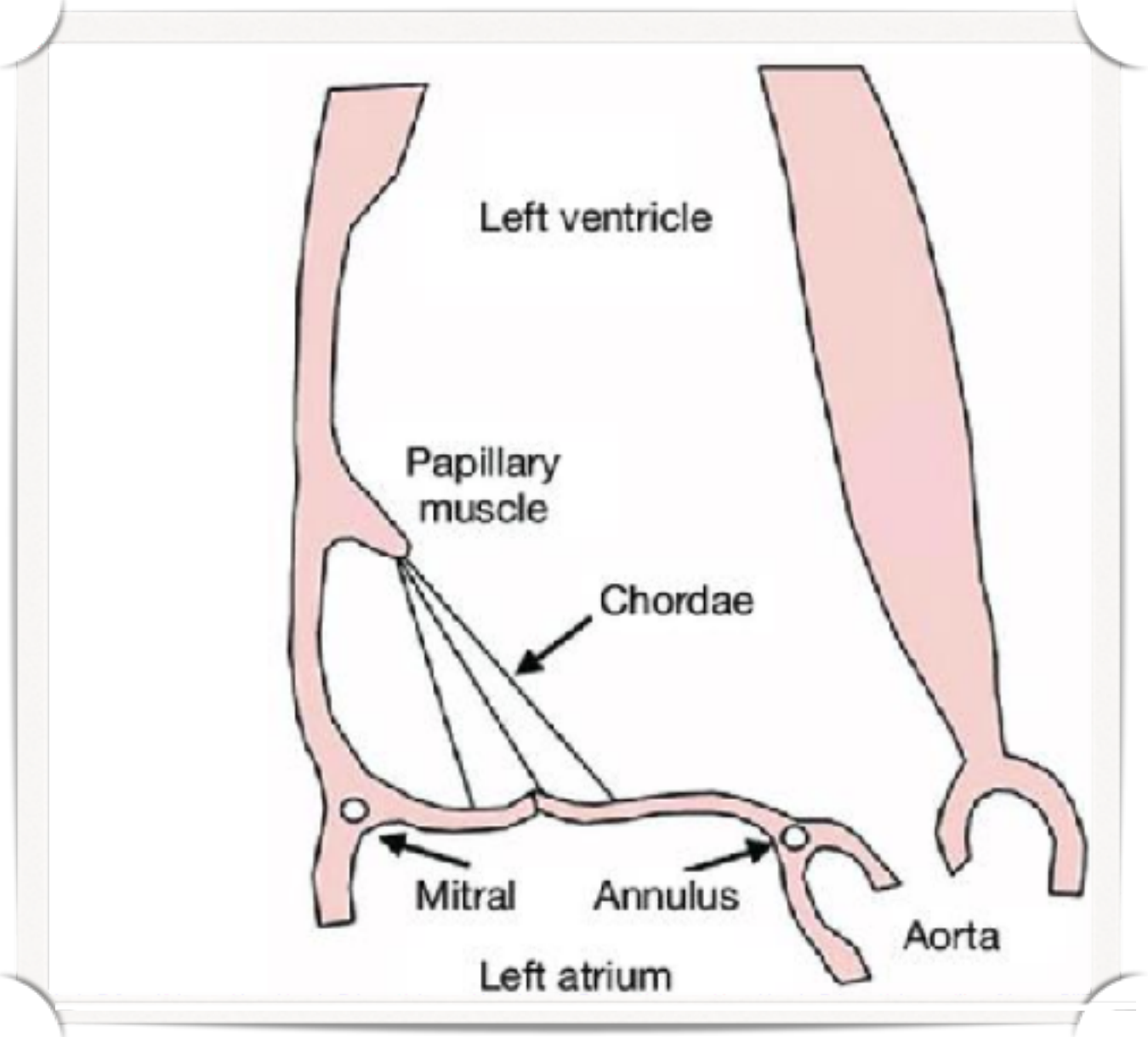


# Secondary Mitral Regurgitation

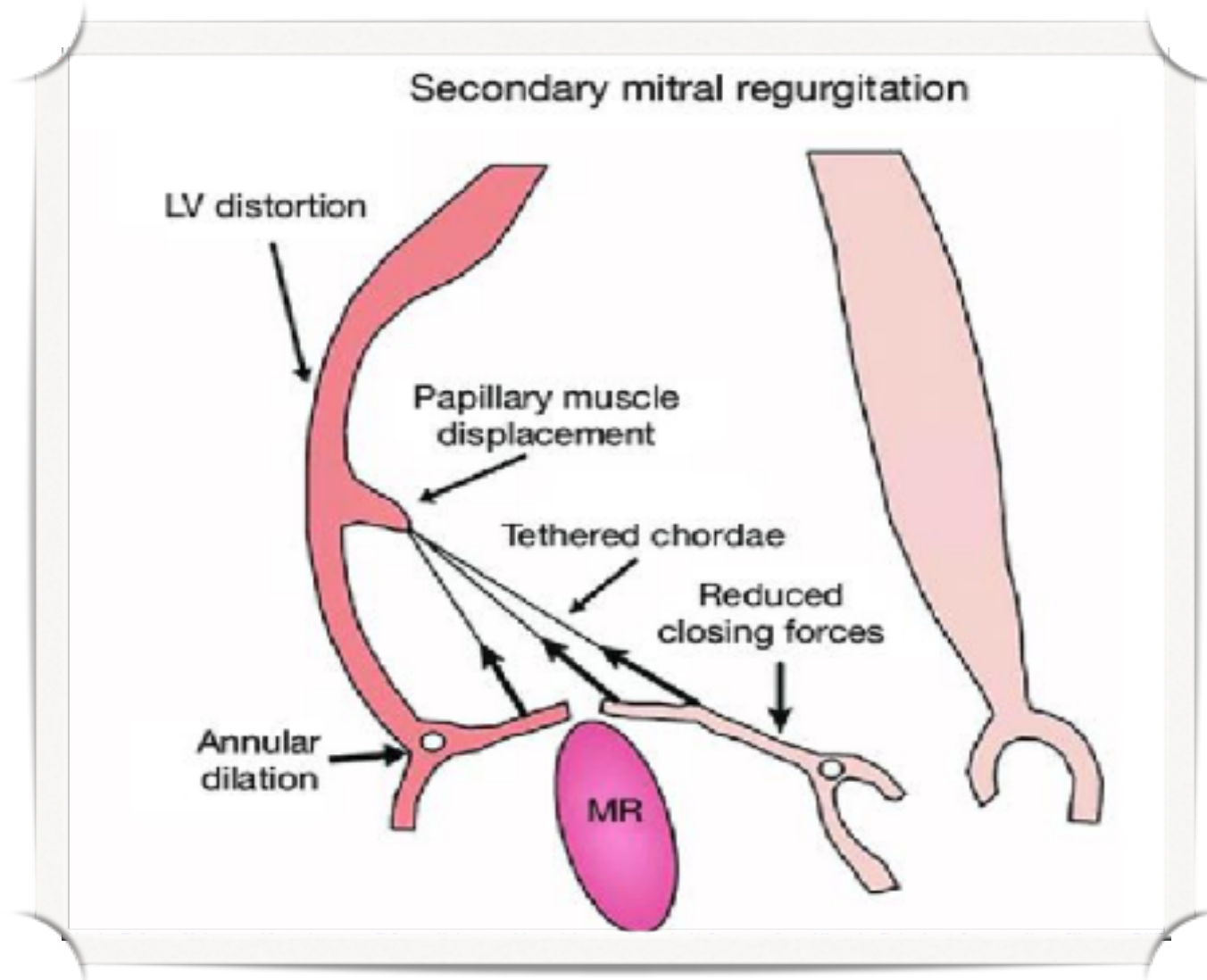
## Time to Re-think

Dr. Abdelmaksoud Elganady MD  
Associate Professor of Cardiology  
Faculty of Medicine  
Al-Azhar University  
Cairo, Egypt  
Saturday, 16th October 2021

# The Mitral Valve and Left Ventricle



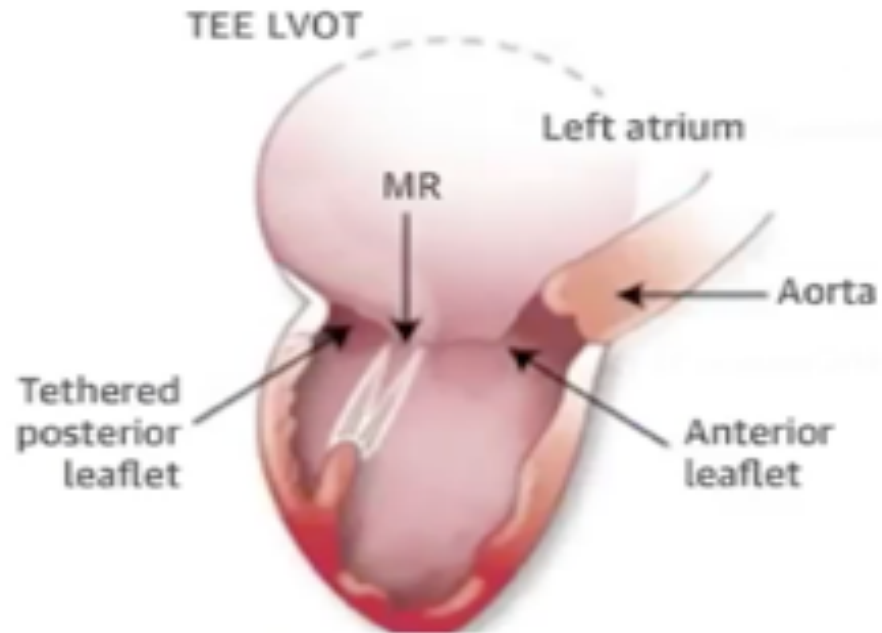
# Secondary Mitral Regurgitation is a Disease of the Left Ventricle



# Secondary Mitral Regurgitation

## Pathophysiology

### Ischaemic CM



- Papillary muscle displacement
- Tethered Chordae
- Restricted leaflet closure
- Annular dilation

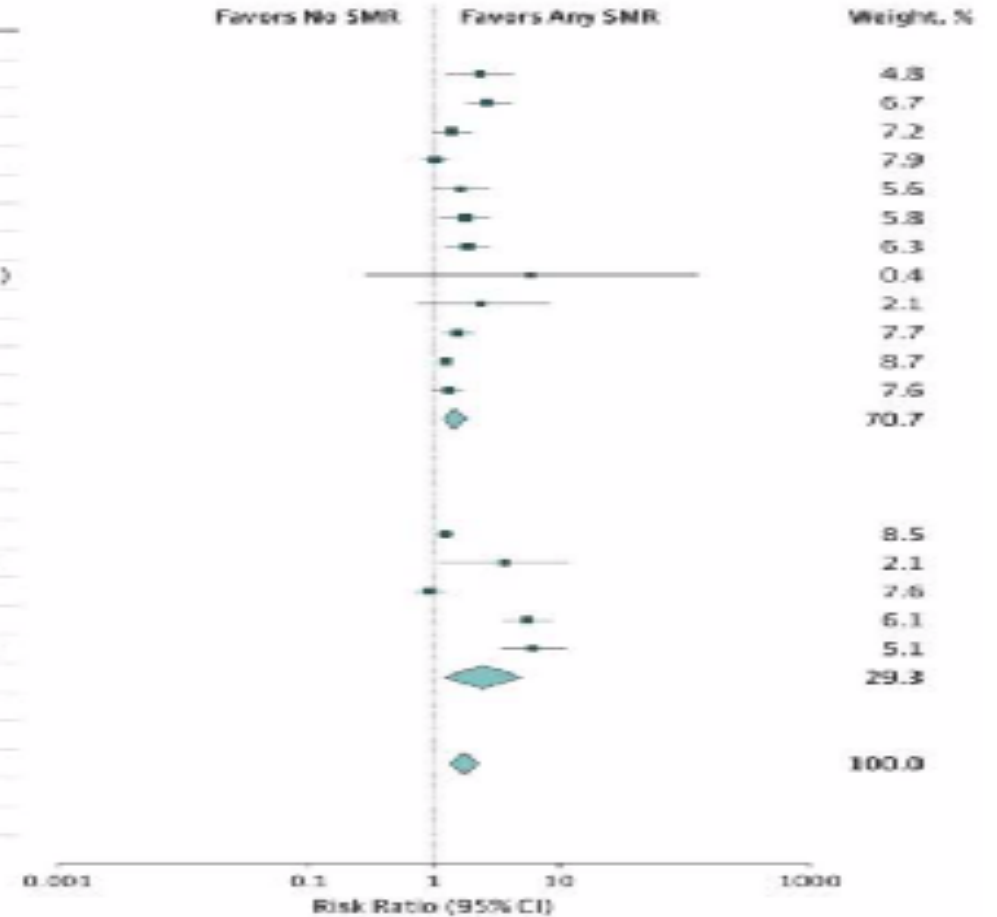
### Dilated CM



changes in LV geometry and function

# Secondary Mitral Regurgitation Prognosis

Source	Log Risk Ratio (SE)	SMR	No SMR	Risk Ratio (SE)
<b>SMR Present vs Absent at Echocardiography</b>				
Agricola et al, <sup>26</sup> 2011	0.8538 (0.3182)	128	70	2.35 (1.26-4.38)
Aronson et al, <sup>6</sup> 2006	1.0188 (0.1977)	548	642	2.77 (1.88-4.08)
Barrs et al, <sup>27</sup> 2012	0.3507 (0.1638)	358	438	1.42 (1.03-1.96)
Calafiore et al, <sup>7</sup> 2008	0.0296 (0.1226)	1421	2805	1.03 (0.81-1.31)
Engström et al, <sup>39</sup> 2010	0.5365 (0.2636)	121	26	1.71 (1.02-2.87)
Faris et al, <sup>21</sup> 2002	0.5878 (0.2513)	NA	NA	1.80 (1.10-2.95)
Grigioni et al, <sup>3</sup> 2003	0.6313 (0.2165)	194	309	1.88 (1.23-2.87)
MacHaalany et al, <sup>43</sup> 2014	1.8183 (1.5567)	79	95	6.16 (0.29-130.24)
Nesković et al, <sup>46</sup> 1999	0.9060 (0.6158)	81	50	2.47 (0.74-8.27)
Pastorius et al, <sup>48</sup> 2007	0.4511 (0.1371)	289	420	1.57 (1.10-2.05)
Trichon et al, <sup>23</sup> 2003	0.2070 (0.0433)	1156	501	1.23 (1.13-1.34)
Upadhyay et al, <sup>55</sup> 2015	0.2852 (0.1404)	368	71	1.33 (1.01-1.75)
<b>Subtotal (95% CI)</b>		<b>4743</b>	<b>5627</b>	<b>1.56 (1.31-1.85)</b>
Heterogeneity: $\tau^2 = 0.05$ ; $\chi^2 = 33.07$ ; ( $P < .001$ ); $I^2 = 67\%$				
Test for overall effect: $Z = 5.08$ , ( $P < .001$ )				
<b>SMR Present vs Absent at Ventriculography</b>				
Hickey et al, <sup>36</sup> 1988	0.2231 (0.0746)	2443	9405	1.25 (1.08-1.45)
Lehmann et al, <sup>41</sup> 1992	1.3083 (0.6189)	27	379	3.70 (1.10-12.45)
Mallidi et al, <sup>9</sup> 2004	-0.0429 (0.1420)	163	326	0.96 (0.73-1.27)
Pellizzon et al, <sup>3</sup> 2004	1.7297 (0.2303)	250	1726	5.64 (3.59-8.66)
Tsong et al, <sup>22</sup> 1992	1.8160 (0.2947)	255	1215	6.15 (3.45-10.95)
<b>Subtotal (95% CI)</b>		<b>3138</b>	<b>12851</b>	<b>2.58 (1.29-5.17)</b>
Heterogeneity: $\tau^2 = 0.54$ ; $\chi^2 = 73.55$ ; ( $P < .001$ ); $I^2 = 93\%$				
Test for overall effect: $Z = 2.67$ , ( $P = .008$ )				
<b>Total (95% CI)</b>		<b>7881</b>	<b>18478</b>	<b>1.79 (1.47-2.18)</b>
Heterogeneity: $\tau^2 = 0.12$ ; $\chi^2 = 107.97$ ; ( $P = .001$ ); $I^2 = 85\%$				
Test for overall effect: $Z = 5.71$ , ( $P < .001$ )				
Test for subgroup differences: $\chi^2 = 1.89$ ; ( $P = .17$ ); $I^2 = 47.2\%$				

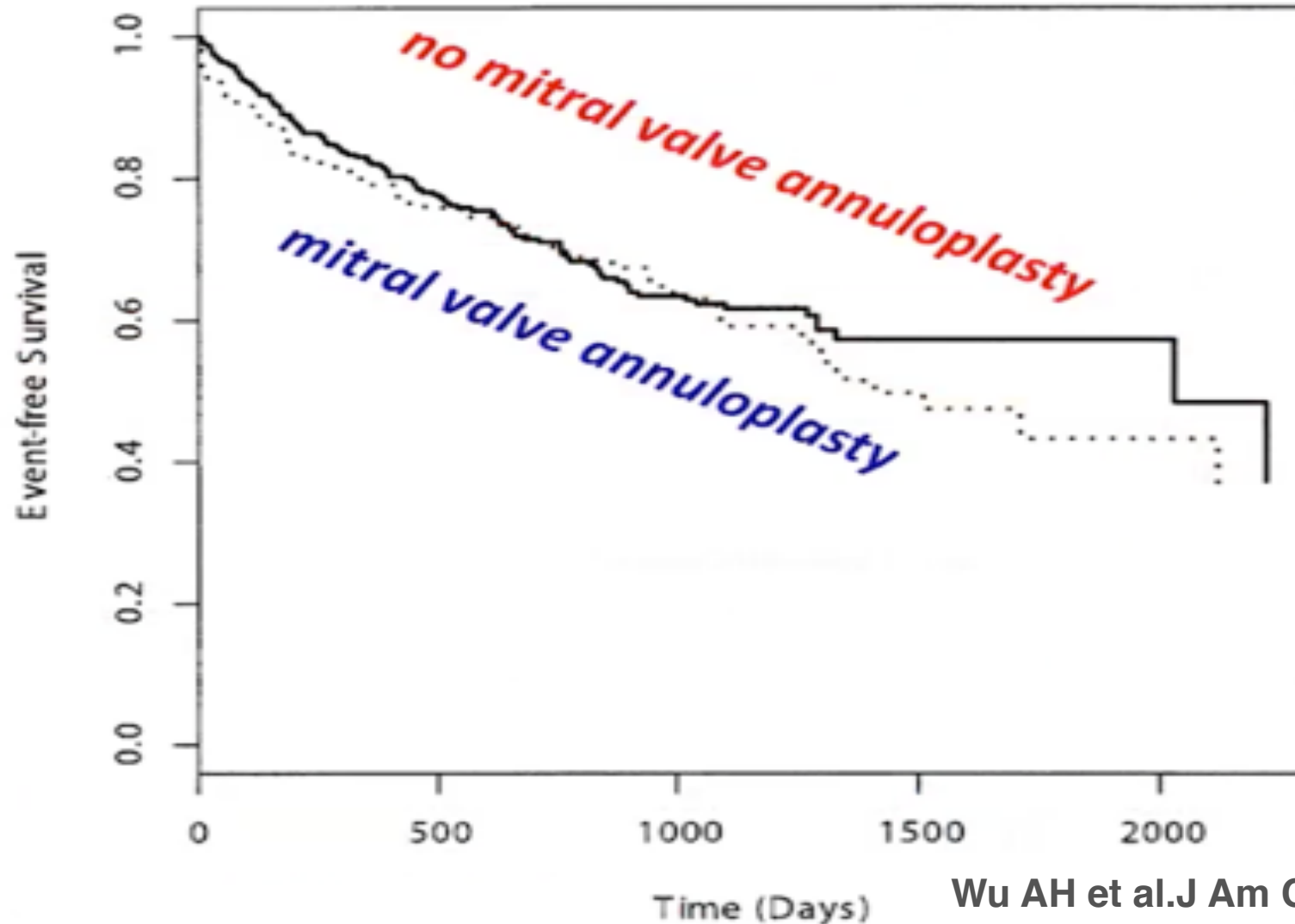


Meta-analysis of 17 studies, 26,359 patients Sannino et al JAMA Cardiol, 2017 oct 1;2(10):1130-1139 RR, 1.96; 95% CI, 1.67-2.31;  $P < .001$

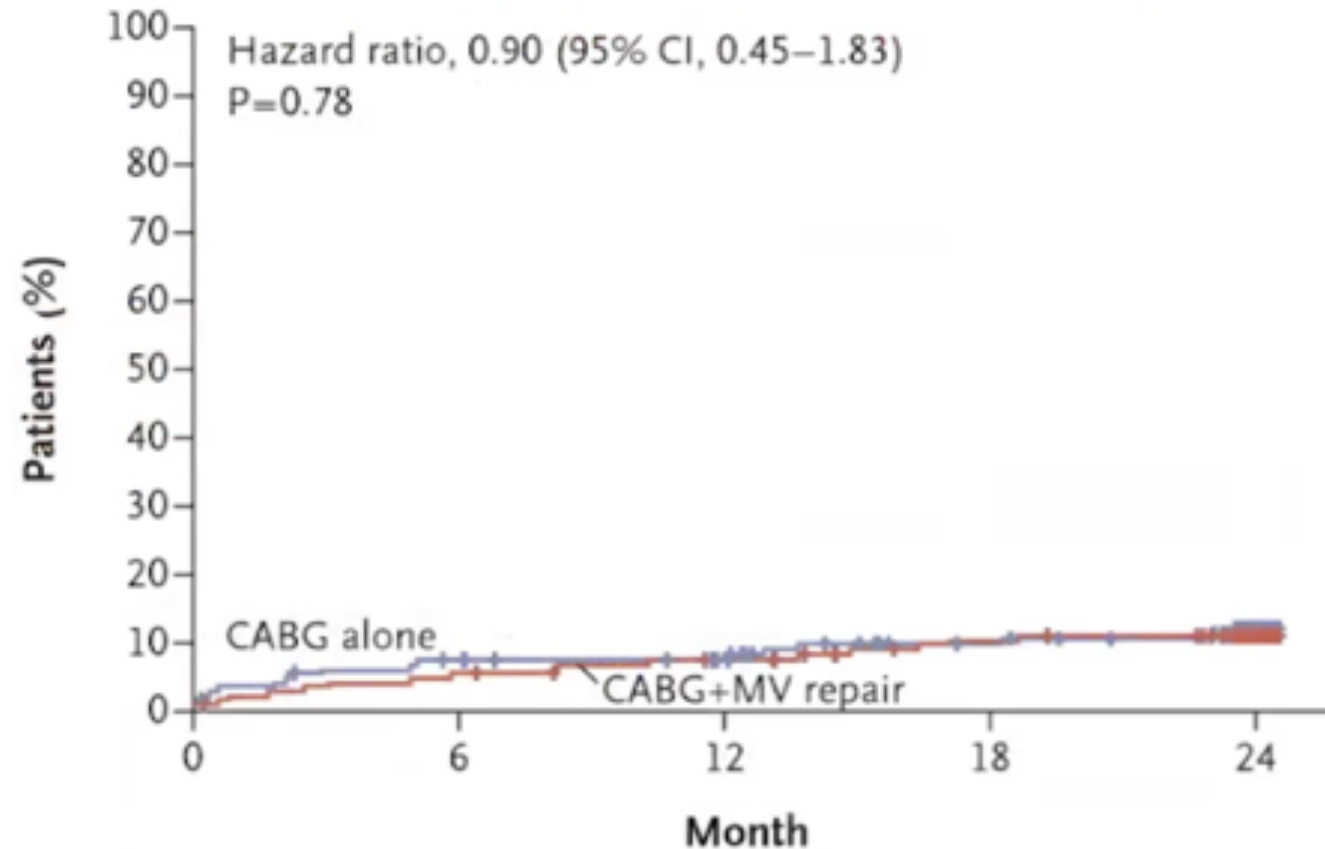
It was **unknown** whether  
intervention to reduce  
secondary mitral regurgitation  
**improved the prognosis!**



# Surgery for Patients with Secondary Mitral Regurgitation



# Surgery for Patients with Secondary Mitral Regurgitation



## No. at Risk

CABG alone	151	138	132	117	66
CABG+MV repair	150	142	136	126	80

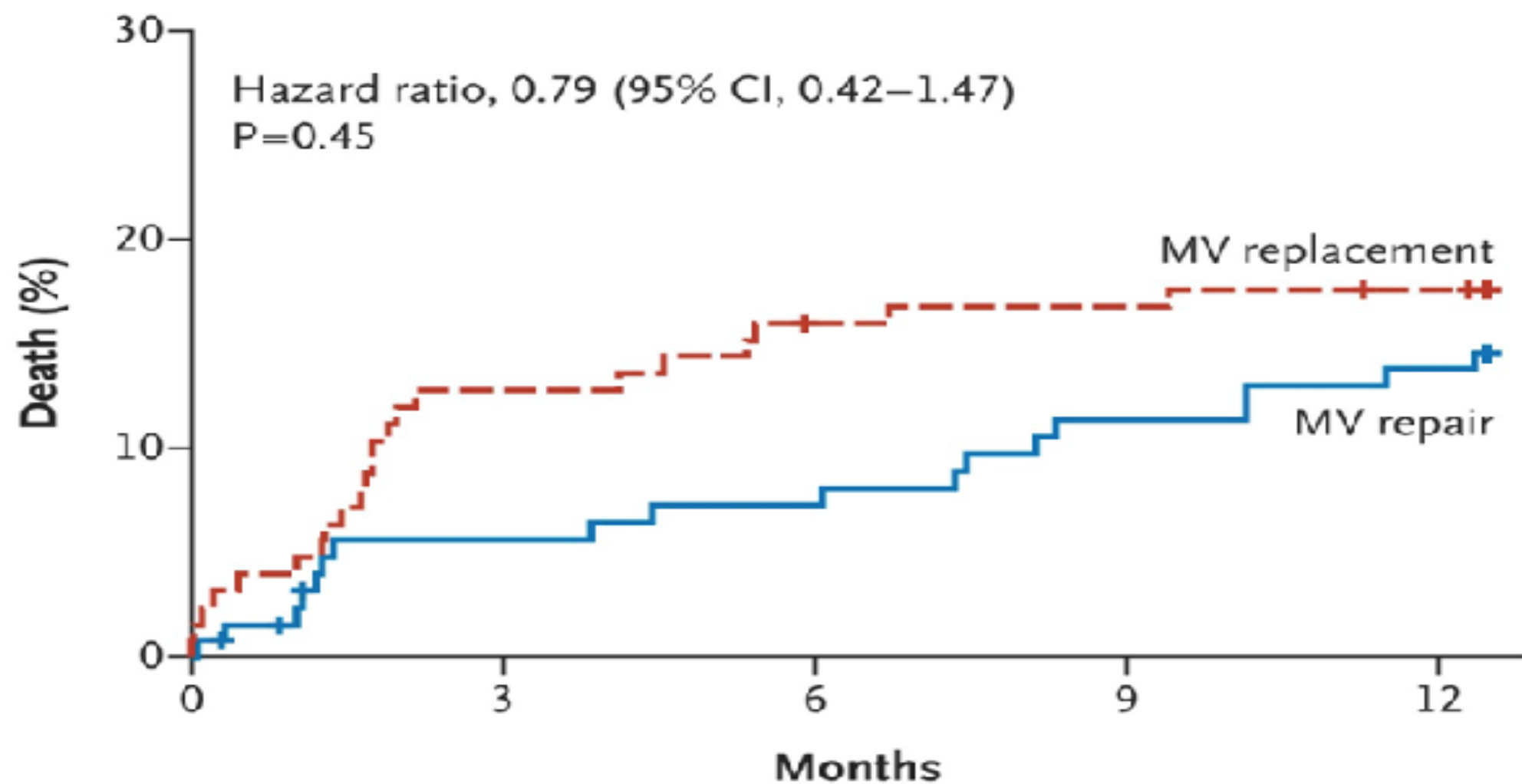


ORIGINAL ARTICLE

# Mitral-Valve Repair versus Replacement for Severe Ischemic Mitral Regurgitation

Michael A. Acker, M.D., Michael K. Parides, Ph.D., Louis P. Perrault, M.D., Alan J. Moskowitz, M.D., Annetine C. Gelijns, Ph.D., Pierre Voisine, M.D., Peter K. Smith, M.D., Judy W. Hung, M.D., Eugene H. Blackstone, M.D., John D. Puskas, M.D., Michael Argenziano, M.D., James S. Gammie, M.D., Michael Mack, M.D., Deborah D. Ascheim, M.D., Emilia Bagiella, Ph.D., Ellen G. Moquete, R.N., T. Bruce Ferguson, M.D., Keith A. Horvath, M.D., Nancy L. Geller, Ph.D., Marissa A. Miller, D.V.M., Y. Joseph Woo, M.D., David A. D'Alessandro, M.D., Gorav Ailawadi, M.D., Francois Dagenais, M.D., Timothy J. Gardner, M.D., Patrick T. O'Gara, M.D., Robert E. Michler, M.D., and Irving L. Kron, M.D., for the CTSN\*

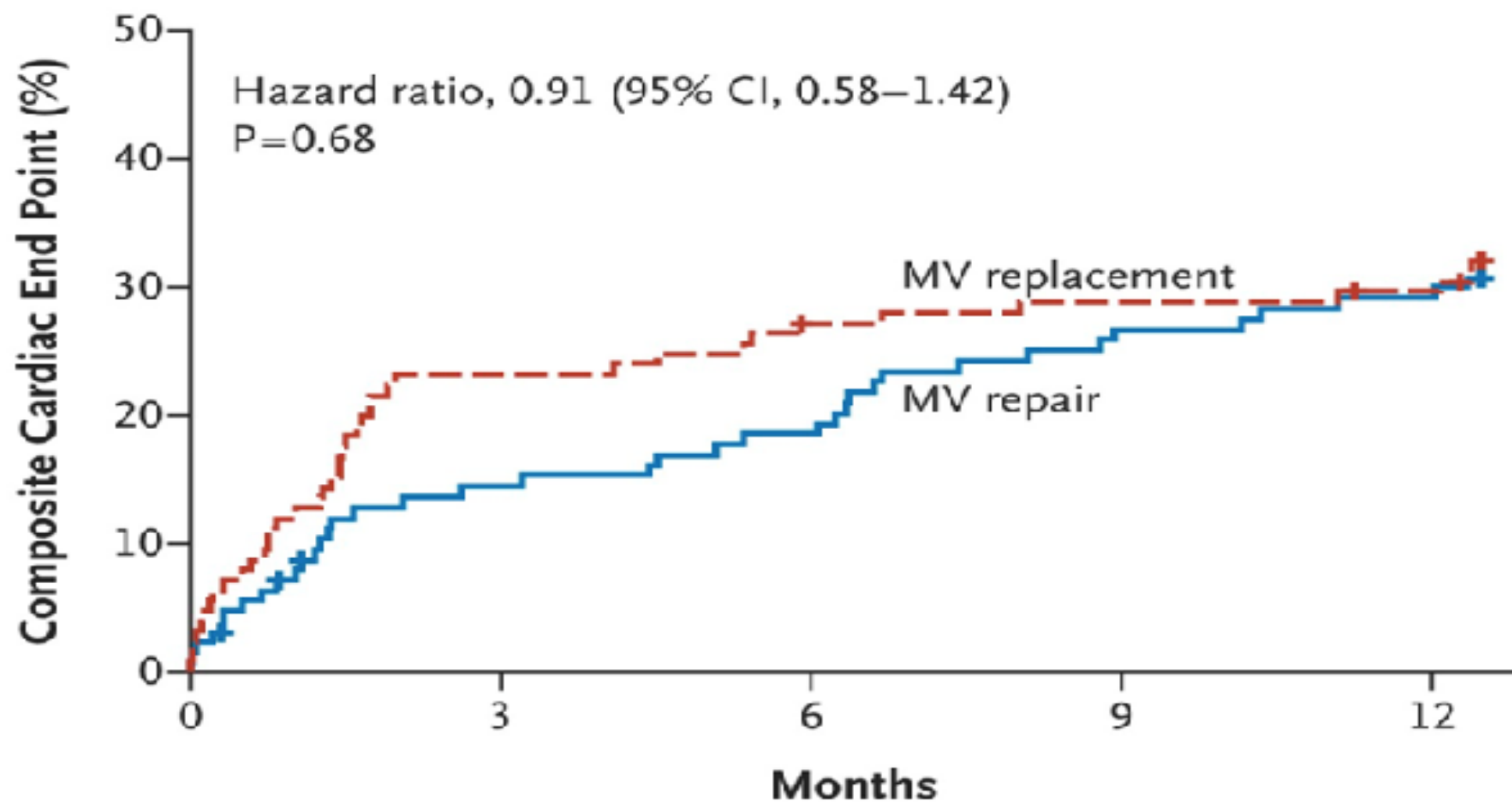
# A Death



## No. at Risk

MV repair	126	116	114	109	106
MV replacement	125	109	104	103	101

## B Composite Cardiac End Point



### No. at Risk

MV repair	126	105	100	90	87
MV replacement	125	96	90	88	86

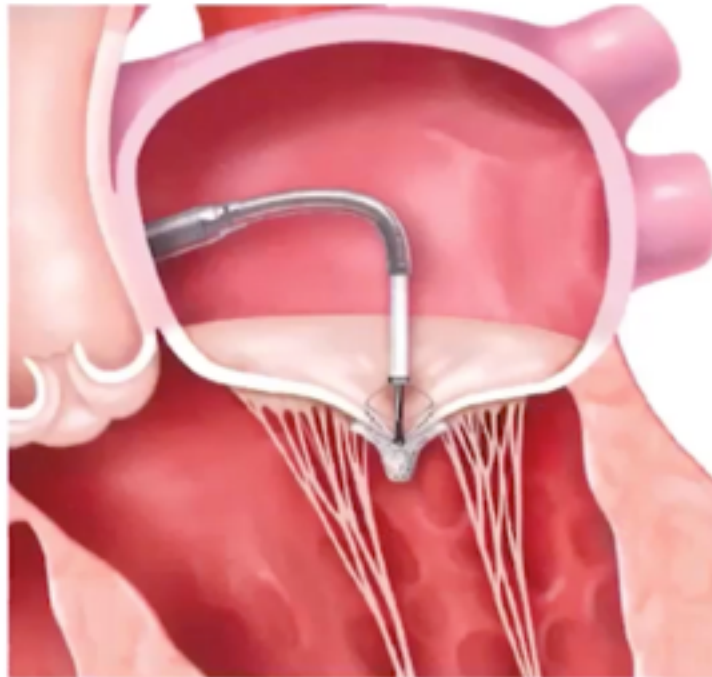
# The Leaflet Approximation Technique

## Replication of Surgical Technique

*ALFIERI -  
SURGICAL*



*MITRACLIP-  
TRANSCATHETER*



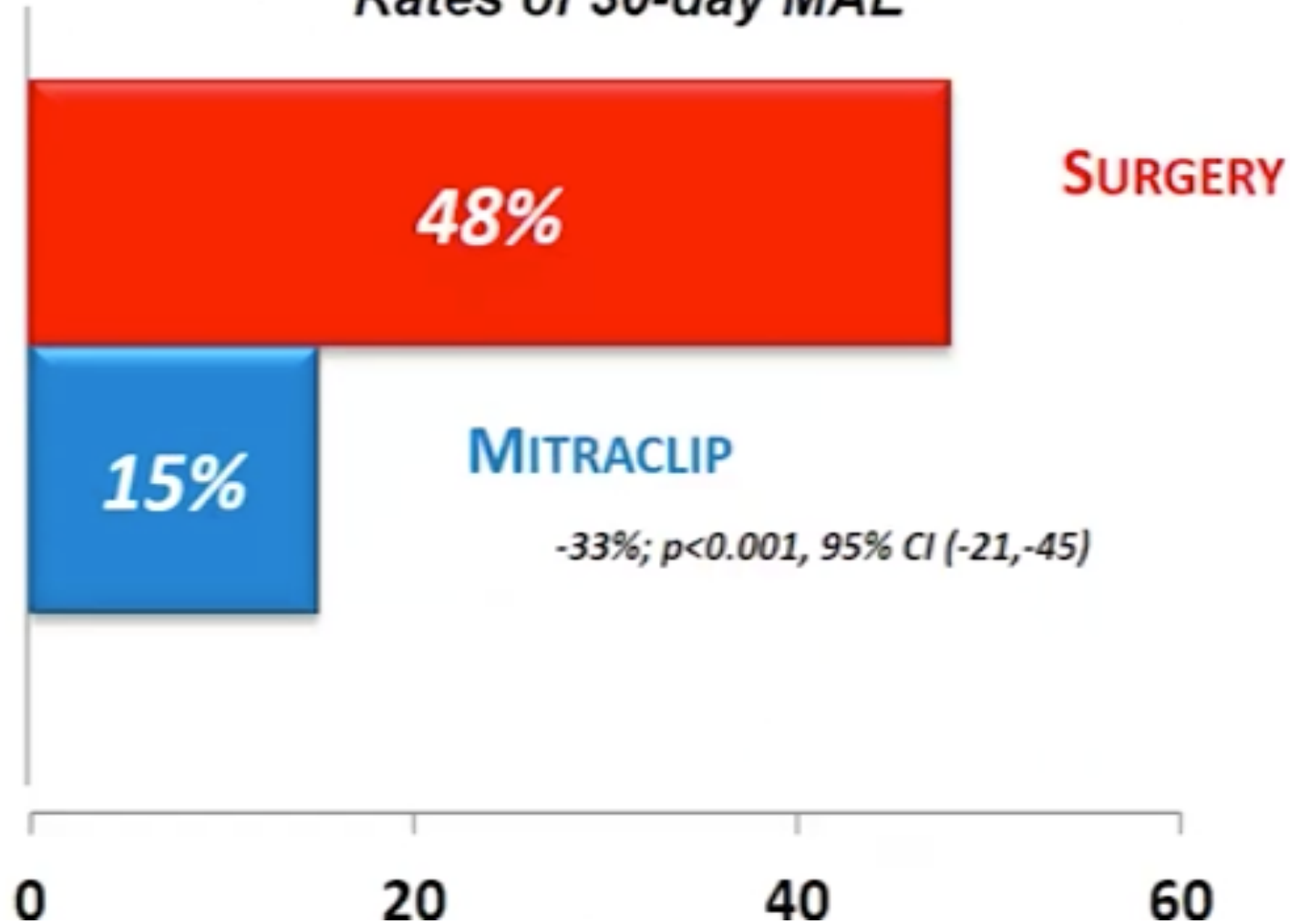
*PASCAL-  
TRANSCATHETER*



# Mitral Clip Safety Profile

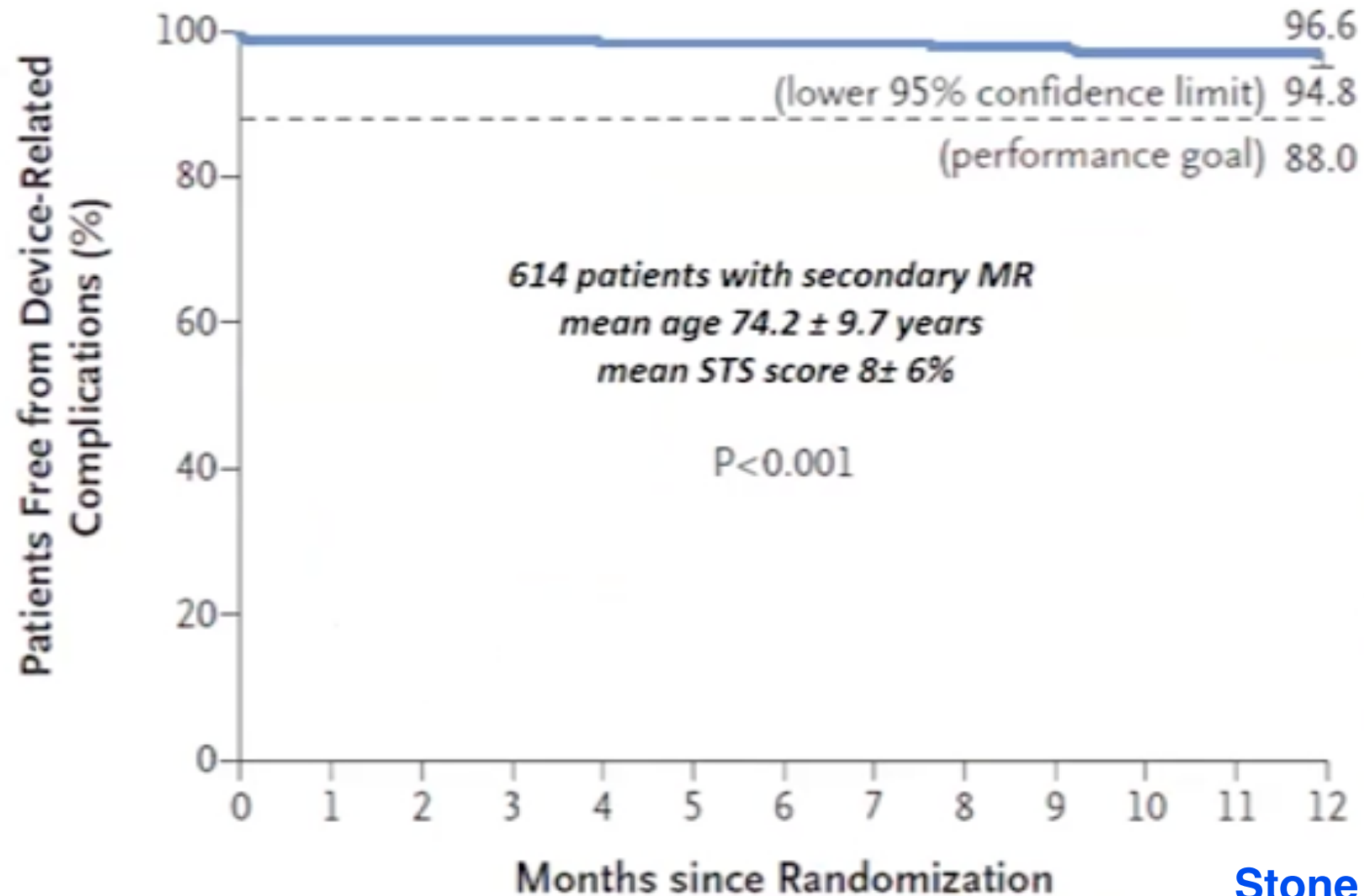
## Everest II RCT

Rates of 30-day MAE



# Mitral Clip Safety Profile

## COAPT RCT



# Percutaneous Repair with the MitraClip Device for Severe Secondary Mitral Regurgitation



# MITRA-FR

Percutaneous Repair with the MitraClip Device for Secondary MR

Multicenter, randomized, open-label, phase 3 trial  
in 304 patients with symptomatic heart failure,  $\downarrow$  LVEF (15-40%)  
and severe secondary MR (EROA  $>20$  mm<sup>2</sup>, RV 30 ml/beat)  
conducted in France (37 centers)

Randomize 1:1

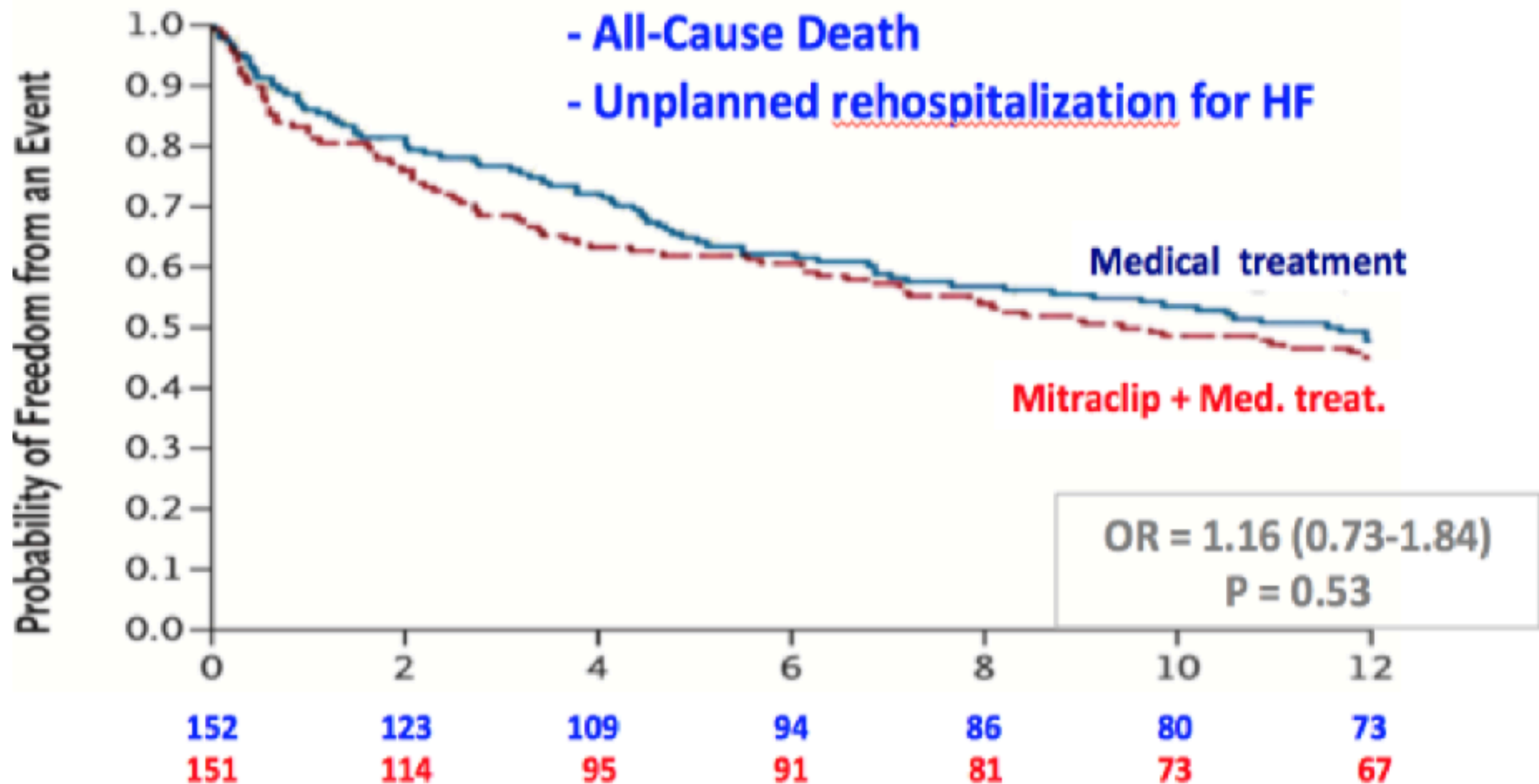
MitraClip + GDMT  
N=152

GDMT alone  
N=152

*Primary endpoint: all-cause death + unplanned hospit. for HF at 12m*



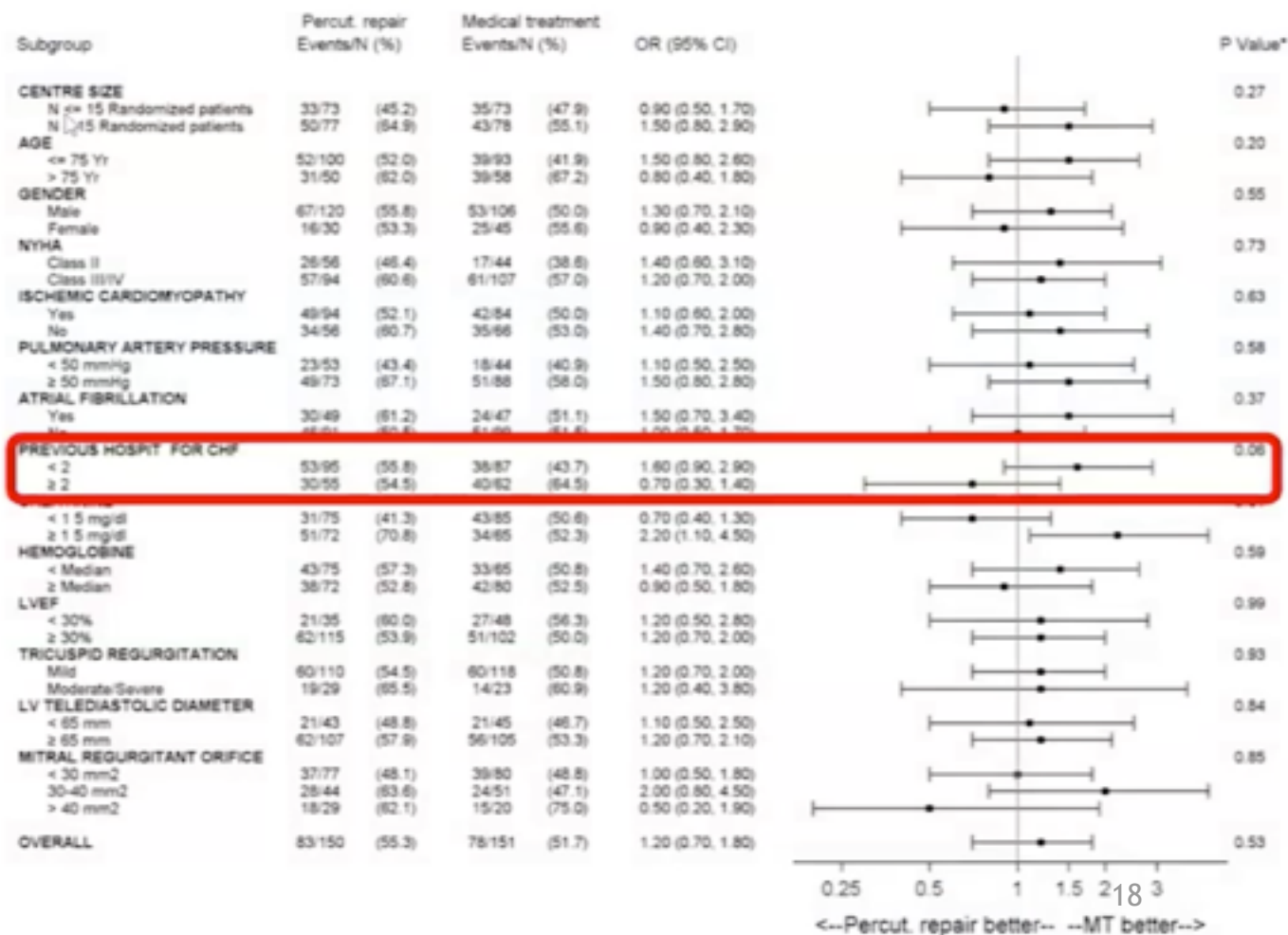
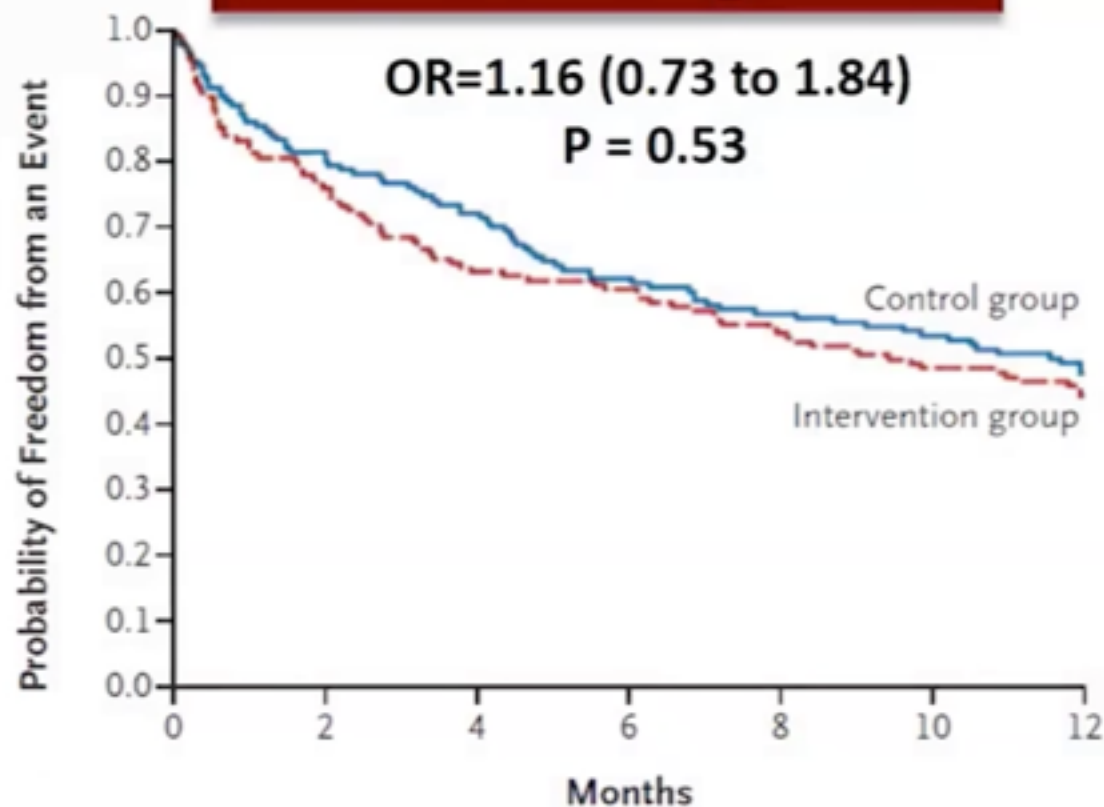
# Primary composite endpoint (99% follow-up)



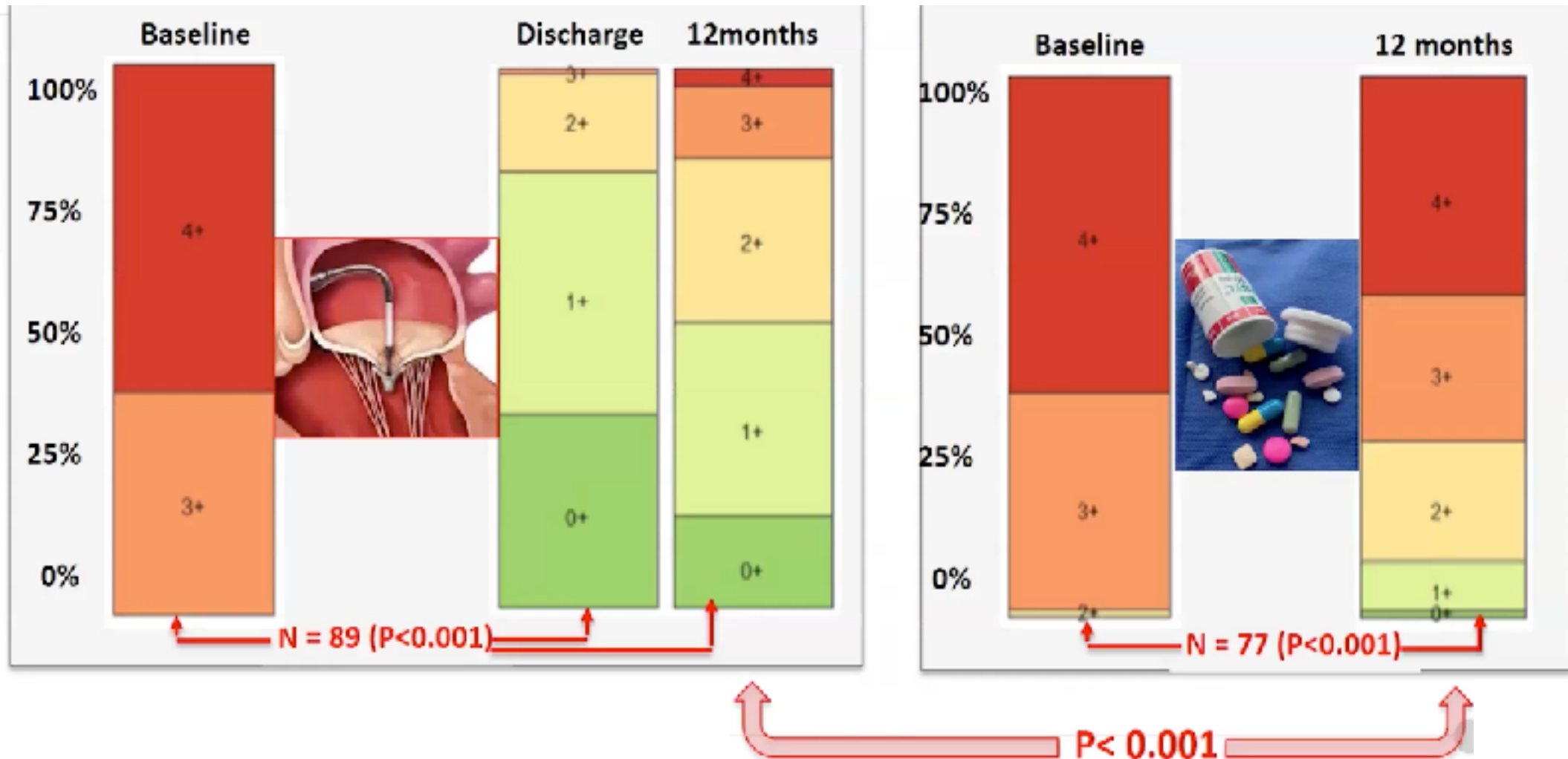
# MITRA-FR – MITRACLIP VS MEDICAL TREATMENT FOR SECONDARY MR: PRIMARY ENDPOINT AND SUBGROUPS

Obadia JF et al. *N Engl J Med* 2018

**Primary Endpoint**  
**All-Cause Death and Re-hosp**  
**for Heart Failure @ 1 Year**



# Mitral Regurgitation Grade Evolution in Both Groups Mitra-FR



**Q:** Is percutaneous correction of secondary mitral regurgitation by mitral clip safe and effective?

**YES**

**Q:** Does correction of secondary mitral regurgitation change the prognosis?

**NO**



# Echocardiographic Criteria for the Definition of Severe Mitral Regurgitation

	Aortic regurgitation	Mitral regurgitation	Tricuspid regurgitation
<b>Qualitative</b>			
Valve morphology	Abnormal/flail/large coaptation defect	Flail leaflet/ruptured papillary muscle/large coaptation defect	Abnormal/flail/large coaptation defect
Colour flow regurgitant jet	Large in central jets, variable in eccentric jets <sup>a</sup>	Very large central jet or eccentric jet adhering, swirling, and reaching the posterior wall of the left atrium	Very large central jet or eccentric wall impinging jet <sup>a</sup>
CW signal of regurgitant jet	Dense	Dense/triangular	Dense/triangular with early peaking (peak <2 m/s in massive TR)
Other	Holodiastolic flow reversal in descending aorta (EDV >20 cm/s)	Large flow convergence zone <sup>a</sup>	–
<b>Semiquantitative</b>			
Vena contracta width (mm)	>6	≥7 (>8 for biplane) <sup>b</sup>	≥7 <sup>c</sup>
Upstream vein flow <sup>c</sup>	–	Systolic pulmonary vein flow reversal	Systolic hepatic vein flow reversal
Inflow	–	E-wave dominant ≥1.5 m/s <sup>d</sup>	E-wave dominant ≥1 m/s <sup>e</sup>
Other	Pressure half-time <200 ms <sup>f</sup>	TVI mitral/TVI aortic >1.4	PISA radius >9 mm <sup>f</sup>
<b>Quantitative</b>		Primary	Secondary <sup>g</sup>
EROA (mm <sup>2</sup> )	≥30	≥40	≥20
R Vol (ml/beat)	≥60	≥60	≥30
+ enlargement of cardiac chambers/vessels	LV	LV, LA	RV, RA, inferior vena cava

# 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 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated GDMT

Randomize 1:1

MitraClip + GDMT  
N=302

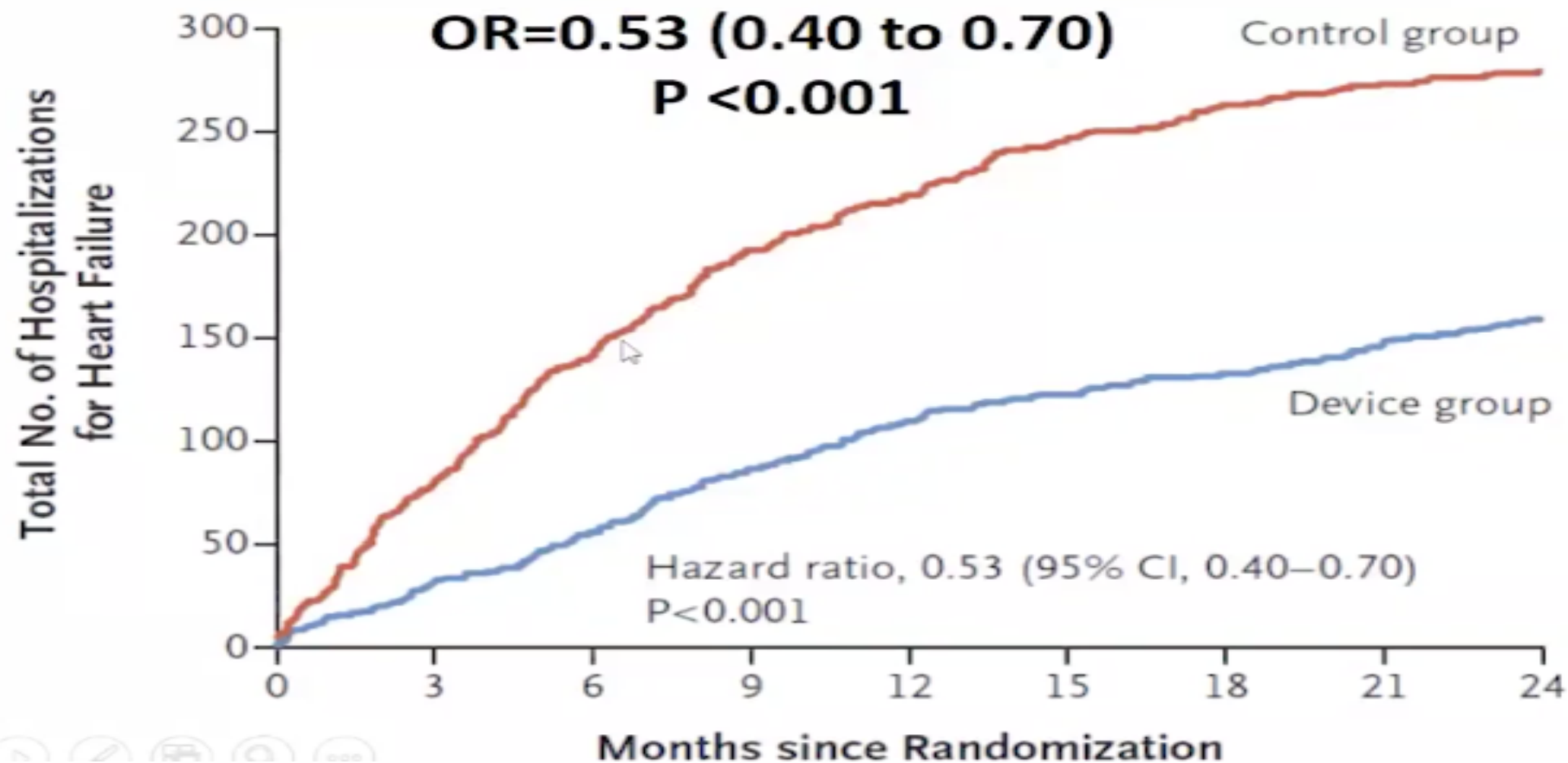
GDMT alone  
N=312

## Primary endpoints:

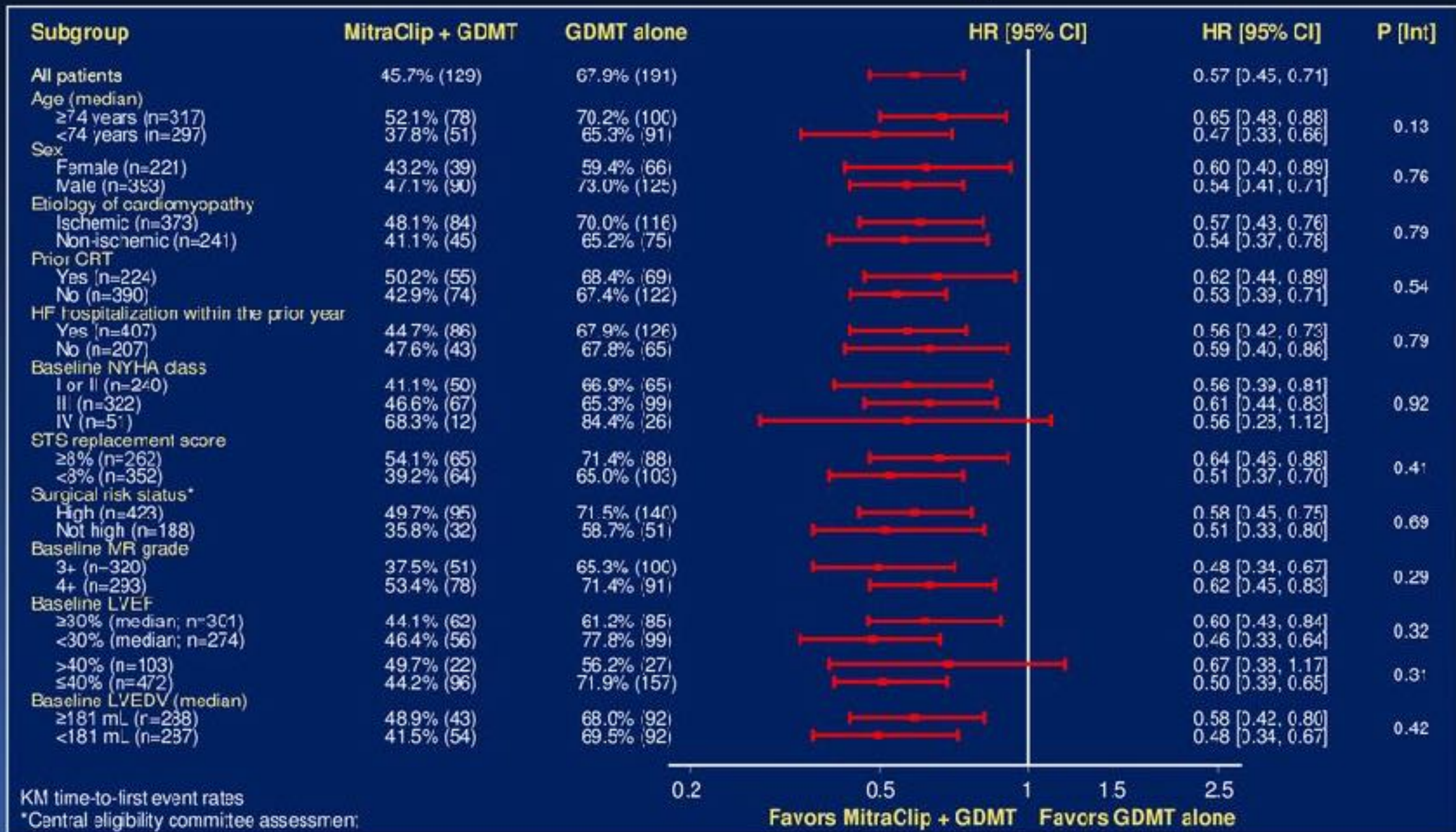
**Effectiveness:** All HF hospitalizations through 24 mos, analyzed when last pt completes 12-mo FU

**Safety:** Freedom from device-related complications through 12 months

**Primary Endpoint  
All-Cause Hospitalisations for  
Heart Failure @ 2 Years**

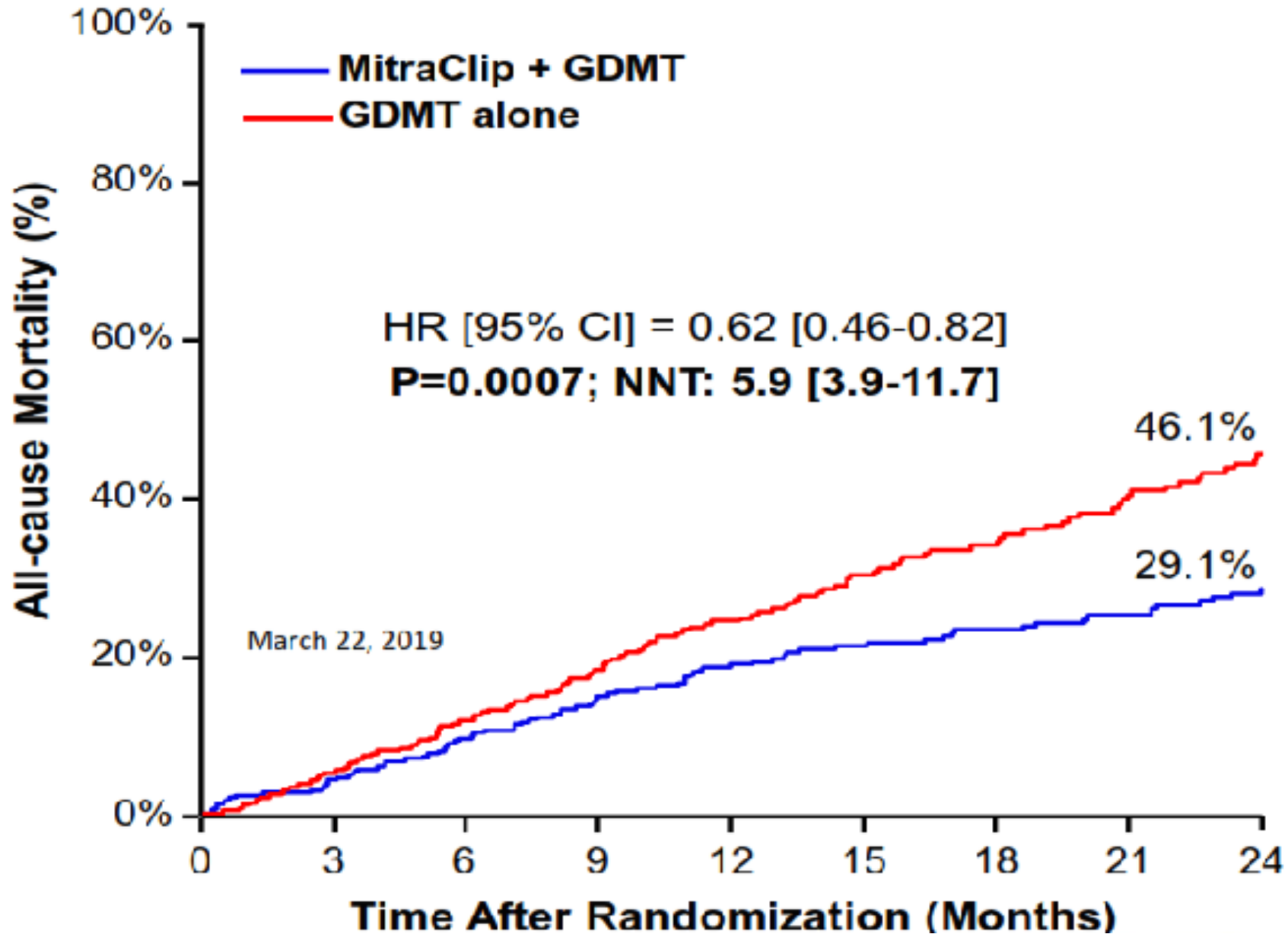


# 24-Month Death or HF Hospitalization

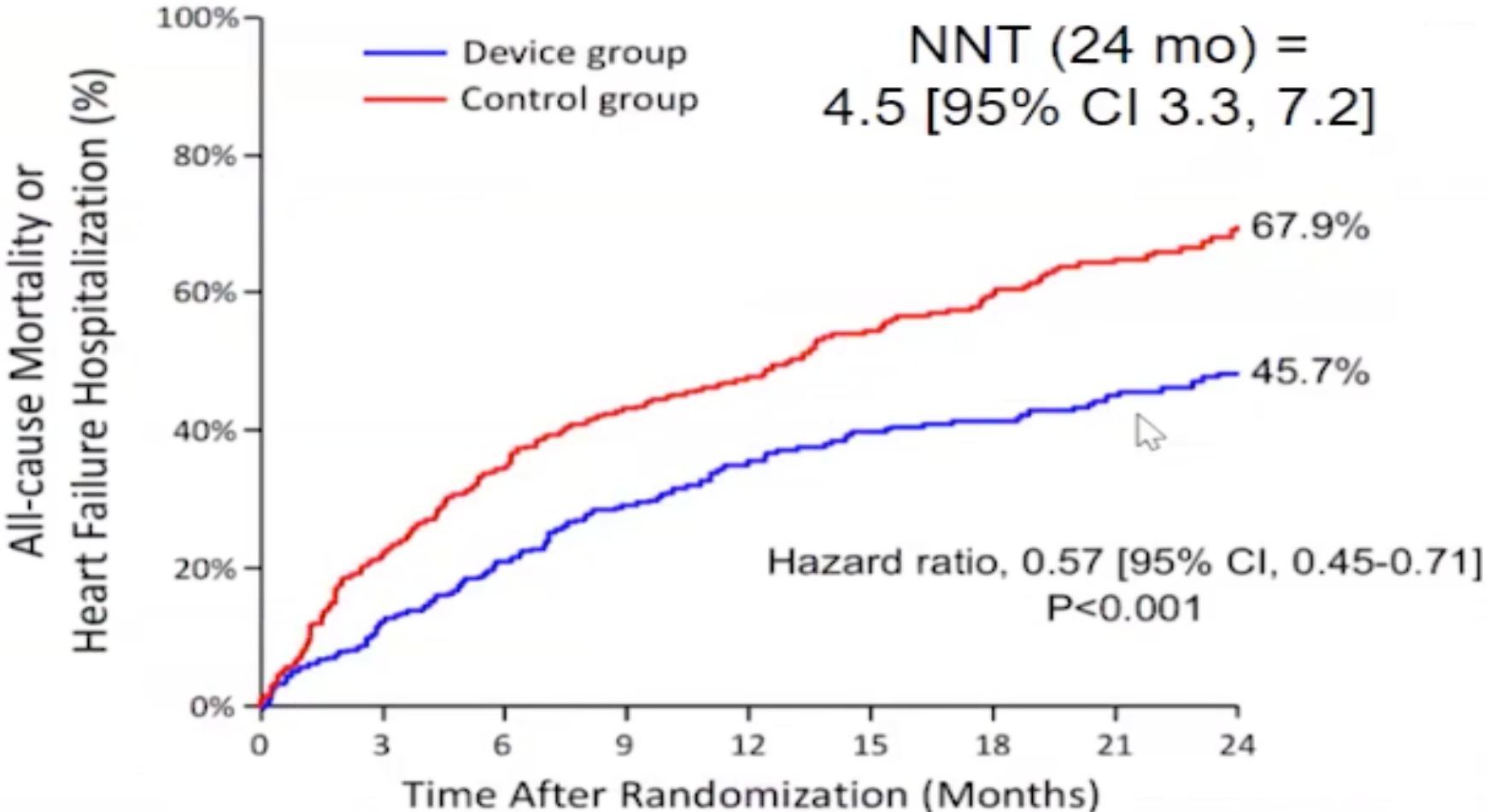




# All-Cause Mortality



# Mortality and HF Hospitalization



No. at Risk:

Device group	302	264	238	215	194	154	145	126	97
Control group	312	244	205	174	153	117	90	75	55

● **TEER with the MitraClip was:**

- Safe.
- Provided durable reduction in MR.
- reduced the rate of HF hospitalizations.
- Significant reduction in all cause mortality.
- Improved quality-of-life and functional capacity during 24-month follow-up.

● **MitraClip** is the first therapy shown to improve the prognosis of patients with HF by reducing secondary MR due to LV dysfunction.

# ACC/AHA Guidelines: Chronic Secondary MR

Grade	Definition	Valve Anatomy	Valve Hemodynamics*	Associated Cardiac Findings	Symptoms
A	At risk of MR	<ul style="list-style-type: none"> <li>Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy</li> </ul>	<ul style="list-style-type: none"> <li>No MR jet or small central jet area &lt;20% LA on Doppler</li> <li>Small vena contracta &lt;0.30 cm</li> </ul>	<ul style="list-style-type: none"> <li>Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities</li> <li>Primary myocardial disease with LV dilation and systolic dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy</li> </ul>
B	Progressive MR	<ul style="list-style-type: none"> <li>Regional wall motion abnormalities with mild tethering of mitral leaflet</li> <li>Annular dilation with mild loss of central coaptation of the mitral leaflets</li> </ul>	<ul style="list-style-type: none"> <li>ERO &lt;0.40 cm<sup>2</sup>†</li> <li>Regurgitant volume &lt;60 mL</li> <li>Regurgitant fraction &lt;50%</li> </ul>	<ul style="list-style-type: none"> <li>Regional wall motion abnormalities with reduced LV systolic function</li> <li>LV dilation and systolic dysfunction due to primary myocardial disease</li> </ul>	<ul style="list-style-type: none"> <li>Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy</li> </ul>
C	Asymptomatic severe MR	<ul style="list-style-type: none"> <li>Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet</li> <li>Annular dilation with severe loss of central coaptation of the mitral leaflets</li> </ul>	<ul style="list-style-type: none"> <li>ERO ≥0.40 cm<sup>2</sup> †</li> <li>Regurgitant volume ≥60 mL</li> <li>Regurgitant fraction ≥50%</li> </ul>	<ul style="list-style-type: none"> <li>Regional wall motion abnormalities with reduced LV systolic function</li> <li>LV dilation and systolic dysfunction due to primary myocardial disease</li> </ul>	<ul style="list-style-type: none"> <li>Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy</li> </ul>
D	Symptomatic severe MR	<ul style="list-style-type: none"> <li>Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet</li> <li>Annular dilation with severe loss of central coaptation of the mitral leaflets</li> </ul>	<ul style="list-style-type: none"> <li>ERO ≥0.40 cm<sup>2</sup> †</li> <li>Regurgitant volume ≥60 mL</li> <li>Regurgitant fraction ≥50%</li> </ul>	<ul style="list-style-type: none"> <li>Regional wall motion abnormalities with reduced LV systolic function</li> <li>LV dilation and systolic dysfunction due to primary myocardial disease</li> </ul>	<ul style="list-style-type: none"> <li>III symptoms due to MR persist even after revascularization and optimization of medical therapy</li> <li>Decreased exercise tolerance</li> <li>Exertional dyspnea</li> </ul>

\*Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

†The measurement of the proximal isovelocity surface area by 2D TTE in patients with secondary MR underestimates the true ERO because of the crescentic shape of the proximal convergence.

# Diverging Guidelines: Chronic Secondary MR

	2017 ESC guidelines	2017 AHA/ACC focused update	2017 ASE guidelines
<b>Semi-quantitative criteria</b>			
Vena contracta (mm)	≥7 (>8 for biplane*)	-	≥7
Pulmonary vein Inflow	Pulmonary vein systolic flow reversal E-wave dominant ≥1.5m/s	-	Pulmonary vein systolic flow reversal -
Other	TVI mitral/TVI aortic >1.4	-	Central large jet > 50% of LA area
<b>Quantitative criteria</b>	<b>Primary</b>	<b>Functional</b>	
EROA (mm <sup>2</sup> )	≥40	≥20	≥40 (or 30-39 with 3 severity criteria or elliptical orifice)
PISA radius	-	-	≥ 1.0 cm at Nyquist 30-40 cm/s
Regurgitant volume (ml)	≥60	≥30	≥60
Regurgitant fraction (%)	-	-	≥50



Traditional approaches to the characterization of secondary **mitral regurgitation** have largely ignored the critical importance of the **left ventricle**

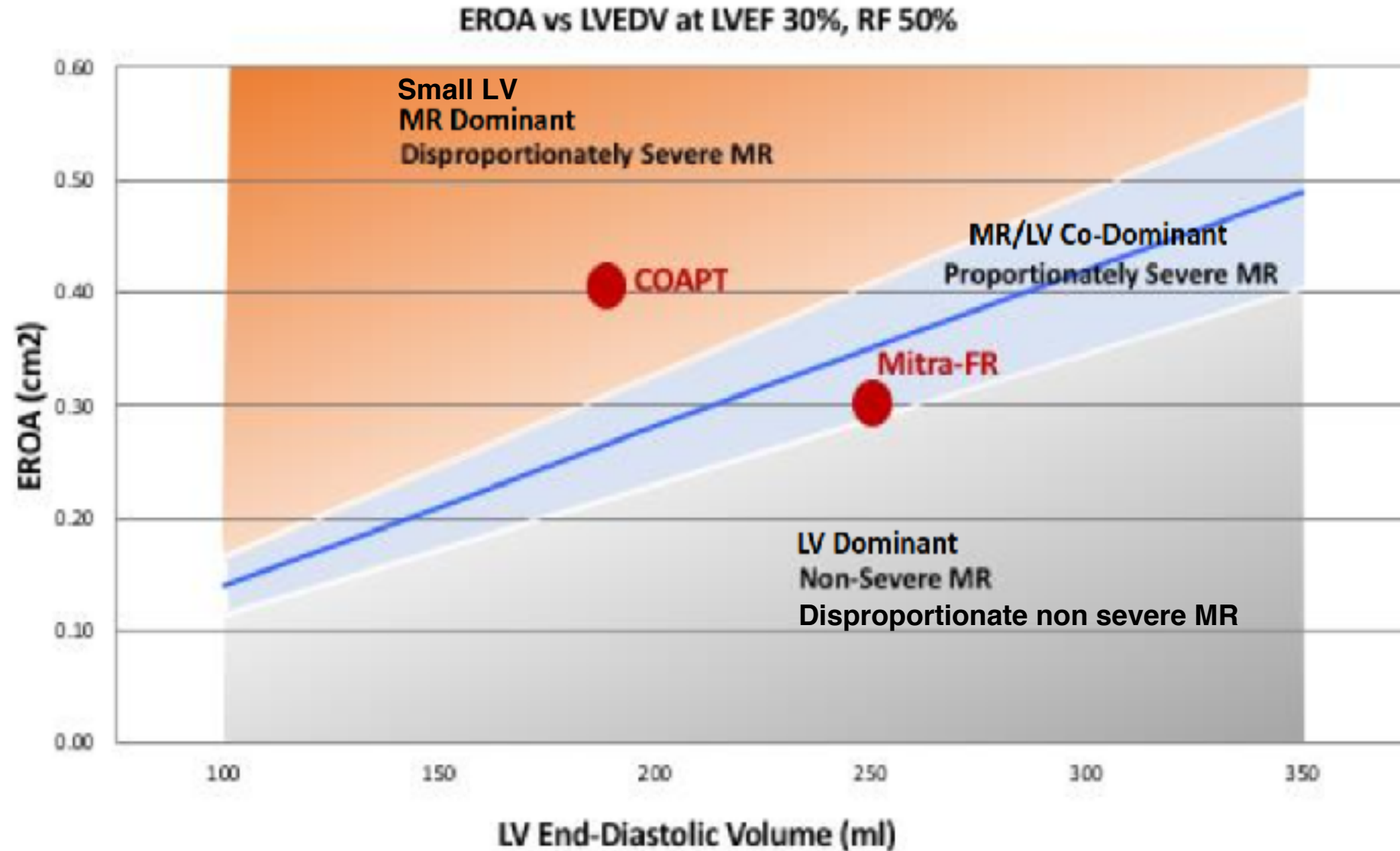




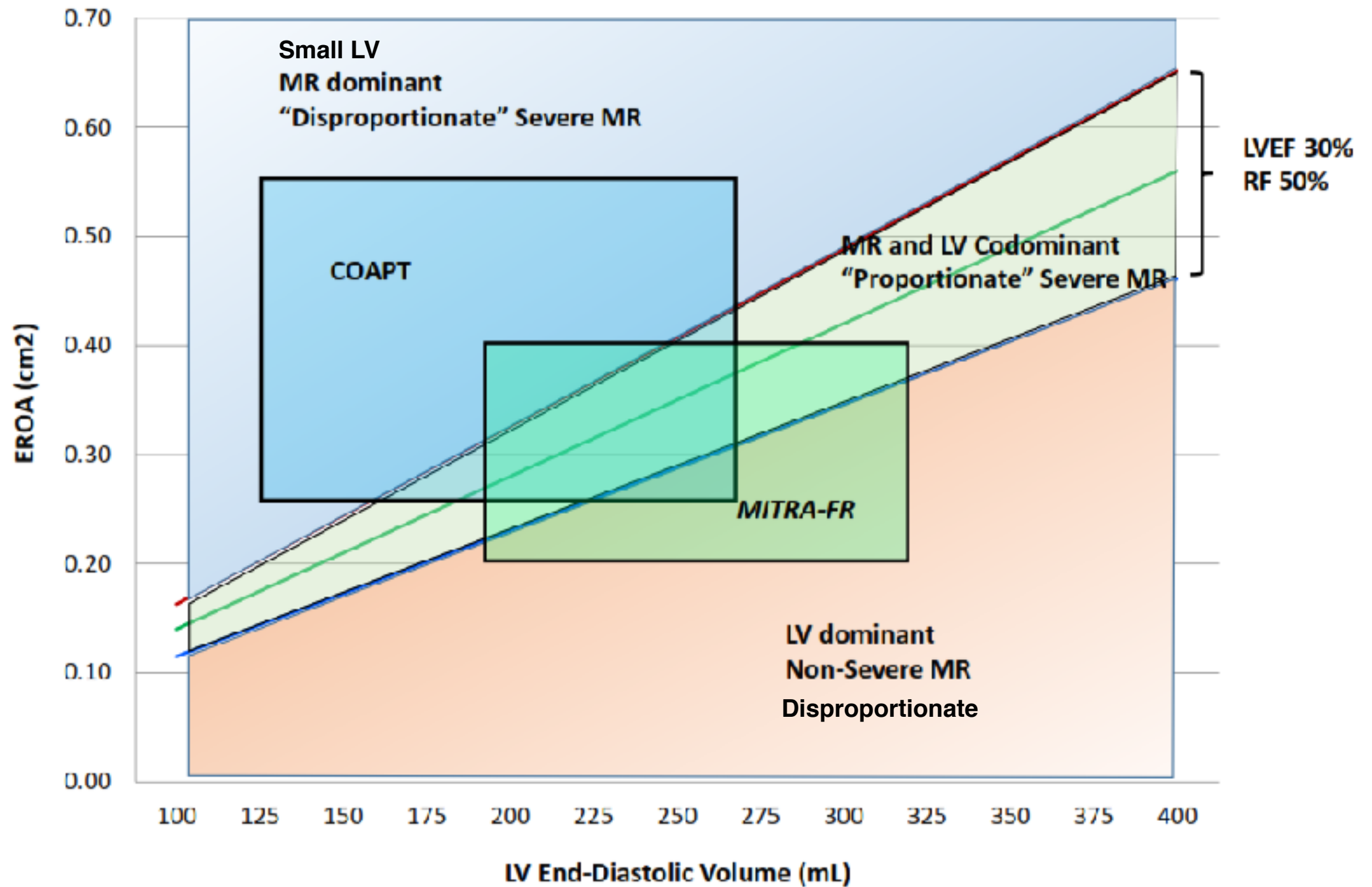
Patients with **secondary mitral regurgitation** represent a heterogeneous group, which can be usefully subdivided based on understanding that the **EROA** is dependent on the **LVEDV**



# Disproportionate vs Proportionate Severe Secondary MR

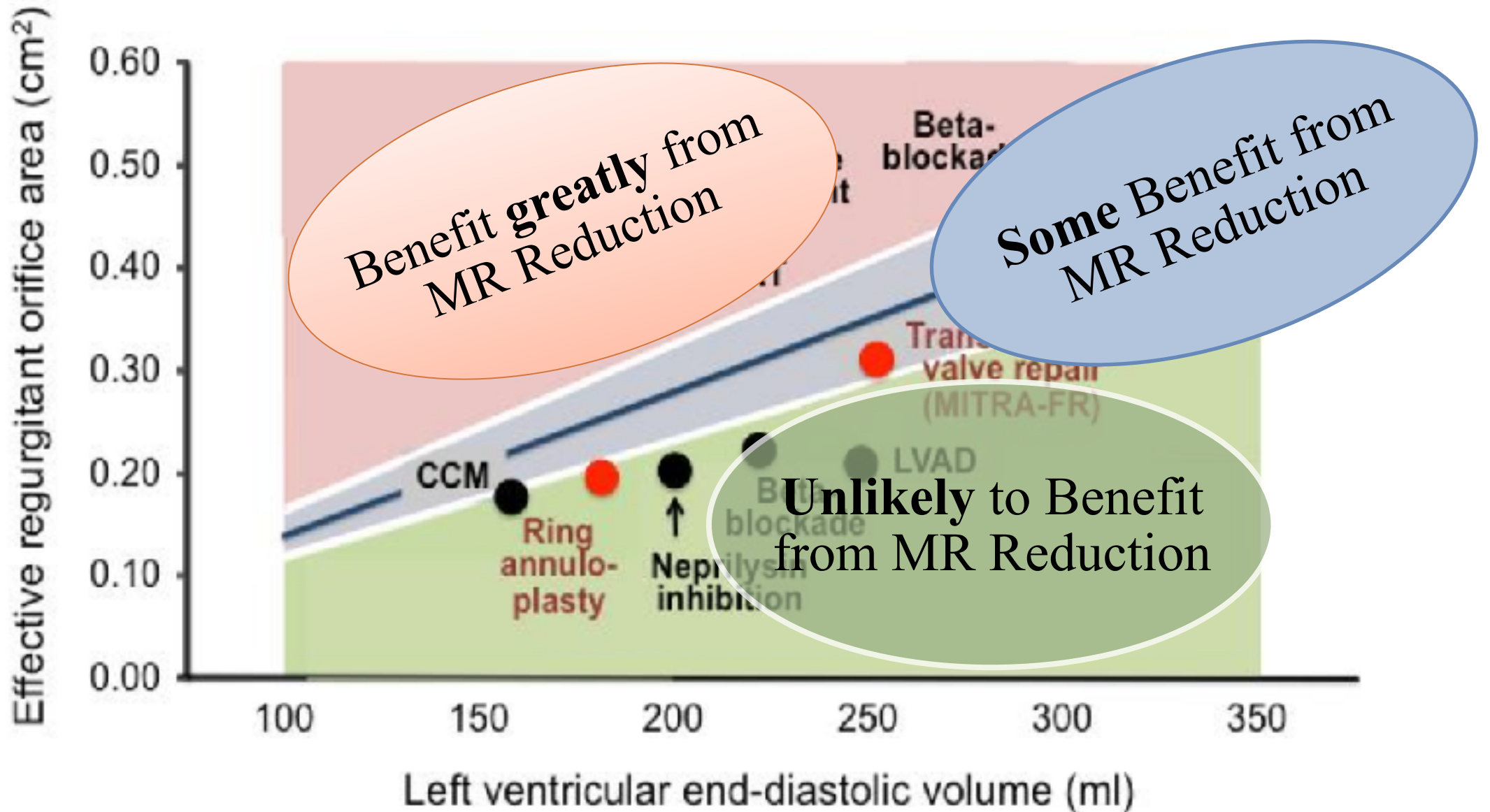






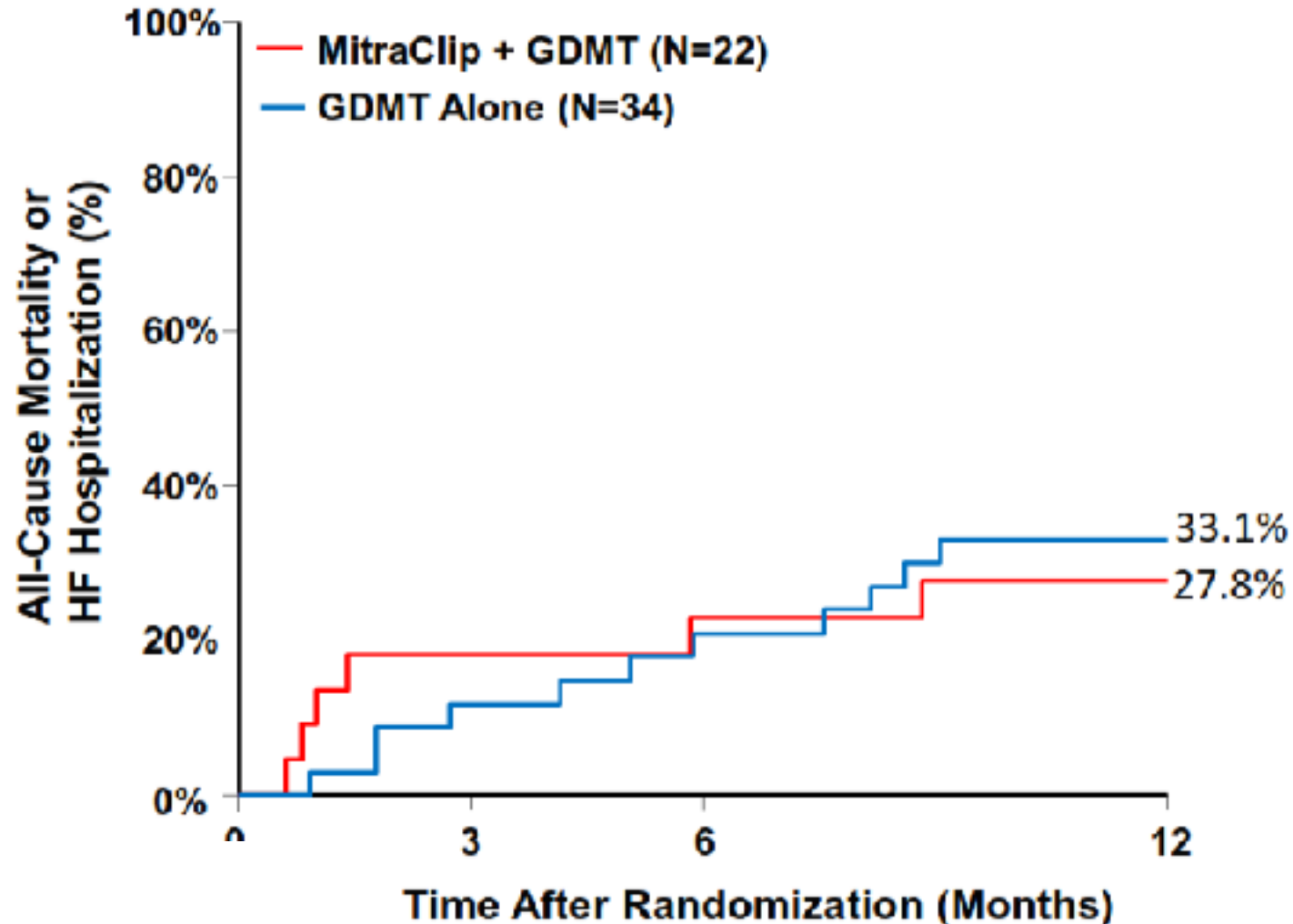
# Trials of HF Therapies and Secondary MR

## Benefit from MR reduction



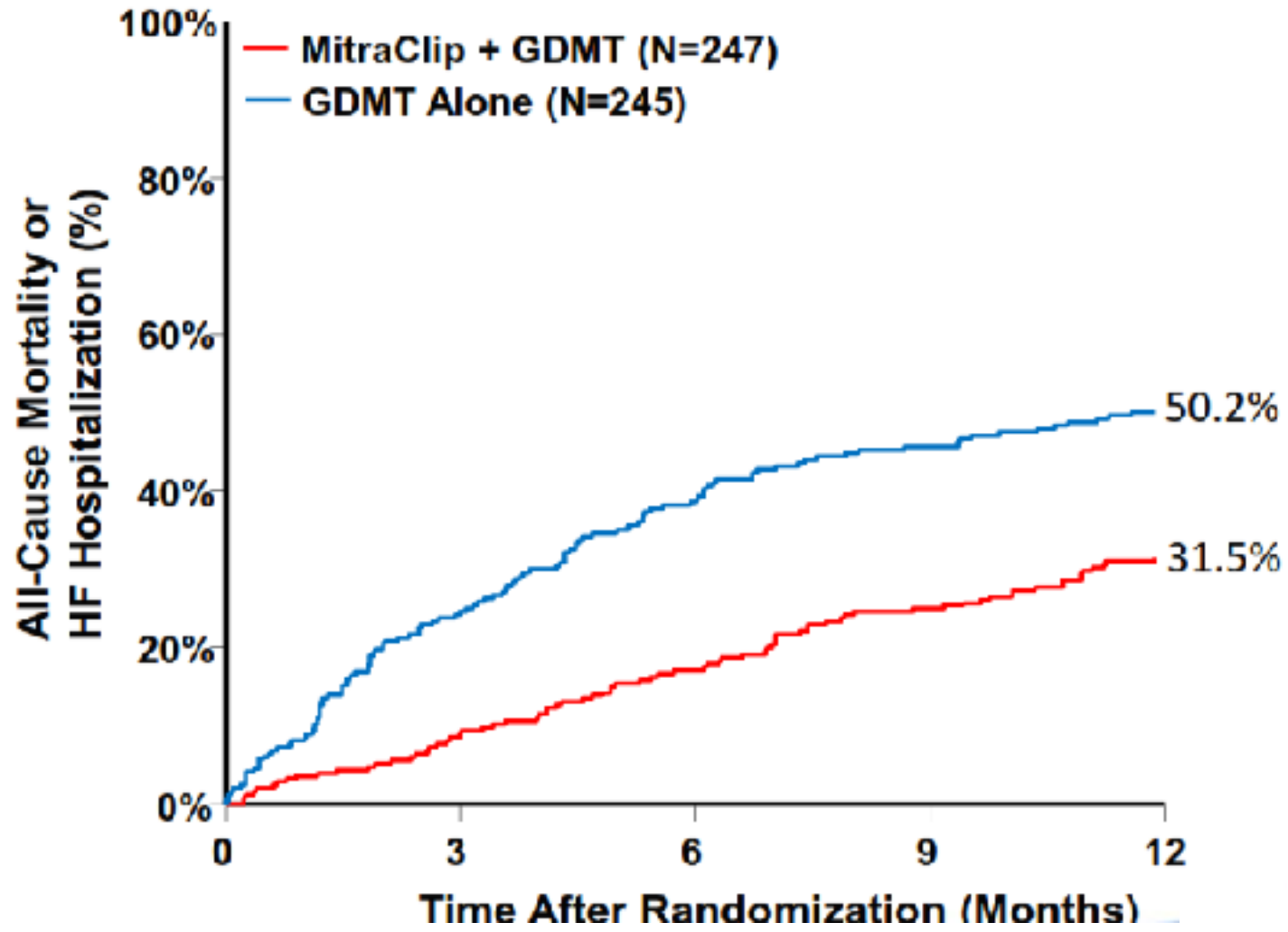
# Mortality and HF Hospitalization at One Year

Group 1: EROA  $\leq 0.30$  cm<sup>2</sup> AND  
LVEDVi  $> 96$  mL/m<sup>2</sup> (N=56)

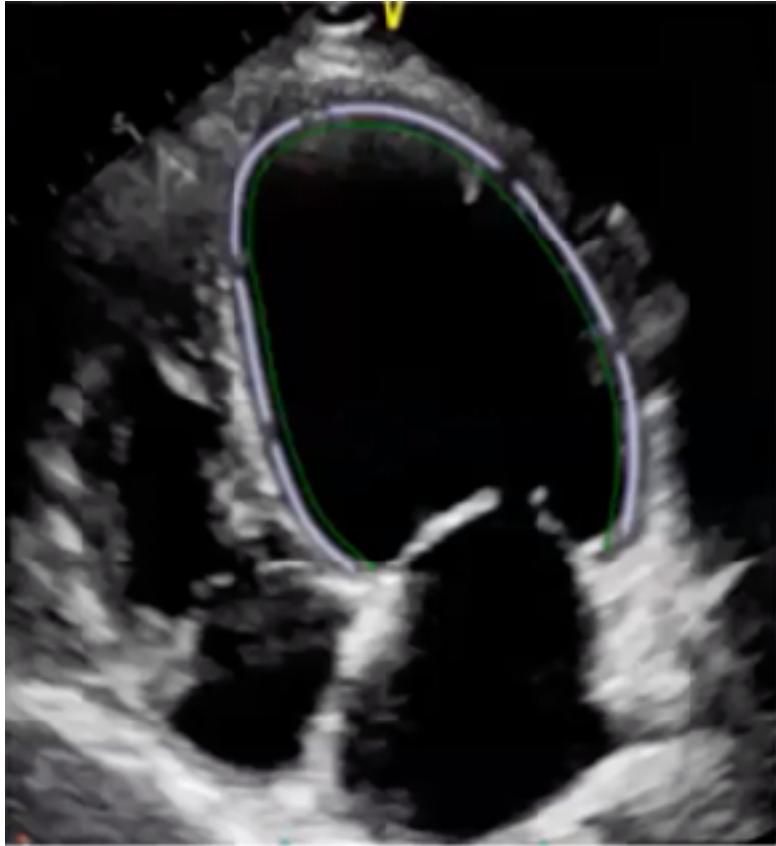


# Mortality and HF Hospitalization at One Year

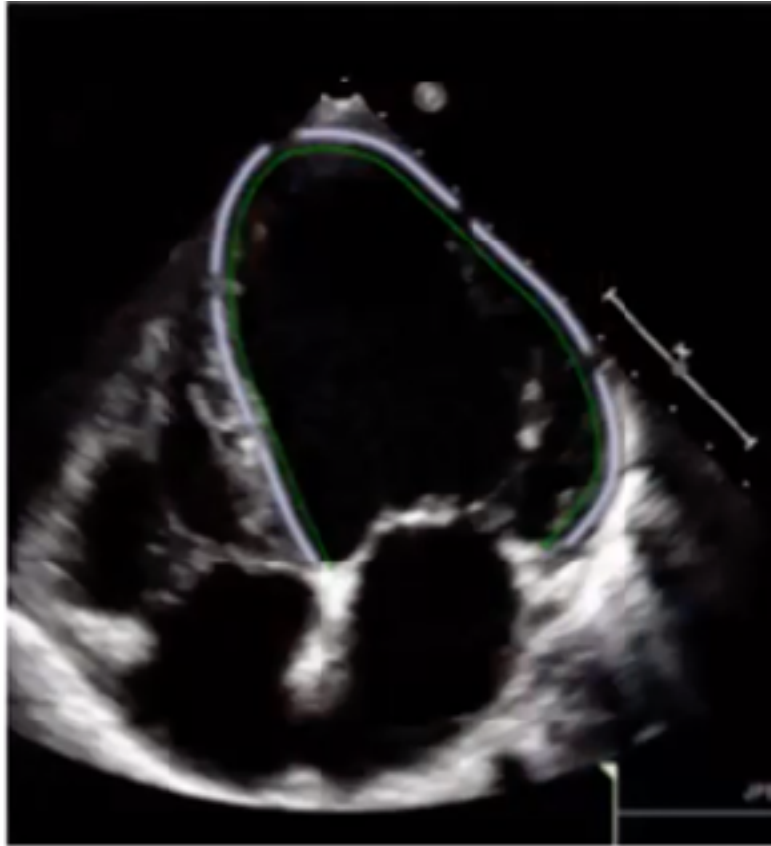
Group 2: EROA > 0.30 OR  
LVEDVi ≤ 96 mL/m<sup>2</sup> (N=492)



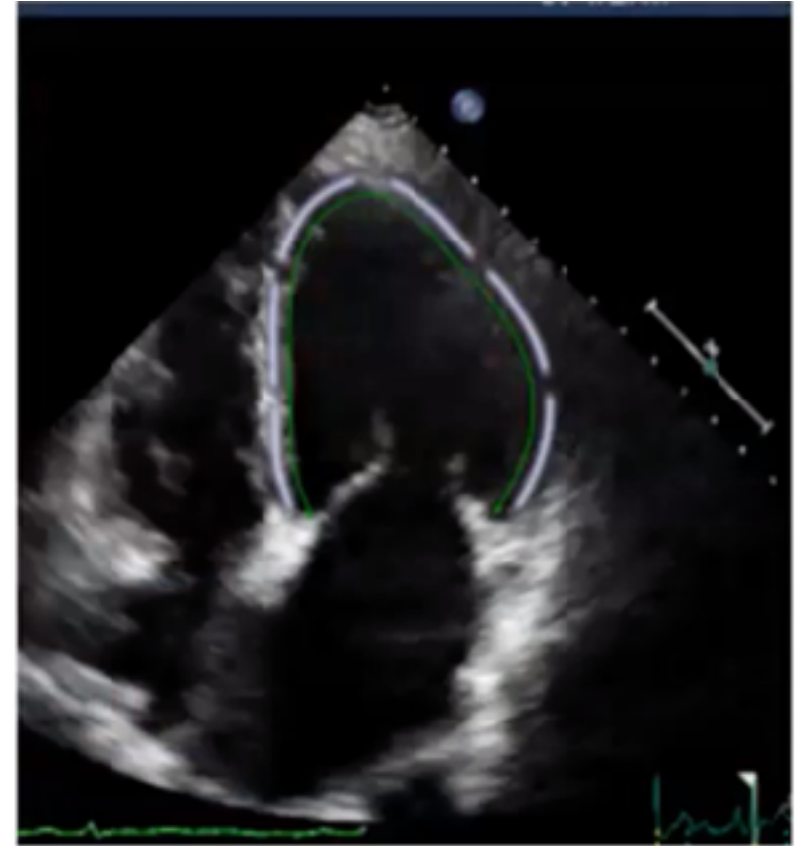
# Three Patients with EROA of 30 mm<sup>2</sup>



LVEF 22%  
LVEDV 310 mL  
GLS -6.8%



LVEF 36%  
LVEDV 197 mL  
GLS -8.4%



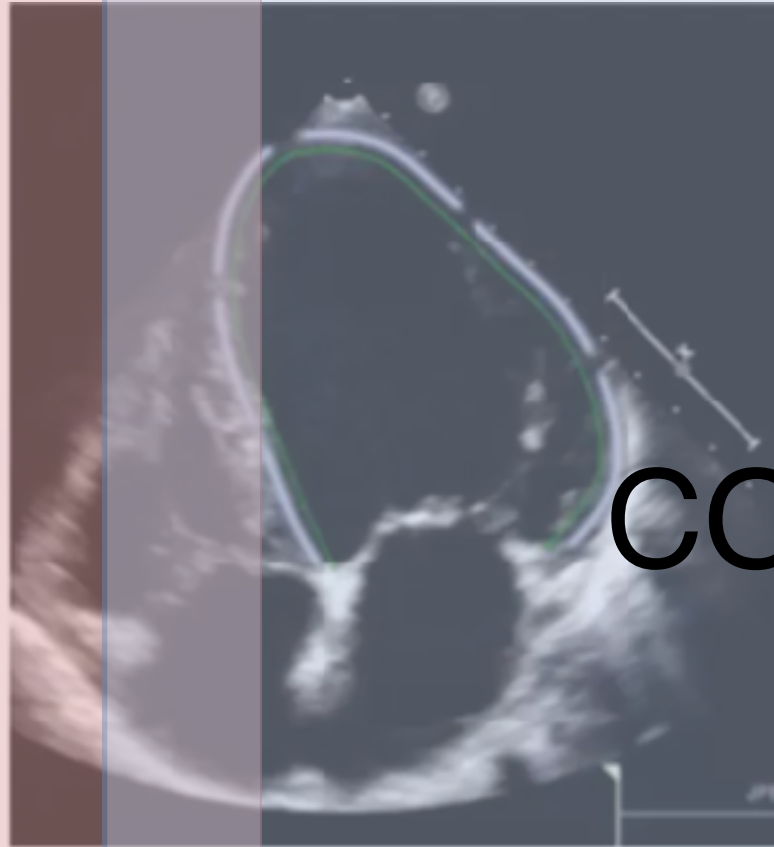
LVEF 60%  
LVEDV 140 mL  
GLS -20.3%

# Three Patients with EROA of 30 mm<sup>2</sup>



Mitra- FR

LVEF 22%  
LVEDV 310 mL  
GLS -6.8%



COAPT

LVEF 36%  
LVEDV 197 mL  
GLS -8.4%



LVEF 60%  
LVEDV 140 mL  
GLS -20.3%

**Characterization of MR as**  
**proportionate or disproportionate**  
**to **LVEDV**** appears to be critical  
to the selection of an optimal  
treatment for patients with **chronic**  
**HF** and **systolic dysfunction**

VILEV  
EDITORIAL VIEWPOINT

# Proportionate and Disproportionate Functional Mitral Regurgitation

A New **Conceptual Framework** That Reconciles the  
Results of the MITRA-FR and COAPT Trials

Paul A. Grayburn, MD, Anna Sannino, MD, Milton Packer, MD



Trans-catheter Edge to Edge  
Repair (**TEER**) vs Trans-catheter  
Mitral Valve Replacement (**TMVR**)  
for Secondary Mitral Regurgitation

# Study Design



**vs**



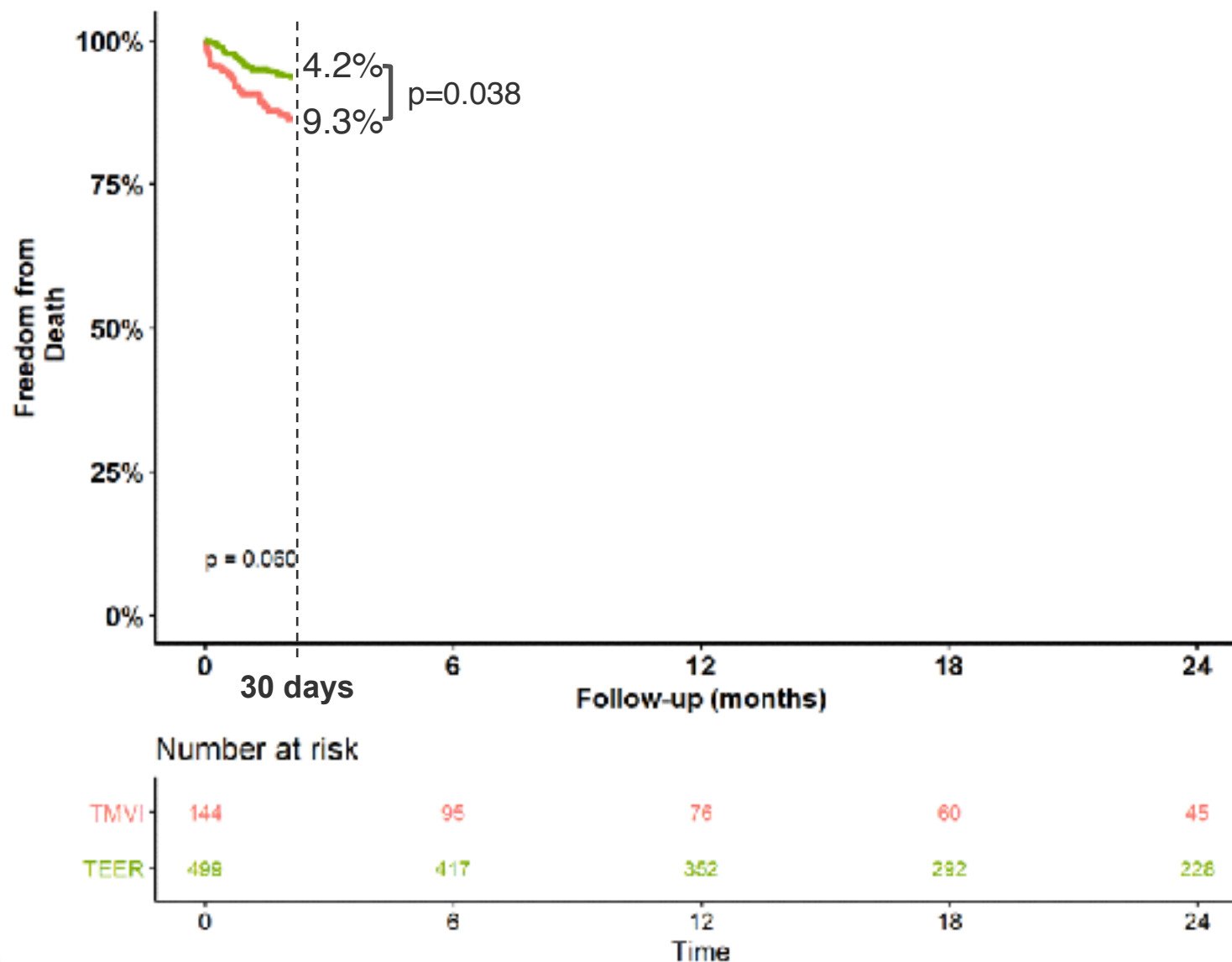
**TEER**

(trans-catheter repair)

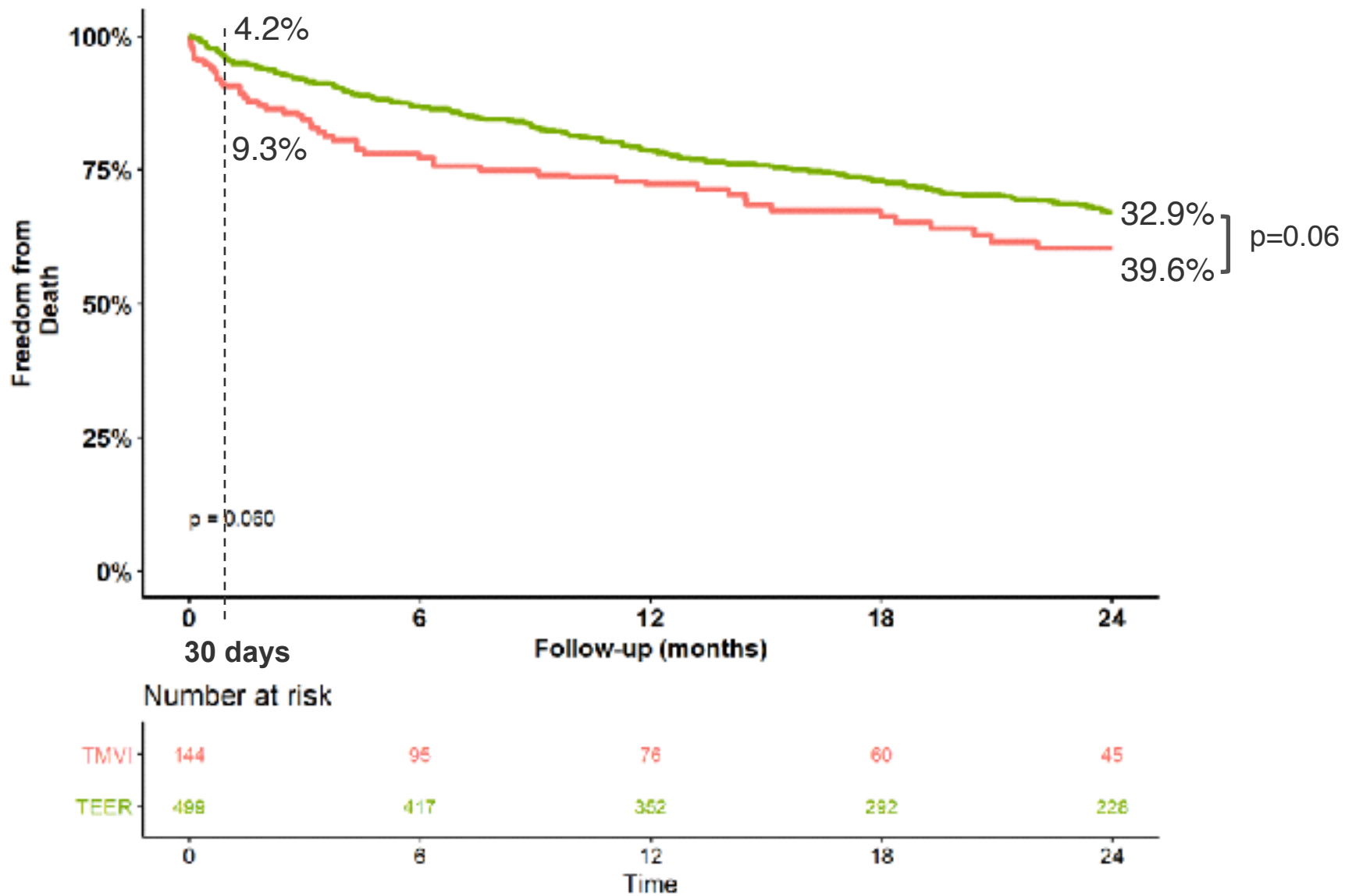
**TMVI**

(Trans-catheter replacement)

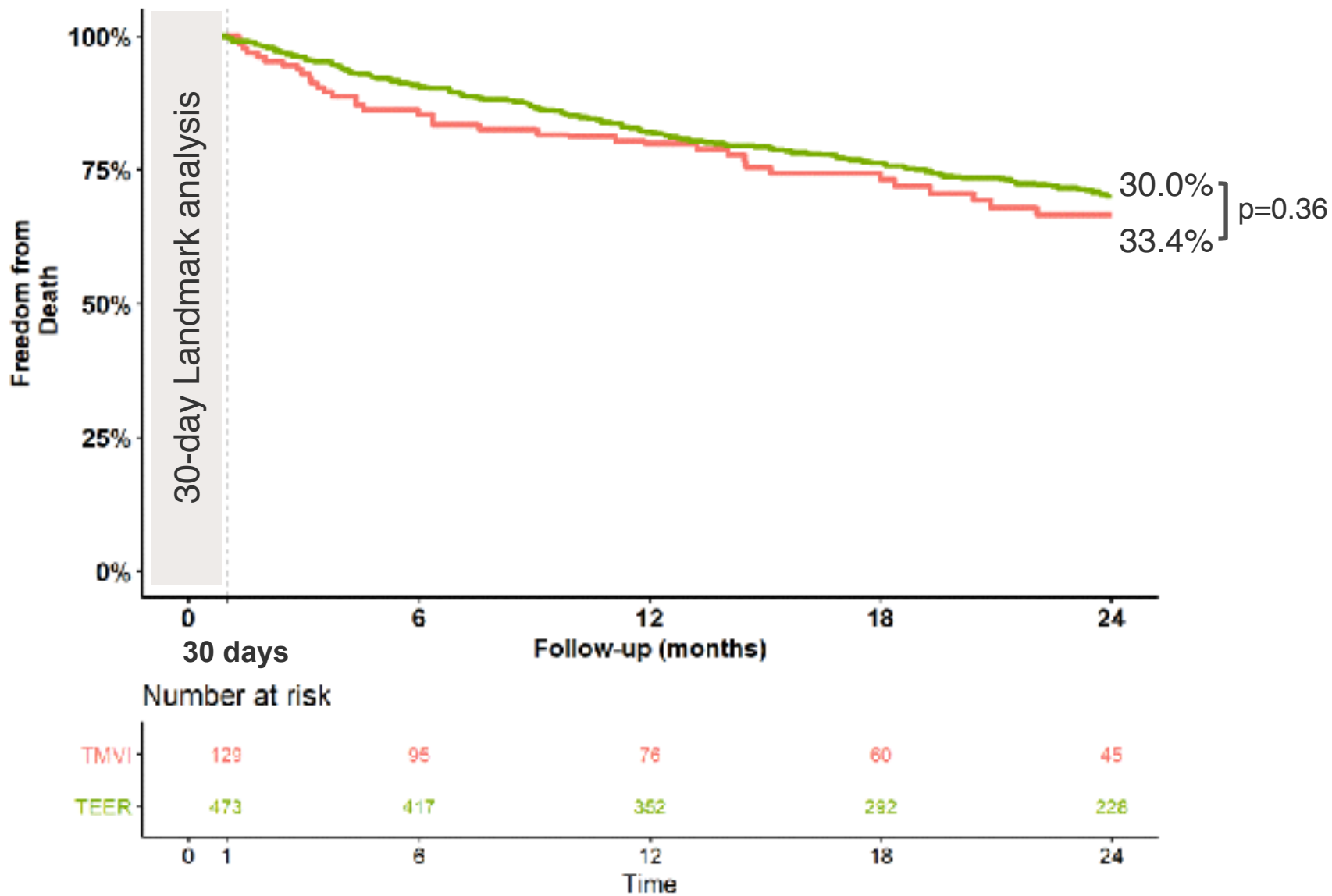
# All-cause Death



# All-cause Death

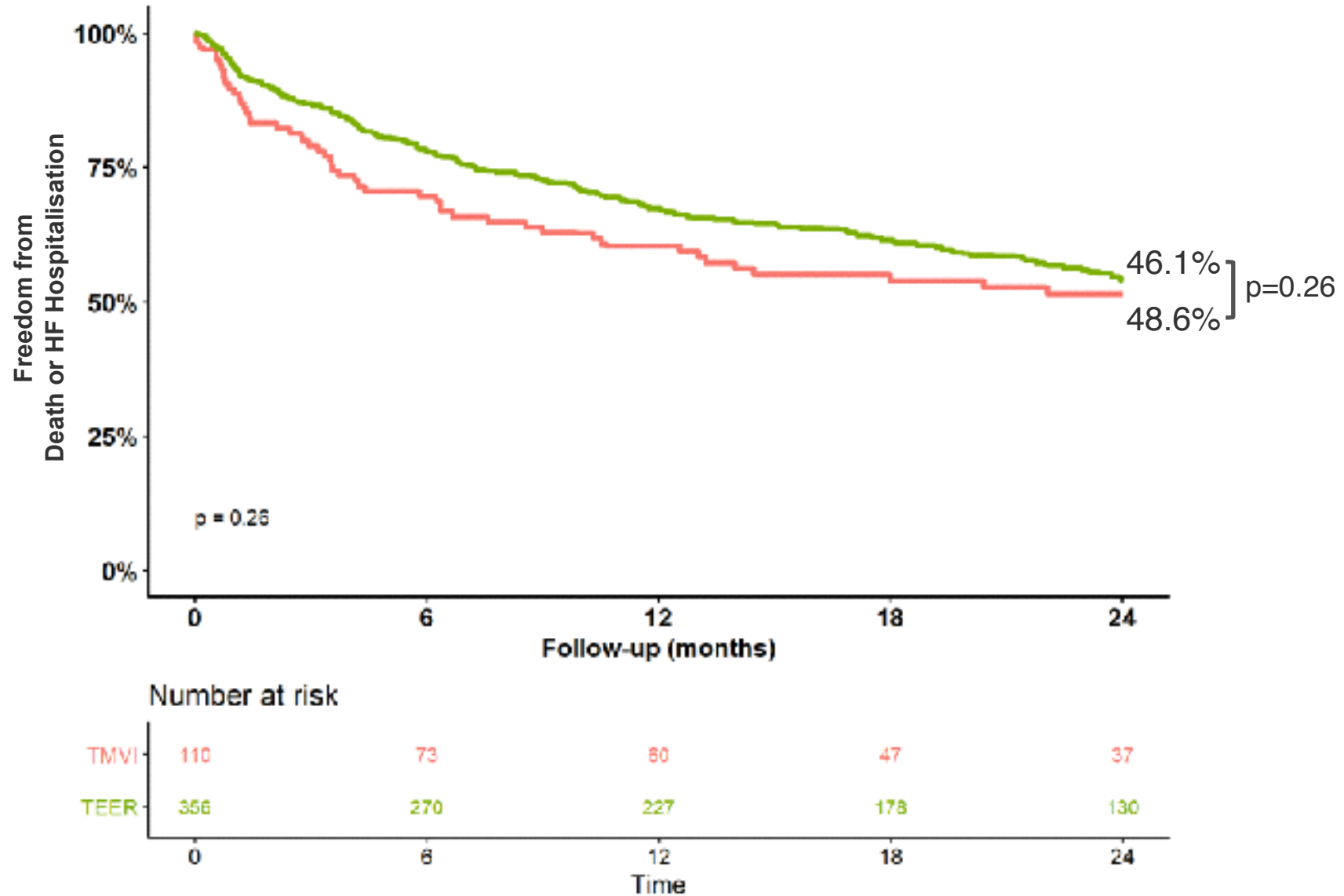


# All-cause Death



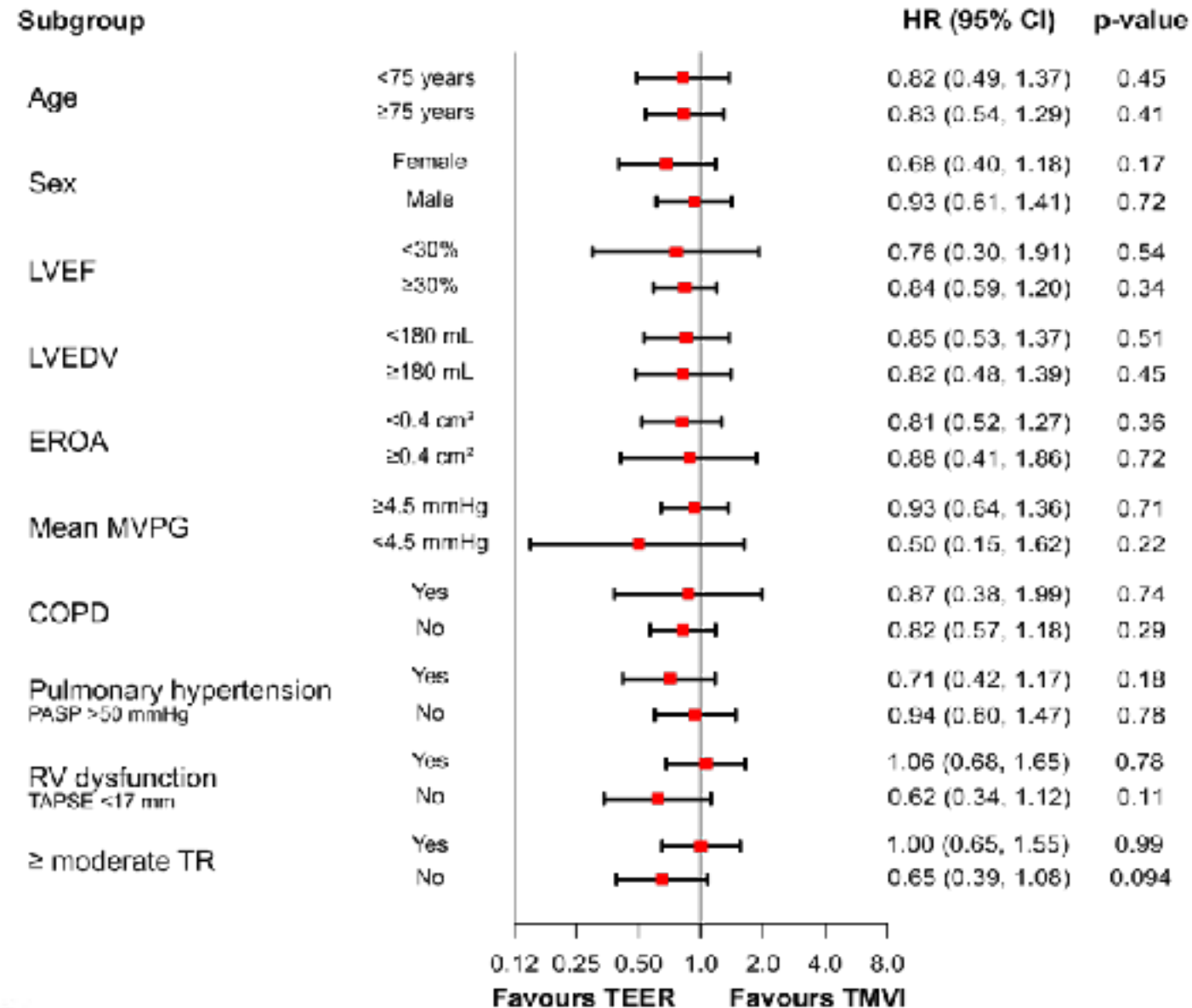
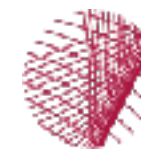
# Combined Endpoint

## All-cause Death or HF Hospitalisation



# Subgroup Analysis

## All-cause Death or HF Hospitalisation

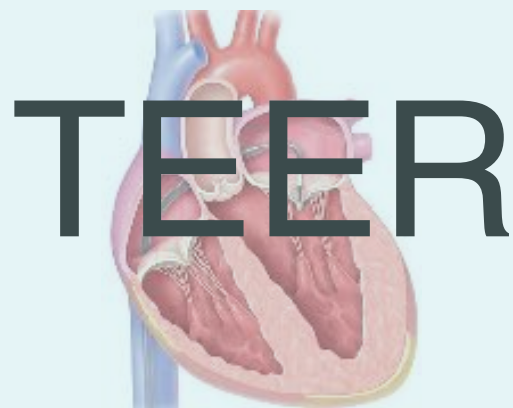


No difference

between TEER and TMVI regarding

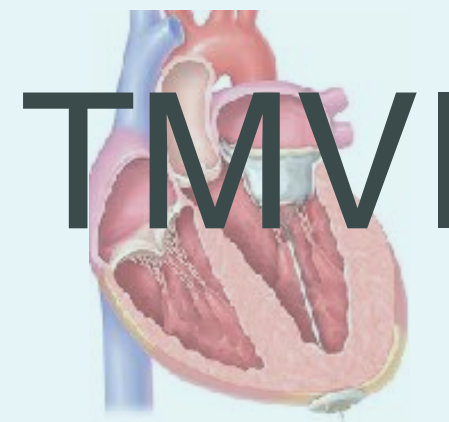
- All-cause Death after 2 years.
- Combined Endpoint after 2 years.





established transcatheter therapy  
excellent safety profile

residual or recurrent MR



novel transcatheter therapy  
predictable MR elimination

elevated short-term mortality

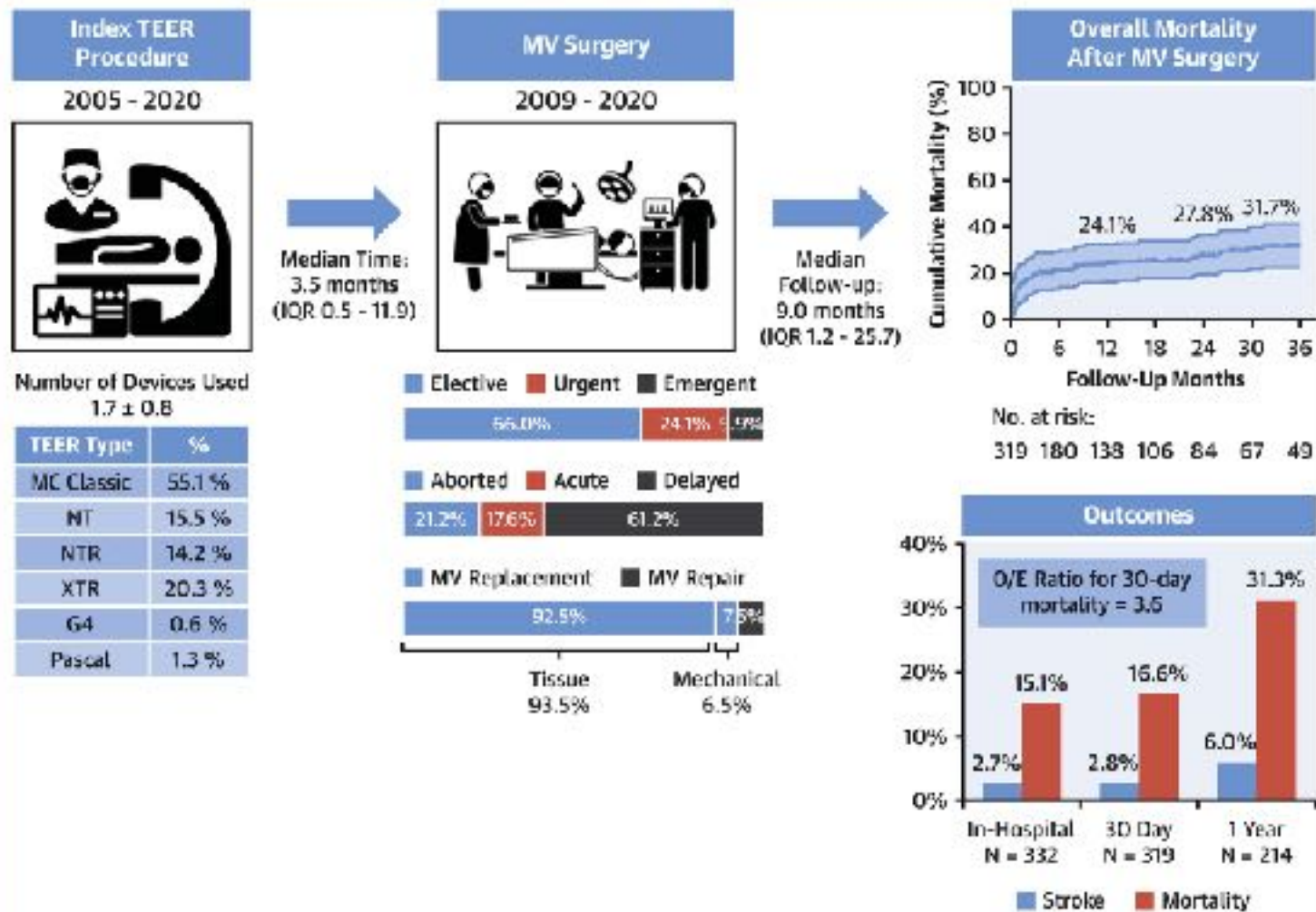
*Prospective randomised trials are needed to define the future role of TMVI among routine SMR treatment options.*

# Learning From Failure at the CUTTING-EDGE of Transcatheter Mitral Valve Therapies\*

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## CENTRAL ILLUSTRATION: Summary of the CUTTING-EDGE International Registry

Mitral Valve Surgery After Transcatheter Edge-to-Edge Repair (TEER): Mid-Term Outcomes From the CUTTING-EDGE International Registry, 34 Centers, 332 Patients



Kaneko, T. et al. J Am Coll Cardiol Interv. 2021;14(18):2010-2021.

- In this first report of the CUTTING-EDGE registry, the mortality and morbidity risks of MV surgery after TEER were not negligible, and only <10% of patients underwent MV repair.
- These registry data provide valuable insights for further research to improve these outcomes.

# Severe mitral regurgitation criteria based on 2D echocardiography (1)

	Primary MR	Secondary MR
<b>Qualitative</b>		
Mitral valve morphology	Flail leaflet, ruptured papillary muscle, severe retraction, large perforation	Normal leaflets but with severe tenting, poor leaflet coaptation
Colour flow jet area	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size
Flow convergence	Large throughout systole	Large throughout systole
Continuous wave Doppler jet	Holosystolic / dense / triangular	Holosystolic / dense / triangular

## Severe mitral regurgitation criteria based on 2D echocardiography (2)

	Primary MR	Secondary MR
<b>Semiquantitative</b>		
<i>Vena contracta</i> width	≥7 (≥8 mm for biplane)	≥7 (≥8 mm for biplane)
Pulmonary vein flow	Systolic flow reversal	Systolic flow reversal
Mitral inflow	E-wave dominant (>1.2 m/s)	E-wave dominant (>1.2 m/s)
TVI mitral/TVI aortic	>1.4	>1.4

## Severe mitral regurgitation criteria based on 2D echocardiography (3)



	Primary MR	Secondary MR
<b>Quantitative</b>		
<u>EROA (2D PISA, mm<sup>2</sup>)</u>	≥40 mm <sup>2</sup>	≥40 mm <sup>2</sup> (may be ≥30 mm <sup>2</sup> if elliptical regurgitant orifice area)
<u>Regurgitant volume (mL/beat)</u>	≥60 mL	≥60 mL (may be ≥45 mL if low flow conditions)
<u>Regurgitant fraction (%)</u>	≥50%	≥50%
<b>Structural</b>		
<u>Left ventricle</u>	Dilated (ESD ≥40 mm)	<u>Dilated</u>
Left atrium	Dilated (diameter ≥55 mm or volume ≥60 mL/m <sup>2</sup> )	Dilated

Adapted from Lancellotti et al., *Eur Heart J Cardiovasc imaging* (2013). DOI: 10.1093/ehjcli/et105 and Zoghbi et al., *J Am Soc Echocardiogr* (2017). DOI: 10.1016/j.echo.2017.01.007.

# Recommendations on indications for mitral valve intervention in chronic severe secondary mitral regurgitation (1)

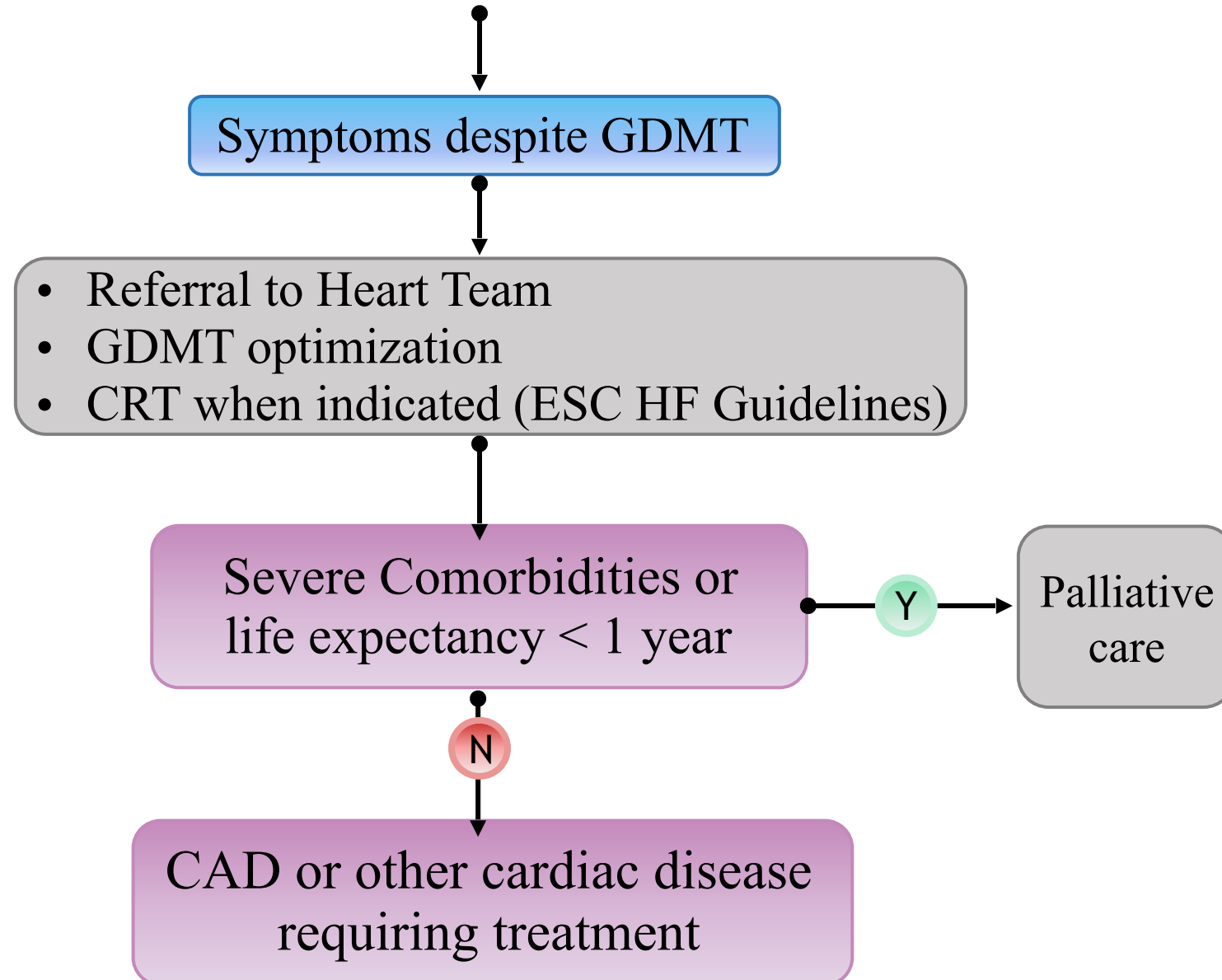
Recommendations	Class	Level
Valve surgery/intervention is recommended only in patients with severe SMR who remain symptomatic despite GDMT (including CRT if indicated) and has to be decided by a structured collaborative Heart Team.	I	B
<b><i>Patients with concomitant coronary artery or other cardiac disease requiring treatment</i></b>		
Valve surgery is recommended in patients undergoing CABG or other cardiac surgery.	I	B
In symptomatic patients, who are judged not appropriate for surgery by the Heart Team on the basis of their individual characteristics, PCI (and/or TAVI) possibly followed by TEER (in case of persisting severe SMR) should be considered.	IIa	C

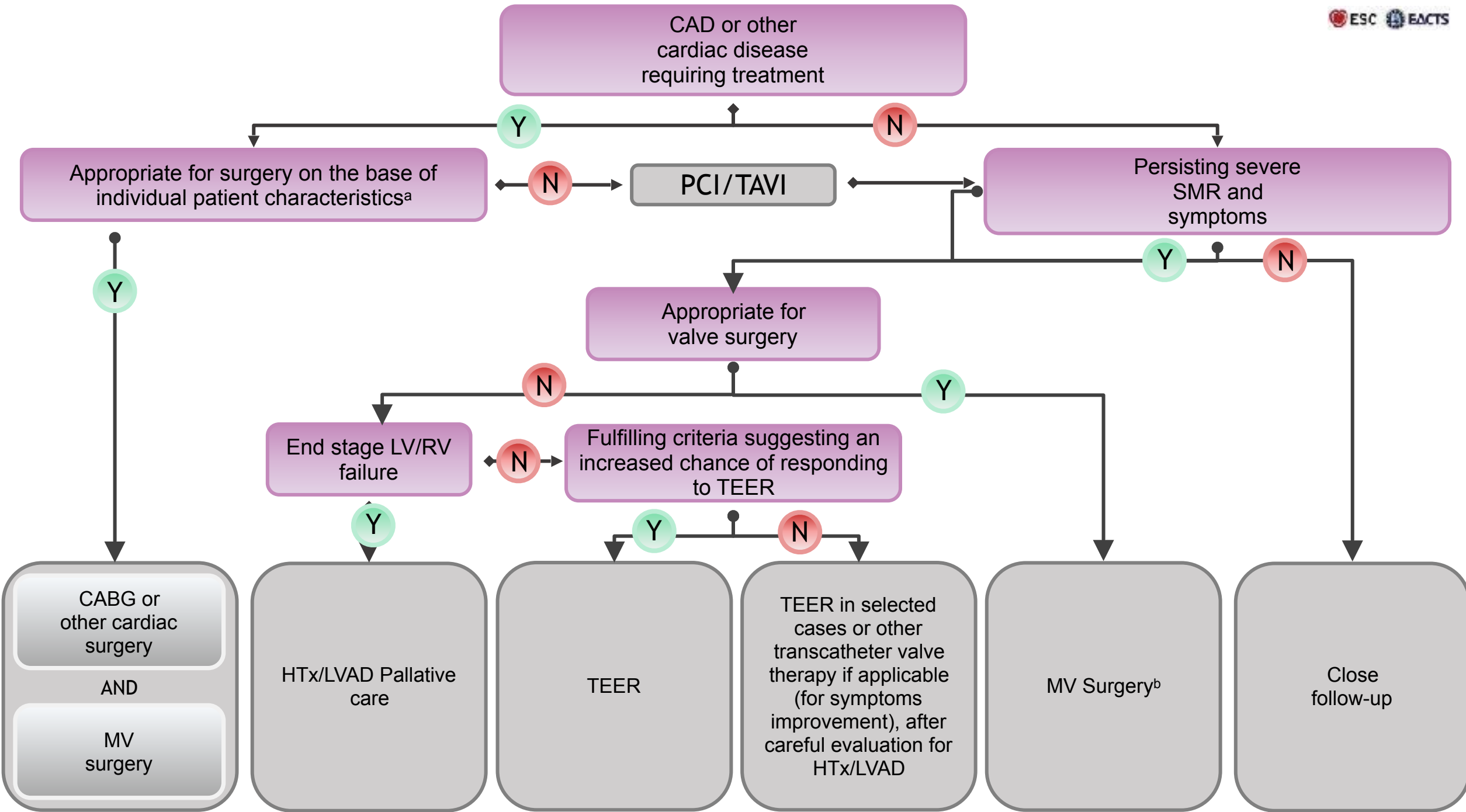


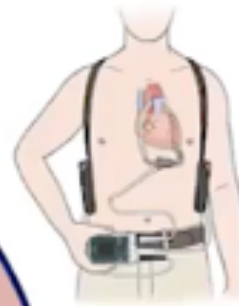
# Recommendations on indications for mitral valve intervention in chronic severe secondary mitral regurgitation (2)

Recommendations	Class	Level
<b><i>Patients without concomitant coronary artery or other cardiac disease requiring treatment</i></b>		
TEER should be considered in selected symptomatic patients, not eligible for surgery and fulfilling criteria suggesting an increased chance of responding to the treatment.	<b>IIa</b>	<b>B</b>
Valve surgery may be considered in symptomatic patients judged appropriate for surgery by the Heart Team.	<b>IIb</b>	<b>C</b>
In high-risk symptomatic patients not eligible for surgery and not fulfilling the criteria suggesting an increased chance of responding to TEER, the Heart Team may consider in selected cases a TEER procedure or other transcatheter valve therapy if applicable, after careful evaluation for ventricular assist device or heart transplant.	<b>IIb</b>	<b>C</b>

# Management of patients with chronic severe secondary regurgitation





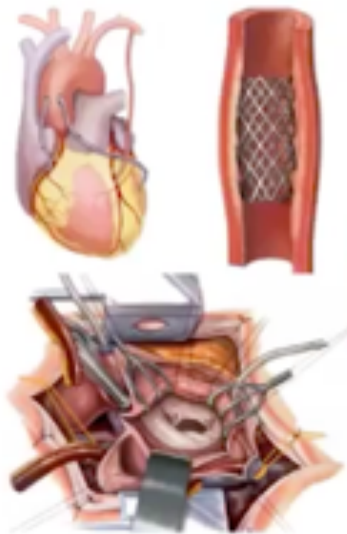


**HEART FAILURE  
SPECIALIST**

**PATIENT  
WITH MR**

**INTERVENTIONAL  
CARDIOLOGIST/  
CARDIAC SURGEON**

**HEART RHYTHM  
SPECIALIST**



# Conclusion

- SMR is a disease of the LV.
- Treat the LV dysfunction first with appropriate titration of medications known to improve survival in HFrEF.
- Consider MV intervention when severe MR persists after appropriate medical therapy, including CRT/PCI (COAPT-like patients).
- Patients in whom MR is the dominant lesion relative to LV dysfunction (Disproportionate SMR), appear to derive the largest benefit of MV intervention in terms of reduced mortality and HF hospitalization.

Thank  
you!

