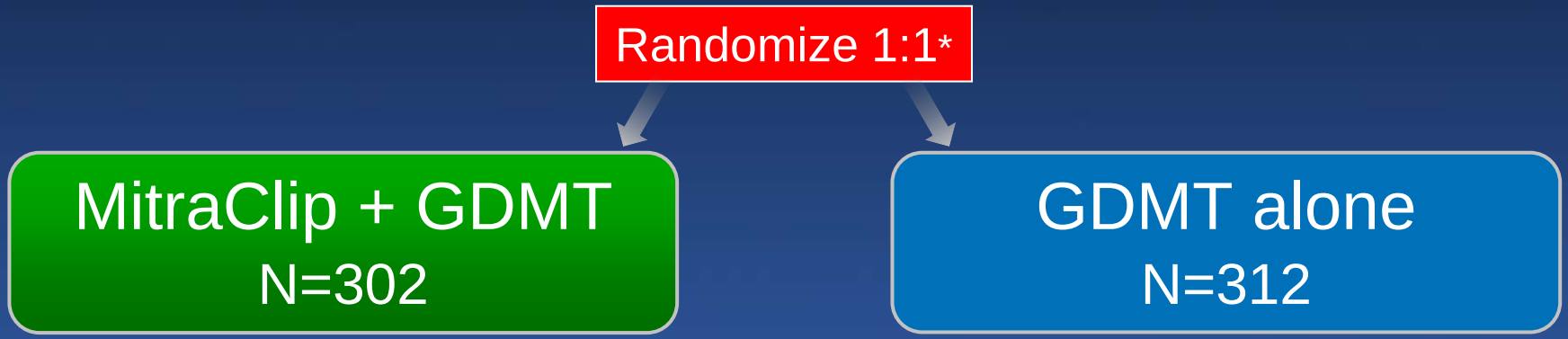
~10% atrial FMR
1˚ annular dilatation

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

The COAPT Trial

Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

A parallel-controlled, open-label, multicenter trial in 614 pts with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR, LVEF 20-50% and LVESD ≤7 cm who remained symptomatic despite maximally-tolerated GDMT

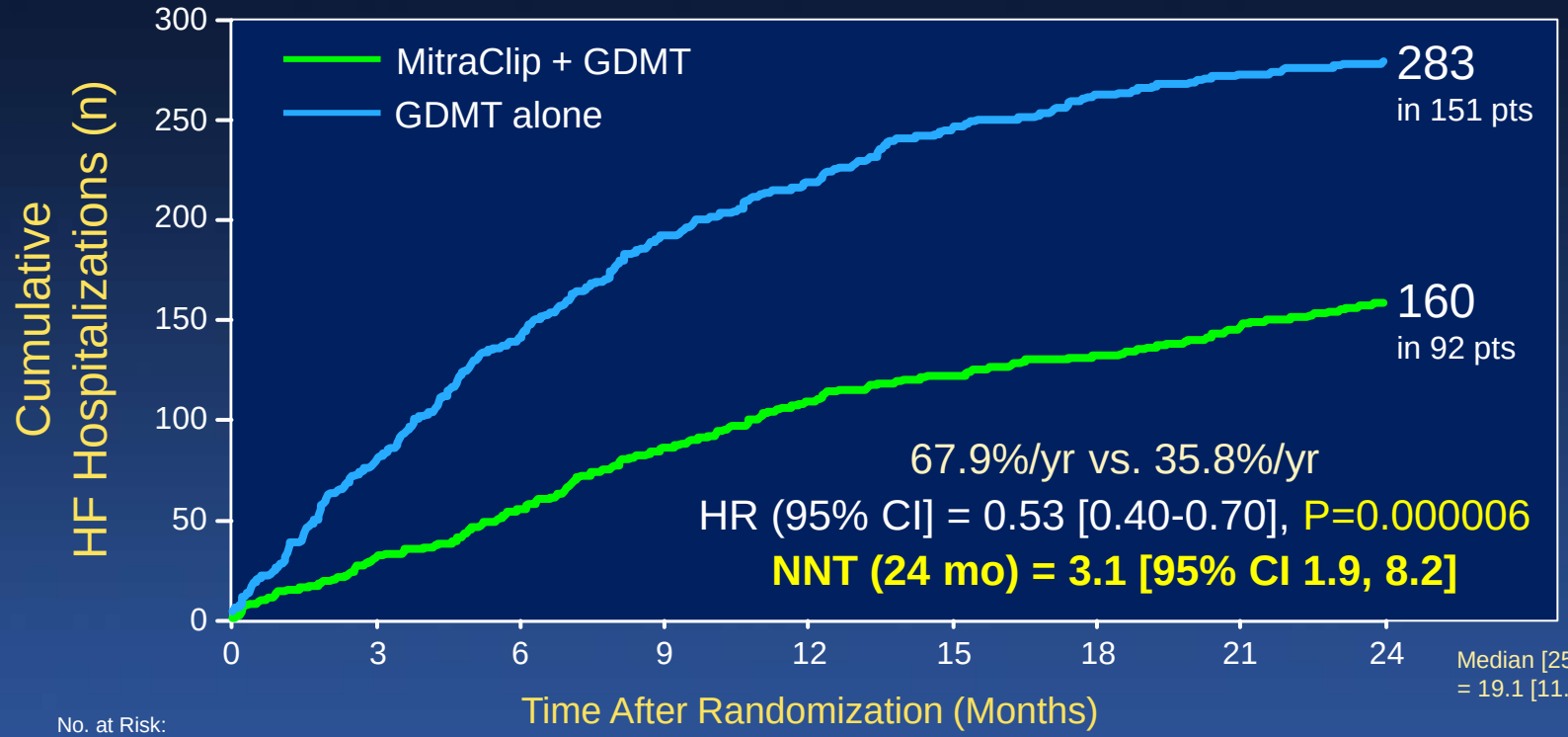


*Stratified by cardiomyopathy etiology (ischemic vs. non-ischemic) and site

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

Primary Effectiveness Endpoint

All Hospitalizations for HF within 24 months



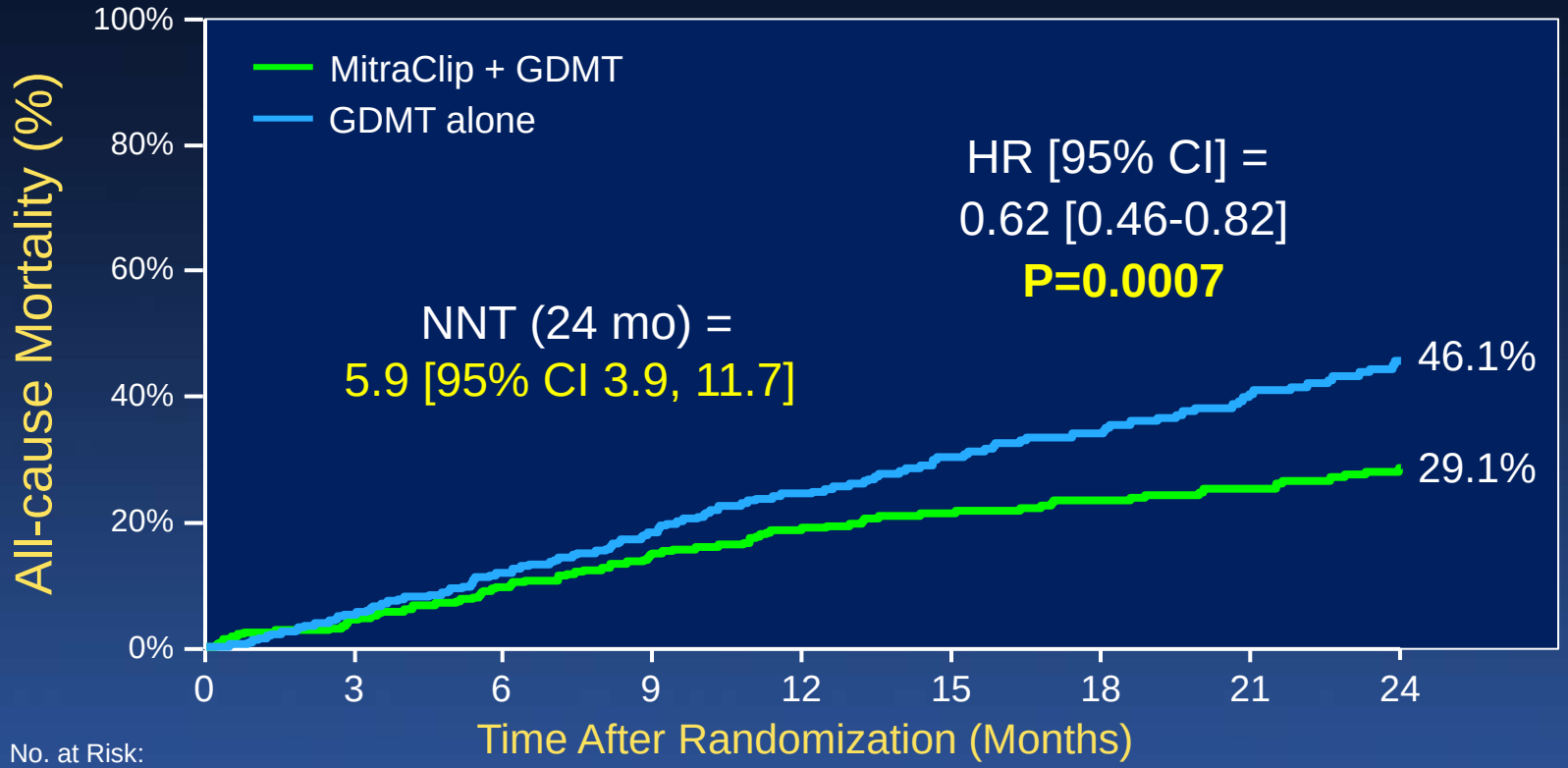
Median [25%, 75%] FU = 19.1 [11.9, 24.0] mos

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

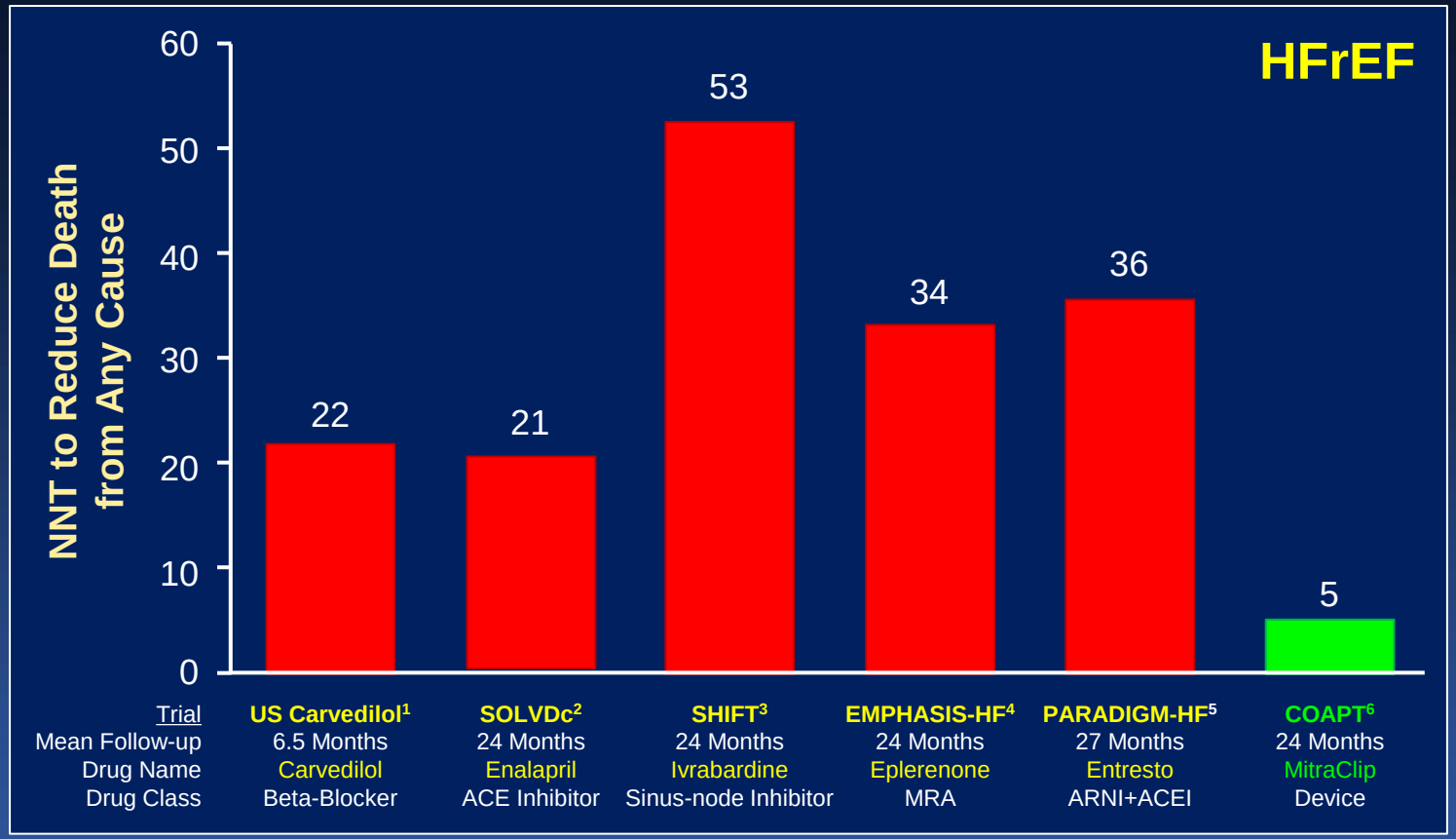
All-cause Mortality



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

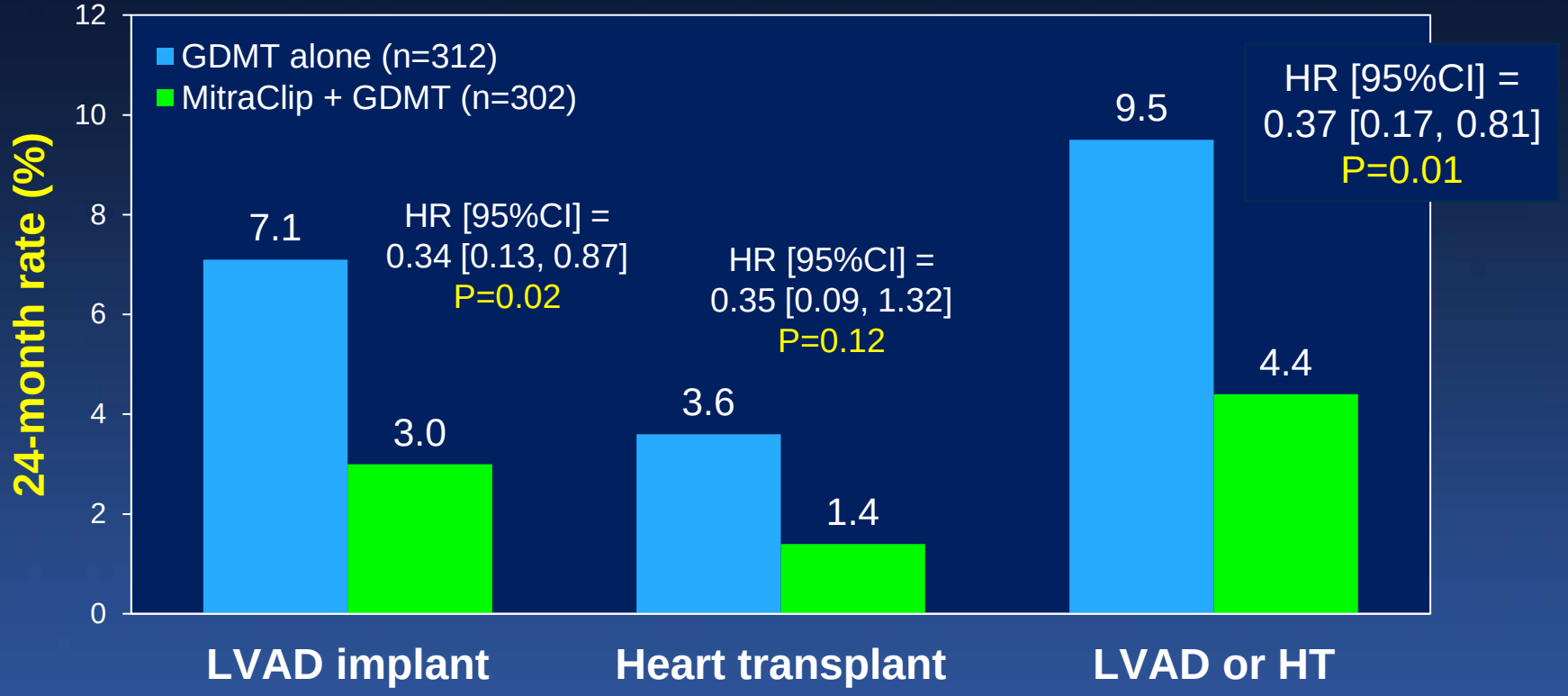
Number Needed to Treat (NNT) to Prevent 1 Death



1. Packer M et al. NEJM 1996;334:1349-1355; 2. SOLVD Investigators. NEJM 1991;325:293-302; 3. Swedberg K et al. Lancet 2010;376:1988;
4. Zannad F et al. NEJM 2011;364:11-21; 5. McMurray JJV et al. NEJM 2014;371:993-1004; 6. Stone GW et al. NEJM 2018;379:2307-18.

COAPT TRIAL

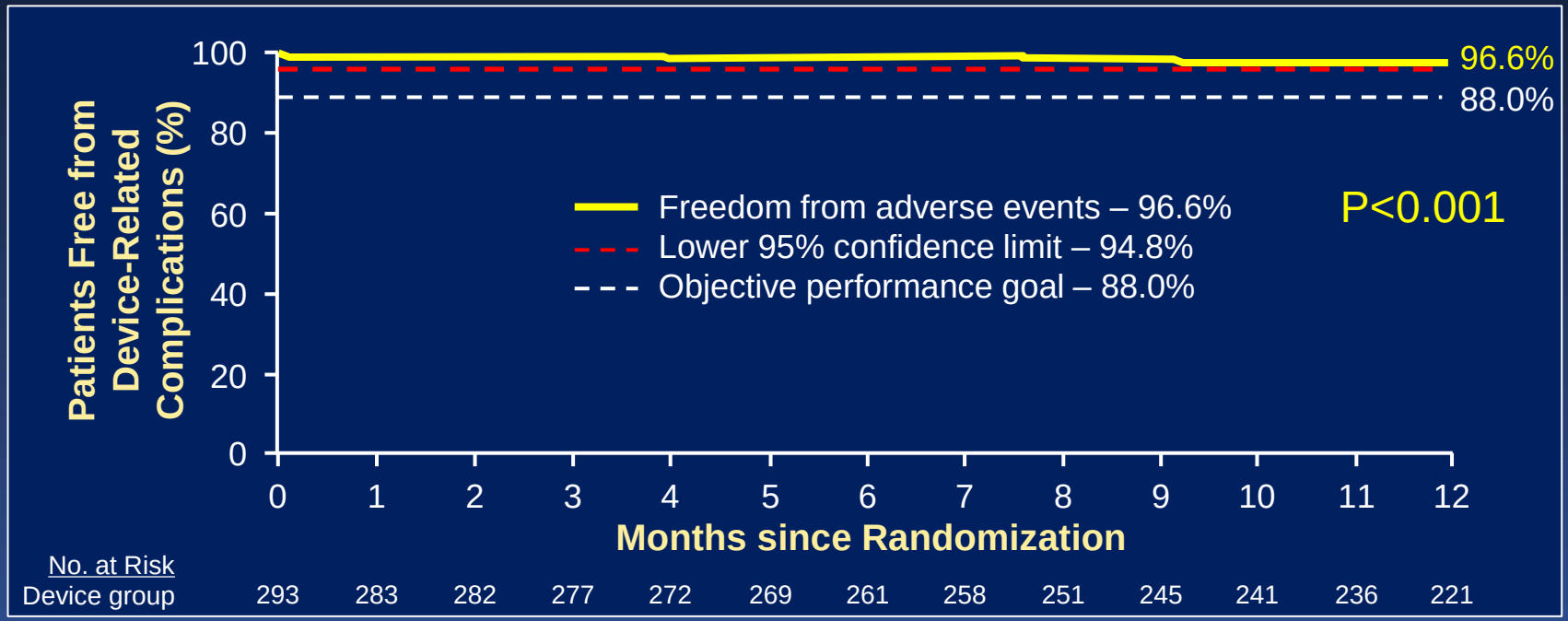
LVAD or Heart Transplant Within 24 Months



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

Primary Safety Endpoint

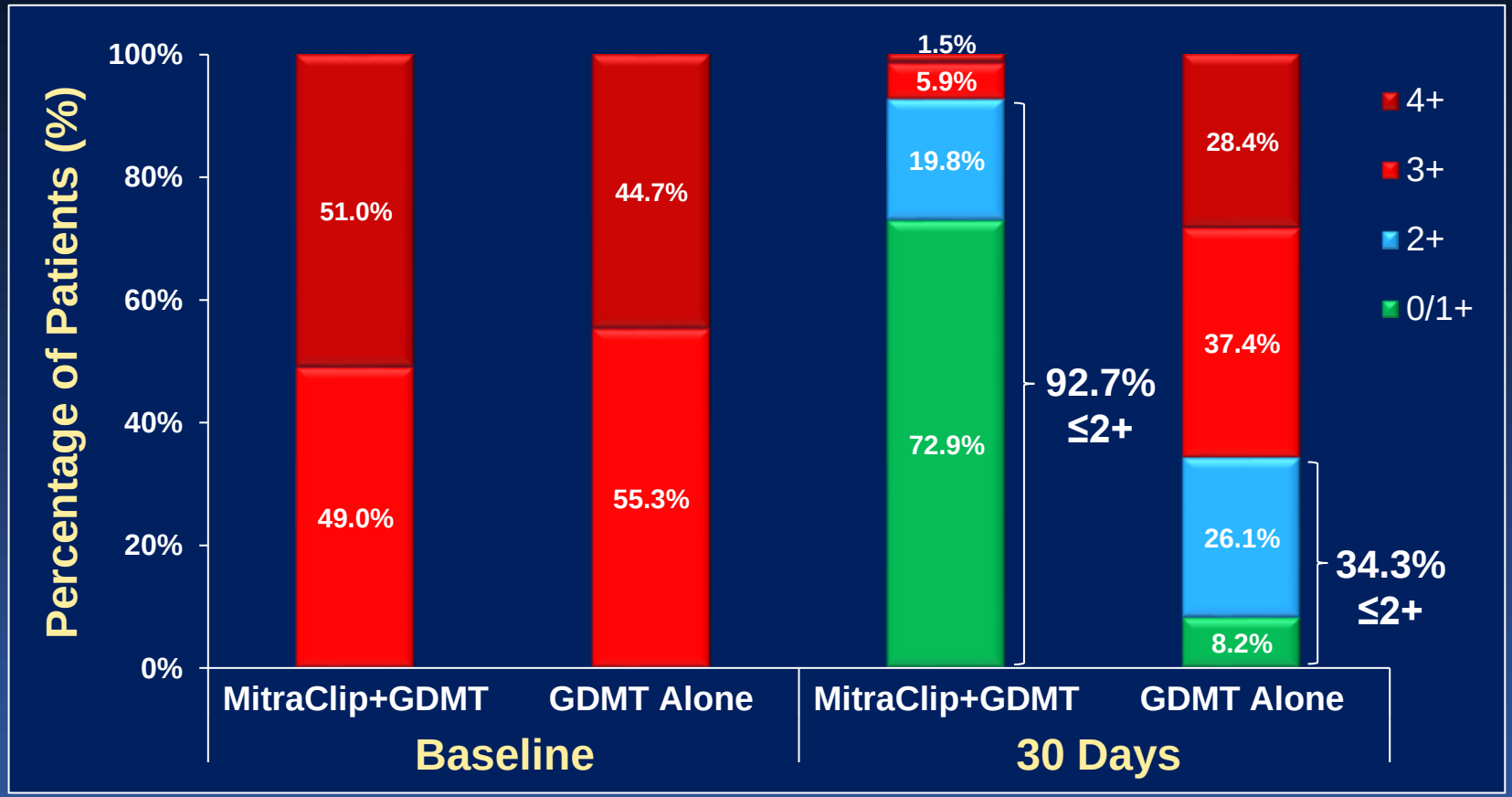
Freedom from device-related complications* within 12 months



* SLDA, device embolization, endocarditis or MS requiring surgery, LVAD, OHT, any device-related compl requiring non-elective CV surgery. *P* value calculated from Z test with Greenwood's method of estimated variance against a pre-specified OPG of 88%

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

MR Reduction in COAPT



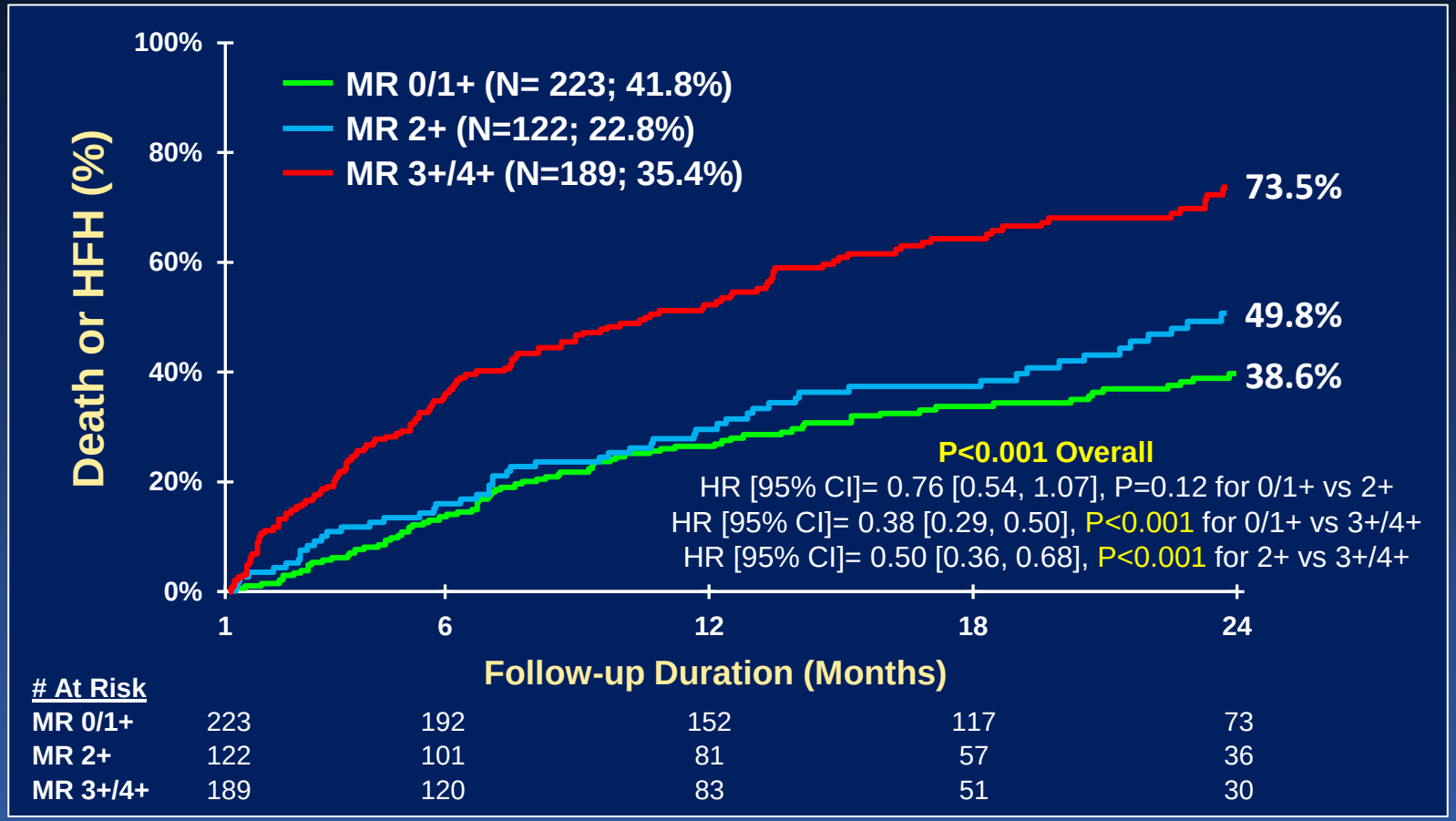
Stone GW et al. N Engl J Med. 2018;379:2307-18

COAPT TRIAL

Time to Death or First HF Hosp

Pooled population, stratified by 30-day residual MR

Kar S et al. Submitted.



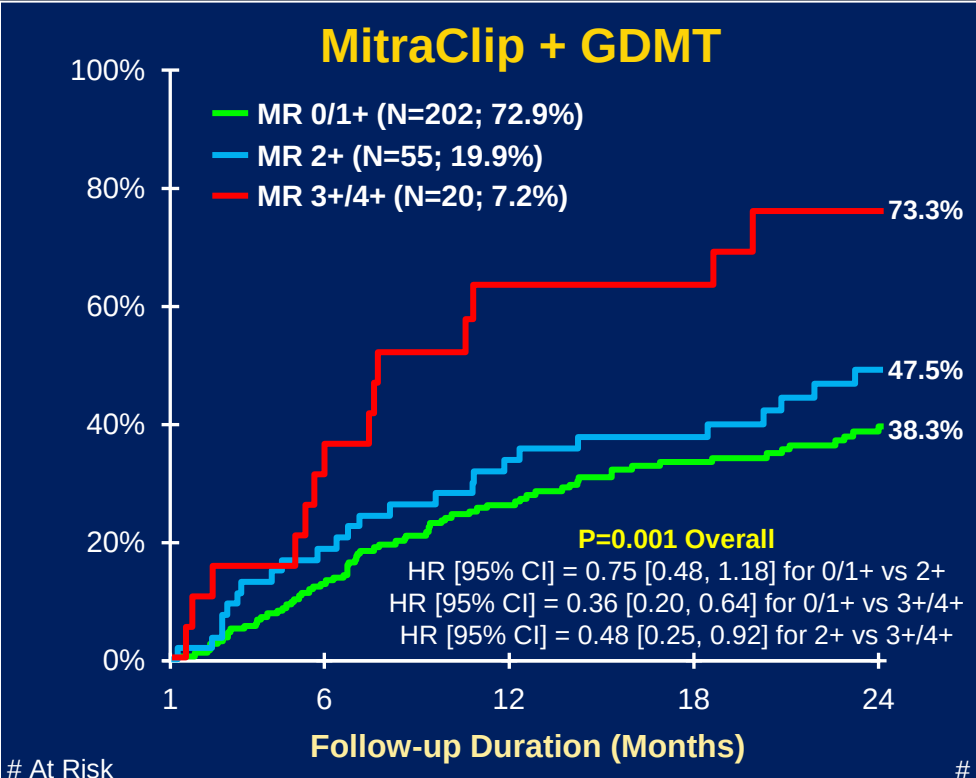
# At Risk					
MR 0/1+	223	192	152	117	73
MR 2+	122	101	81	57	36
MR 3+/4+	189	120	83	51	30

Time to Death or First HF Hosp

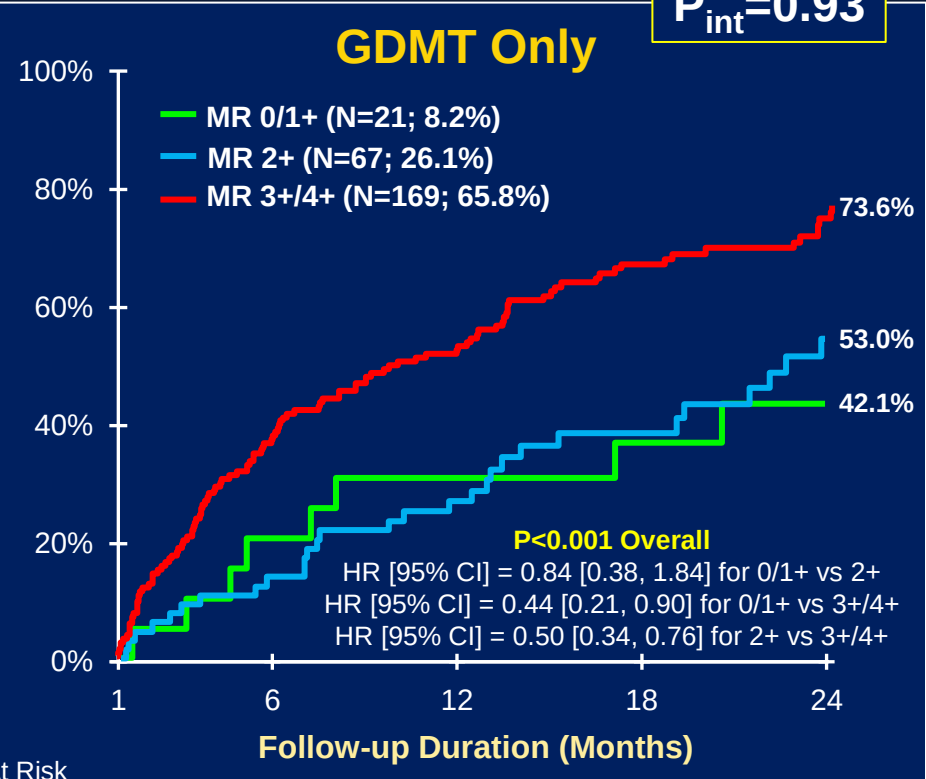
Randomization groups stratified by 30-day residual MR

Kar S et al. Submitted.

P_{int}=0.93



# At Risk					
MR 0/1+	202	176	139	106	66
MR 2+	55	45	37	31	21
MR 3+/4+	20	13	7	7	4



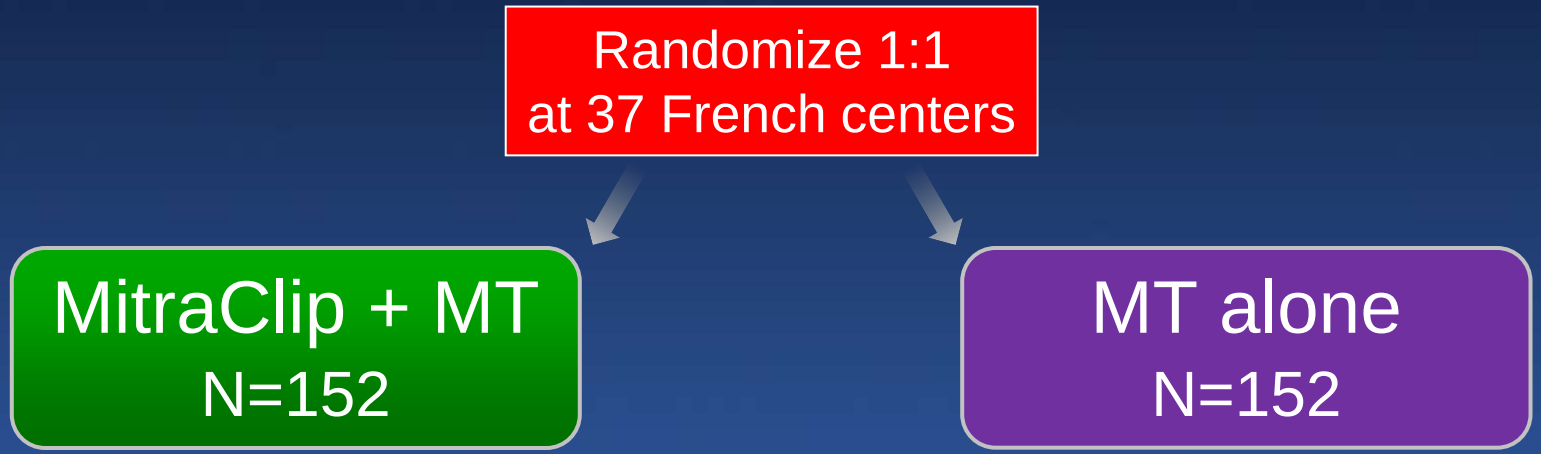
# At Risk					
MR 0/1+	21	16	13	11	7
MR 2+	67	56	44	26	15
MR 3+/4+	169	107	76	44	26

The MITRA-FR Trial

304 pts with SMR due to LV dysfunction with LVEF 15-40%, NYHA II-IVa, hospitalization for HF within the previous 12 mos, not eligible for mitral surgery

MR defined by EU “severe” criteria as EROA >20 mm² or RVol >30 mL/beat

Both groups with “real-world” HF meds (not maximally-tolerated GDMT)

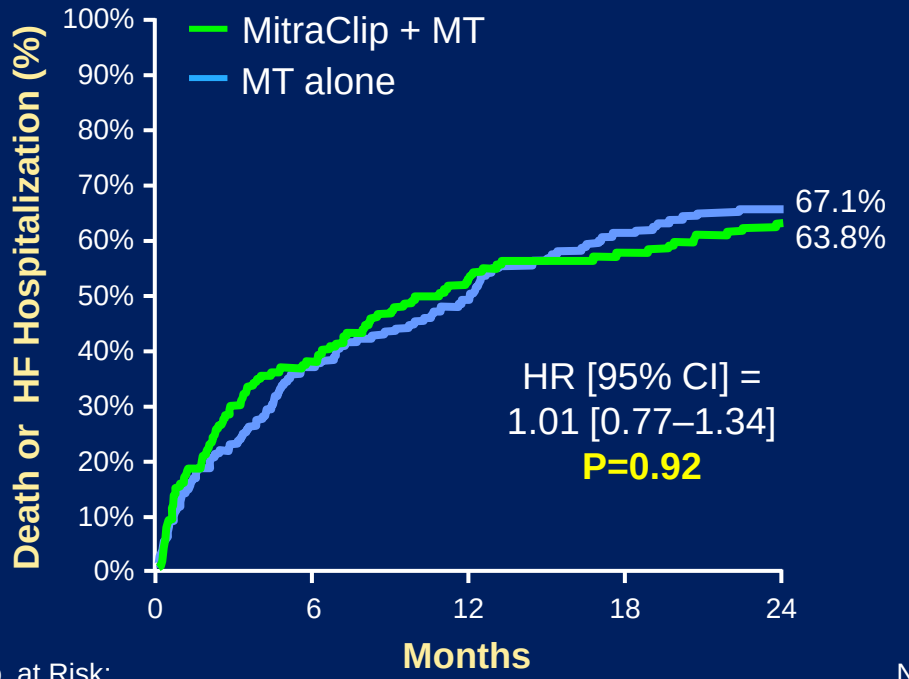


Primary endpoint: Freedom from death or HF hospitalizations through 12 months

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

COAPT vs. MITRA-FR: 24-Month Death or HF Hosp

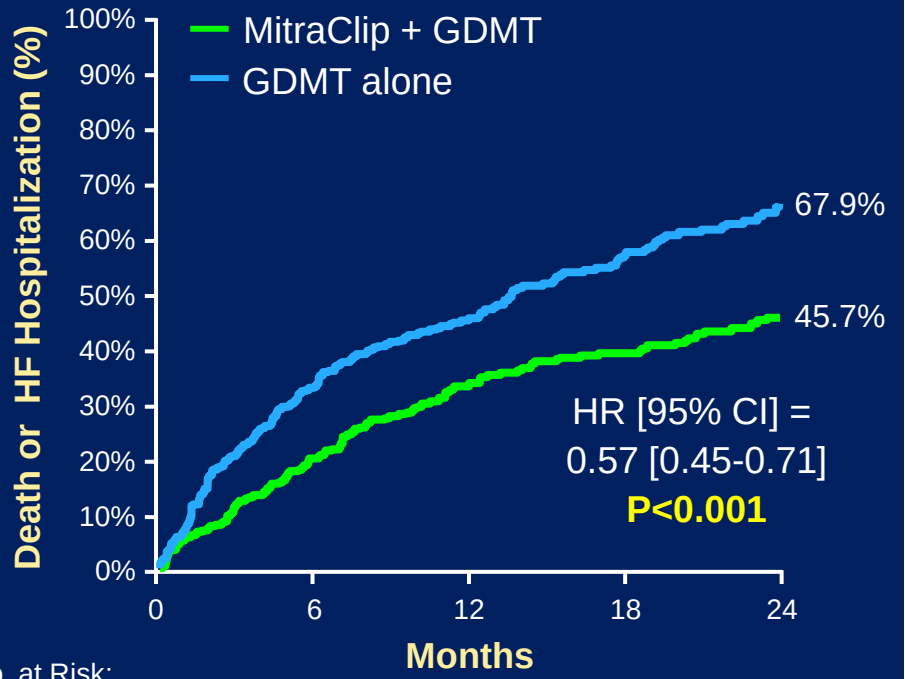
MITRA-FR



No. at Risk:

Control Group	152	94	73	56	31
Device Group	151	91	67	61	38

COAPT



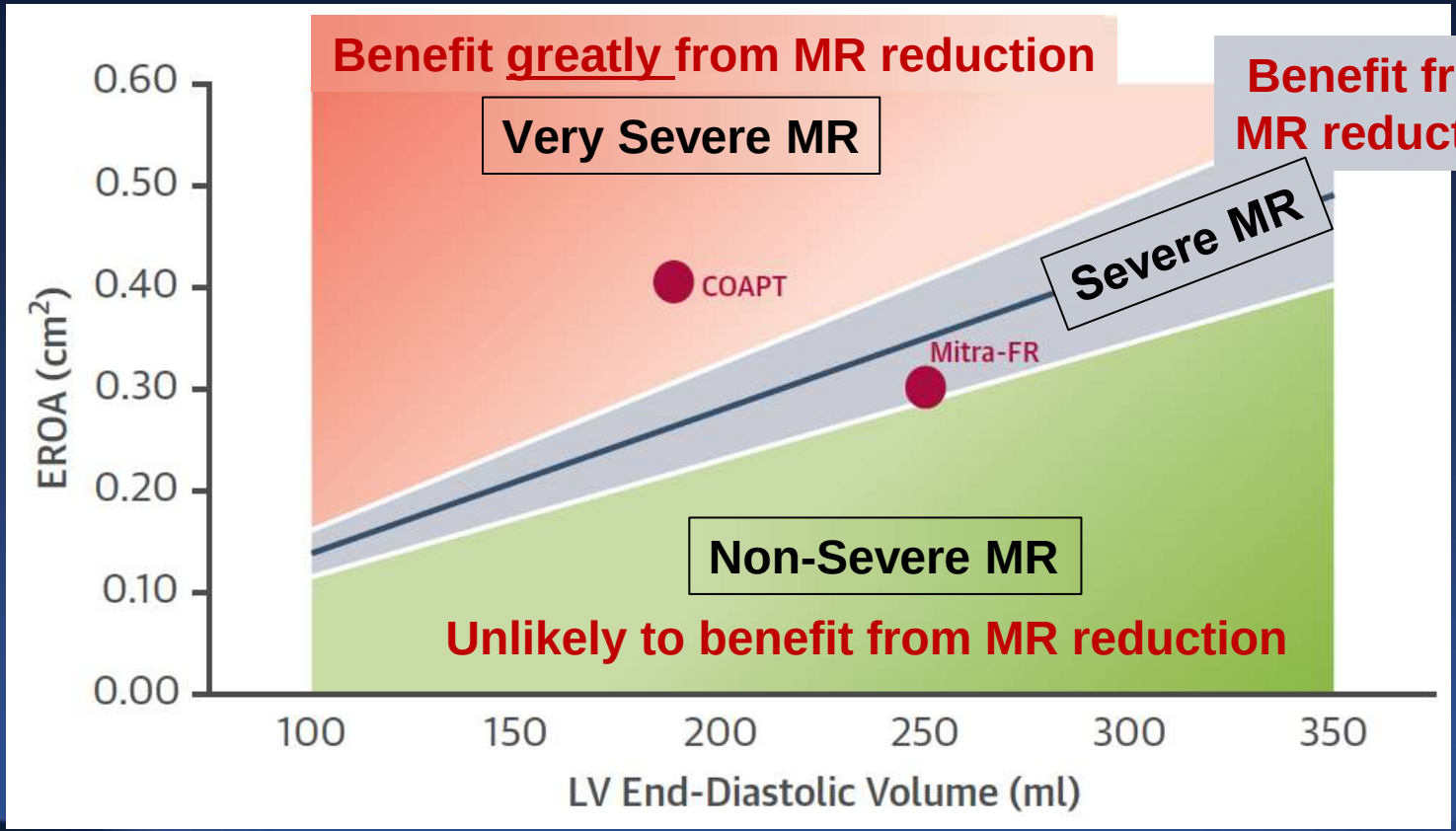
No. at Risk:

Control Group	312	205	153	90	55
Device Group	302	238	194	145	97

Iung B et al. Eur J Heart Fail 2019:on-line

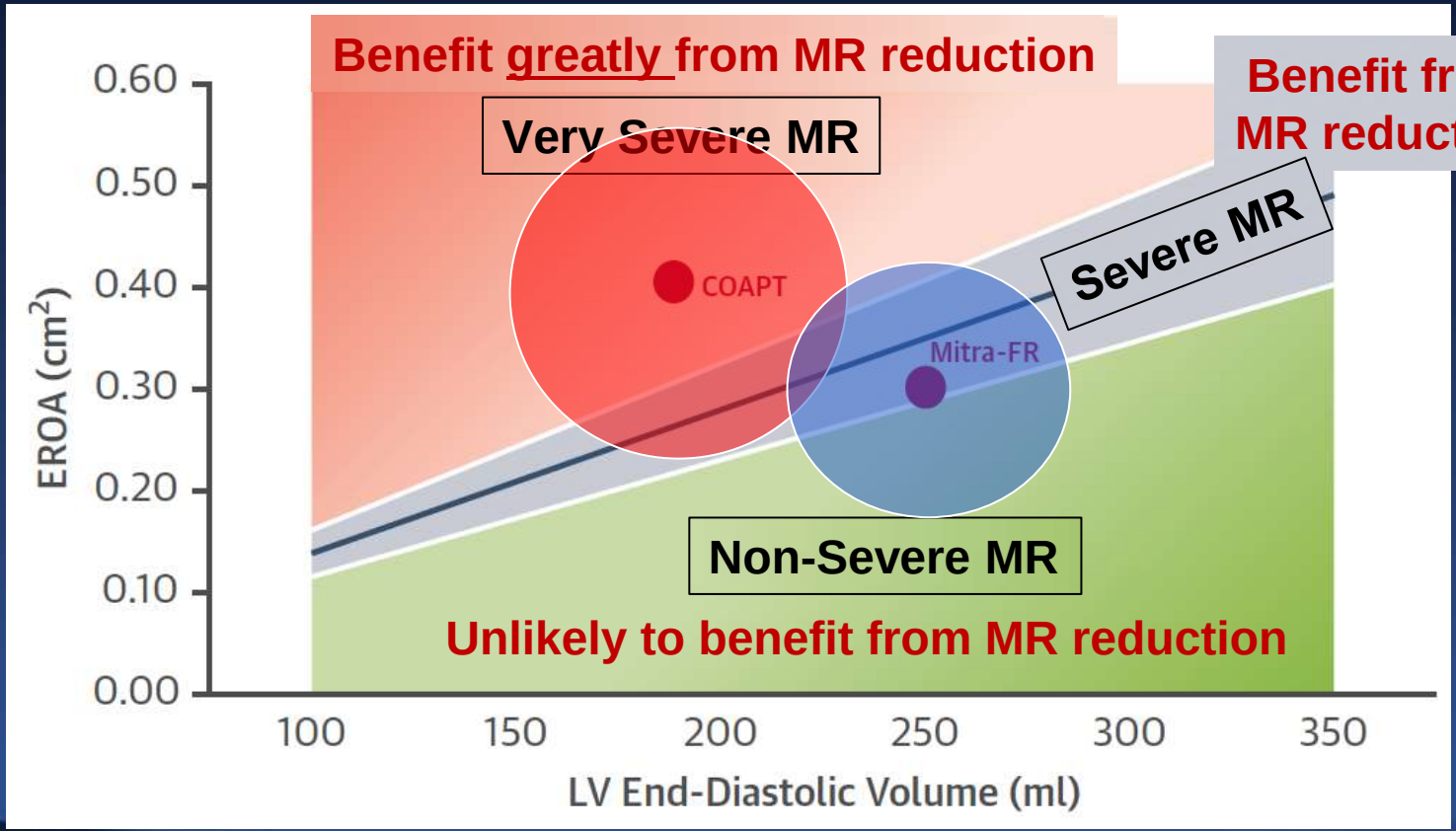
Stone GW et al. N Engl J Med. 2018;379:2307-18

Proportionate vs. Disproportionate MR



Grayburn PA et al. JACC CV Im 2019;12:353–62

Proportionate vs. Disproportionate MR



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Grayburn PA et al. JACC CV Im 2019;12:353–62

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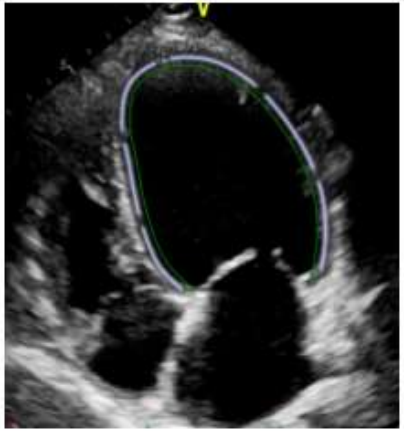
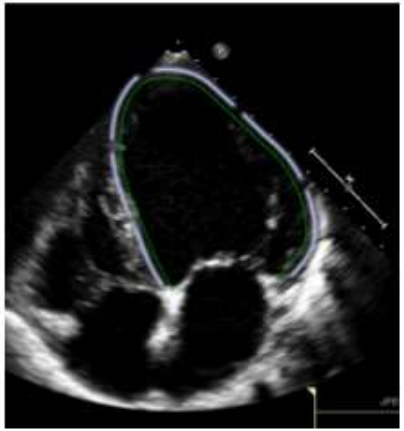
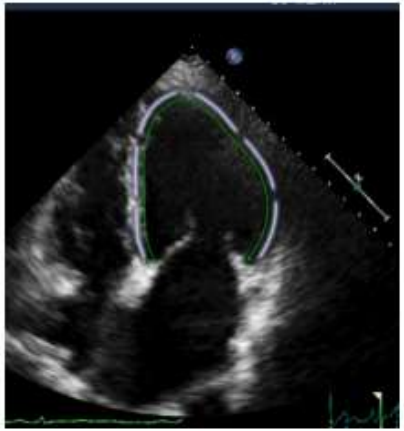
3 Patients with EROA of 30 mm^2



LVEF 22%
LVEDV 310 mL
GLS -6.8%



LVEF 36%
LVEDV 197 mL
GLS -8.4%



LVEF 60%
LVEDV 140 mL
GLS -20.3%

LVAD, transplant, hospice

Spectrum of LV dysfunction

MR correction likely to be beneficial

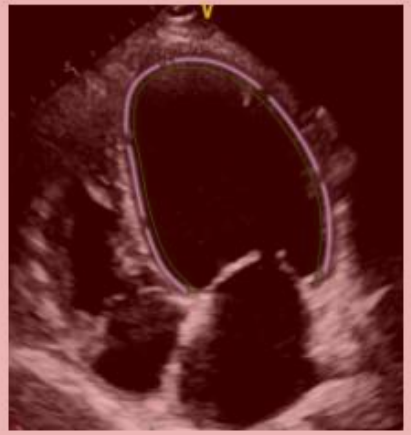
LVEF, LV size, LV geometry
Severely abnormal

LVEF, LV size, LV geometry
Mild-to-moderately abnormal

LVEF, LV size, LV geometry
Normal

3 Patients with EROA of 30 mm^2

MITRA-FR



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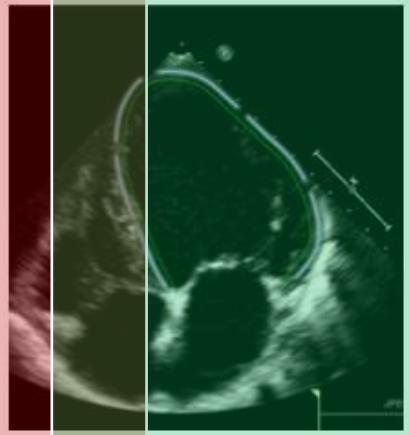

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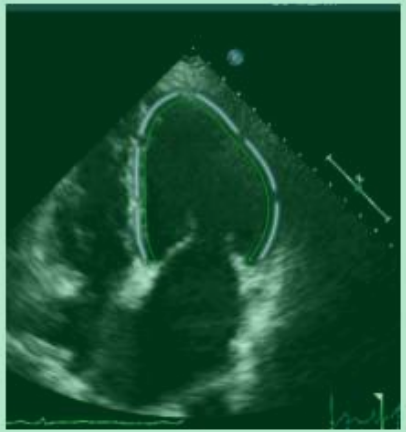

LVEF 60%
LVEDV 140 mL
GLS -20.3%

COAPT

LVAD, transplant, hospice

Spectrum of LV dysfunction

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Severely abnormal

LVEF, LV size, LV geometry
Mild-to-moderately abnormal

LVEF, LV size, LV geometry
Normal

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Multiparametric Echo MR Assessment

Secondary MR, Severity 3+ or 4+
(graded by 1 of 3 criteria)

Tier 1

EROA ≥ 0.3 cm^2

or

PV systolic flow reversal

N=570 (85.7%)

Tier 2

EROA 0.2 cm^2 - <0.3 cm^2

With any 1 of the following:

- RV ≥ 45 ml/beat
- RF ≥ 40%
- VC width ≥ 0.5 cm

N=70 (10.5%)

Tier 3

EROA not measured or <0.2 cm^2

With at least 2 of the following:

- RV ≥ 45 ml/beat
- RF ≥ 40%
- VC width ≥ 0.5 cm
- PISA radius > 0.9 cm, but CW of MR jet not done
- Large (≥ 6.0 cm) holosystolic jet wrapping around LA
- Peak E velocity ≥ 150 cm/s

N=25 (3.8%)

+ LVEF 20%-50% and LVESD ≤70 mm

No severe PHTN or RV failure

FDA MitraClip Label Expansion

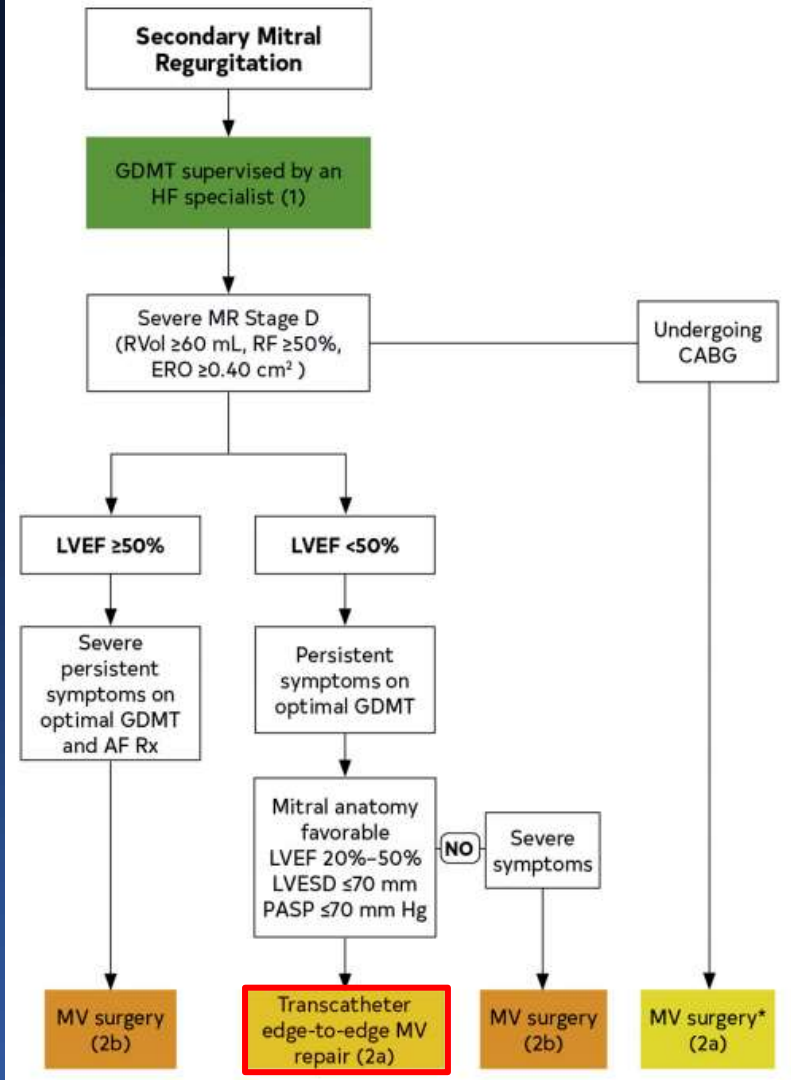
3/14/2019
FDA approves MitraClip for treatment of select pts with severe secondary MR who remain symptomatic despite GDMT

Label: The MitraClip™ NTR/XTR Clip Delivery System, when used with maximally tolerated guideline-directed medical therapy (GDMT), is indicated for the treatment of symptomatic, moderate-to-severe or severe secondary (or functional) mitral regurgitation (MR; MR ≥ Grade III per American Society of Echocardiography criteria) in patients with a left ventricular ejection fraction (LVEF) ≥20% and ≤50%, and a left ventricular end systolic dimension (LVESD) ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease.

2020 ACC AHA Valve Guidelines

2a	B-R

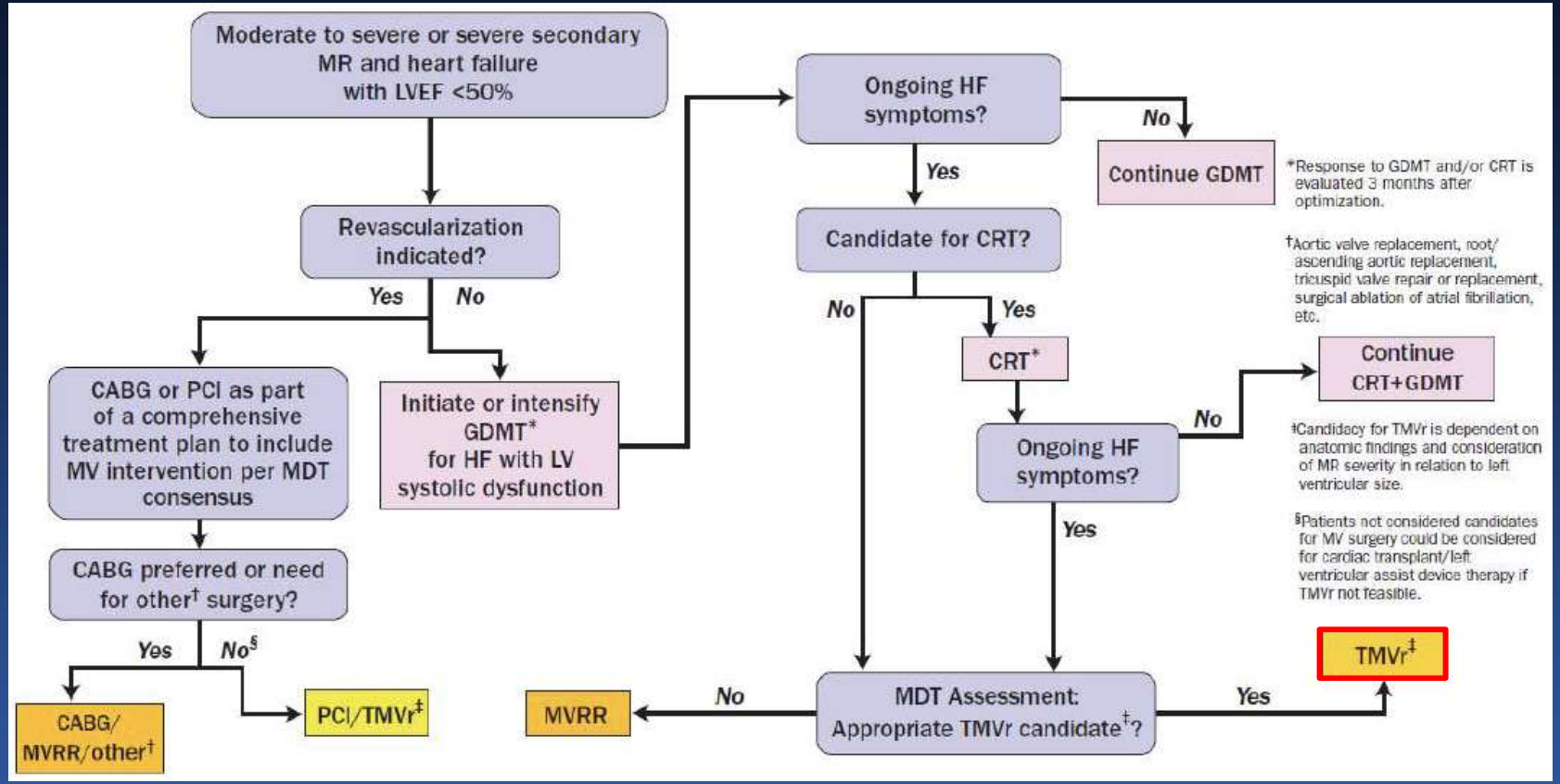
In pts with chronic severe secondary MR related to LV systolic dysfunction (LVEF <50%) who have persistent symptoms (NYHA class II, III, or IV) while on optimal GDMT for HF (Stage D), TEER is reasonable in patients with appropriate anatomy as defined on TEE and with LVEF between 20% and 50%, LVESD ≤70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



Otto CM et al. JACC 2020:on-line

Intervention for Symptomatic Secondary MR

2020 Focused Update of the 2017 ACC Expert Consensus Decision Pathway for MR



Bonow RO et al. JACC 2020, doi: https://doi.org/10.1016/j.jacc.2020.02.005

CMS Coverage for Transcatheter Edge-to-Edge Repair (TEER) for FMR and DMR - Jan. 19, 2021

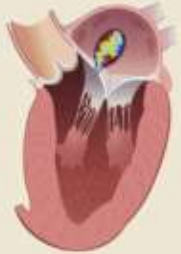
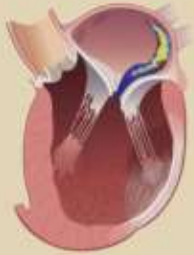
- Mod/sev or sev FMR in symptomatic pt despite max-tolerated GDMT + CRT if appropriate, *or* significant symptomatic DMR according to an FDA-approved indication, and when all of the following are met:
  - FDA-approved TEER system
  - Pre-op and post-op heart team care, including documentation of Rx plan:
    - Heart team = cardiac surgeon, IC, interventional echocardiographer, HF cardiologist (FMR only), others; volume criteria for each
    - DMR: IC and cardiac surgeon have independent face to face meetings with the pt
    - FMR: IC f2f meeting with the pt; HF cardiologist either f2f meet or records review
  - Appropriate hospital infrastructure and experience (specific criteria provided)
  - Heart team and hosp participate in a prospective, national, audited registry

https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=297

Implications of the COAPT and MITRA-FR Trials

- COAPT and MITRA-FR provide complementary guidance for pt selection, demonstrating which pts with HF and secondary MR are likely and unlikely to benefit from MR reduction
- The FDA has approved and guidelines support the MitraClip for pts with HF and secondary MR meeting COAPT criteria; strict reliance to these criteria should allow duplication of the COAPT results in the “real world” (and avoid over-treatment)
- Ongoing and future trials investigating surgical and transcatheter MV repair and replacement techniques and devices in HF pts with secondary MR who meet COAPT criteria should include the MitraClip as an active control arm

Severe MR: To Clip or Not to Clip?

	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)
Primary MR (with appropriate clinical/echo indications)	 Leaflet Perforation Cleft	 Mitral Valve Prolapse	 Rheumatic Valve Disease Mitral Annular Calcification Drug Induced MR	
Secondary MR	 Atrial MR  Nonischemic Cardiomyopathy			 Ischemic Cardiomyopathy

Clip candidates

Pts at high surgical risk
?Intermediate risk

COAPT criteria
Symptomatic
on max GDMT
3+/4+ MR
LVEF 20-50%
LVESD ≤7cm
?Others*

*Asymptomatic, not on max GDMT, 2+ MR with non-dilated LV or 3+/4+ with very dilated LV, stage D or shock, higher or lower LVEF, atrial SMR

Transcatheter MV Repair: Device Landscape

Edge-to-edge

- Abbott MitraClip***
- Edwards Pascal**
- MitralStich*
- ValveClamp*
- MitraFlex
- Cardica

Direct and indirect annuloplasty

- CDI Carillon**
- Mitralign TAMR**
- Edwards Cardioband**
- Ancora Heart Accucinch*
- Millipede IRIS*
- MVRx Arto*
- Mardil VenTouch*
- Mitraspan TASRA*
- Valcare Amend*
- Micardia enCor*
- MitraLoop Cerclage*
- Cardiac Implants RDS*
- Medtentia CathHELIX
- QuantumCor (RF)
- Valfix

MV replacement

- Edwards CardiAQ*
- Edwards Sapien M3*
- Edwards Evoque*
- Neovasc Tiara*
- Medtronic Intrepid*
- Abbott Tendyne*
- Abbott Cephea*
- HighLife*
- NCSI NaviGate*
- MValve*
- CardioValve*
- MitrAssist MitraFix*
- 4C AltaValve*
- St. Jude
- ValveXchange
- Braile Quattuor
- Sinomed Accufit
- Valcare Corona
- Epigen
- MitralHeal
- Lutter valve
- HT Consultant Saturn
- Transcatheter Technologies

MV replacement (cont)

- Tresillo
- Venus
- Verso
- Transmural Systems
- Saturn (InnovaHeart)

Other approaches

- NeoChord DS 1000**
- Harpoon neochords*
- ChordArt (CoreMedic)*
- Babic chords*
- MitralStich Chordal*
- St. Jude leaflet plication*
- Cardiosolutions Mitra-Spacer*
- Mitralix*
- Pipeline Medical (Gore)

Mitraltech Vchordal

- CardioMech
- Mitral Butterfly
- Polares (former Middle Peak)
- Sutra (posterior hemivalve)
- Coramaze Mitramaze
- Nyra Med Carlen leaflet enhancement
- Cardiac Success

*In patients
*CE mark
*FDA approved