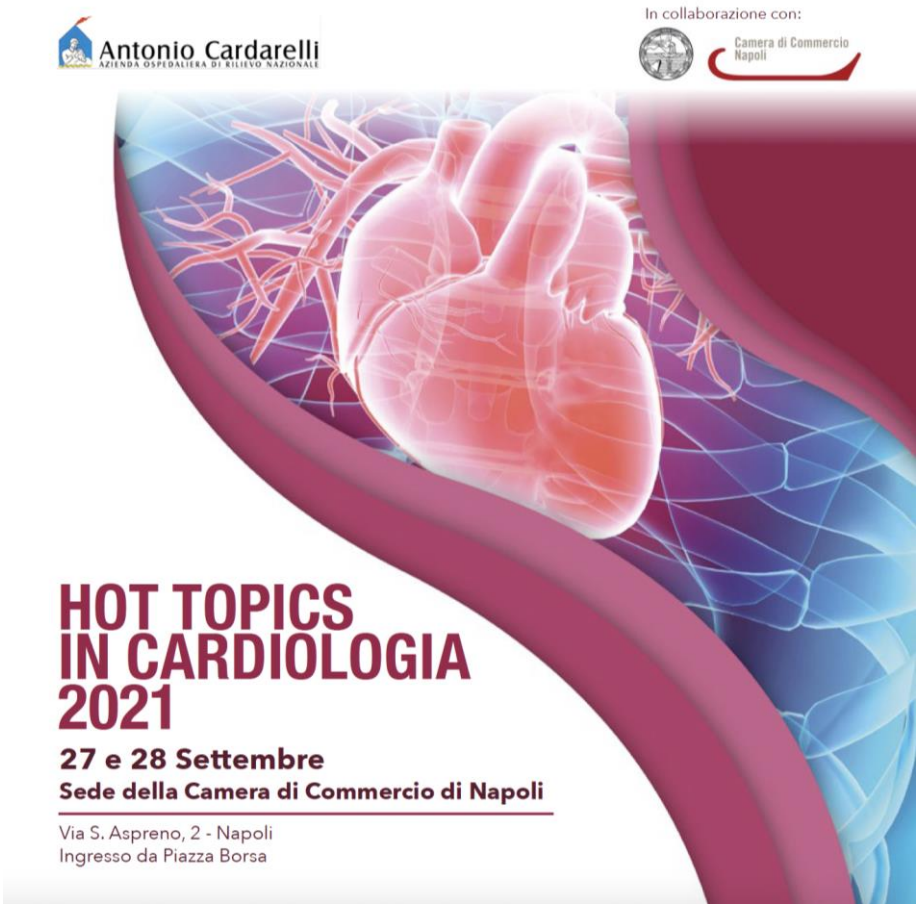
Insufficienza mitralica: trattamento interventistico



Giuseppe Musumeci
SC Cardiologia
Ospedale Mauriziano, Torino

L'insufficienza Mitralica (IM) trattamenti e outcomes

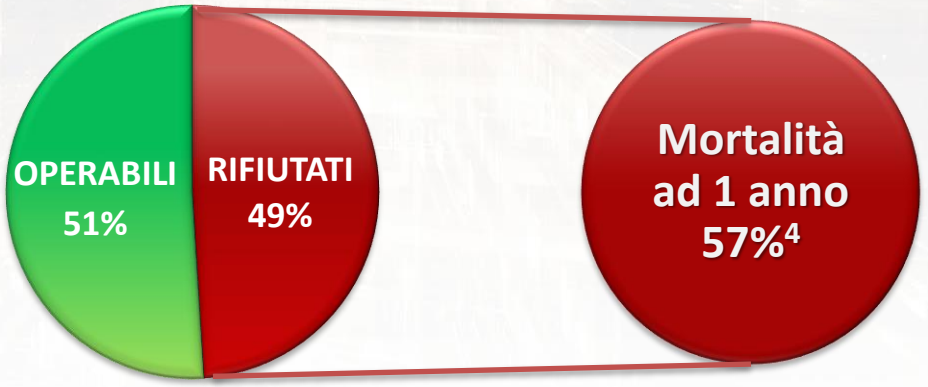
600.000 Pazienti <u>in Italia</u> con Insufficienza Mitralica (Moderata/Severa)[1,2]

Il 10% della popolazione over 75 ha IM di grado moderato-severo

1,5 % trattati[3]

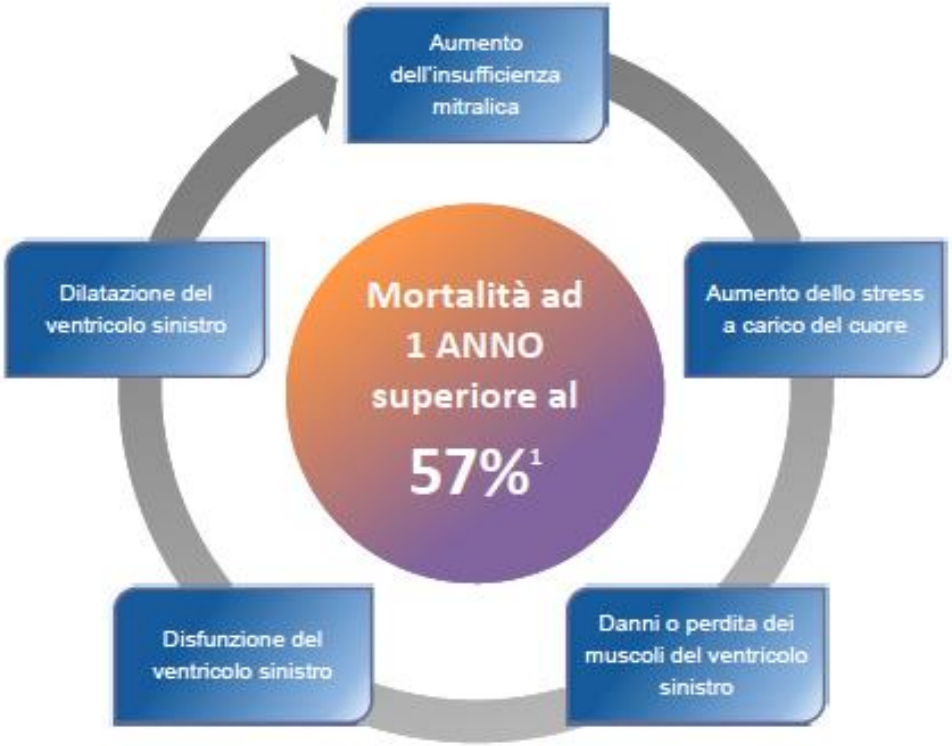
Nell'Euro Heart Survey dell'ESC, circa **il 50%** dei pazienti con IM severa non erano candidabili a chirurgia a causa di numerose comorbidità[4]

In una popolazione anziana, **se non trattata**, l'IM innesca una cascata di eventi che portano alla **morte[5]**



1.Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (The Framingham Heart Study). Am J Cardiol 1999; 83:897–902; Nkomo, Vuyisile T., et al. "Burden of valvular heart diseases: a population-based study." The Lancet 368.9540 (2006): 1005-1011.
2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics - 2017 update: a report from the American Heart Association. Circulation 2017 Jan 25
3. Dati Gise 2017, stime interventi cardiochirurgia 2017
4. Mirabel M, Iung B, Baron G, Messika-Zeitoun D, Detaint D, Vanoverschelde JL, et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? European heart journal. 2007 Jun;28(11):1358-. PubMed PMID: 17350971.
5. Cioffi et al. Functional mitral regurgitation predicts 1-year mortality in elderly patients with systolic chronic heart failure. The european Kournal of Heart failure. 7 (2005) 1112– 1117

L'Insufficienza Mitralica porta allo Scompenso Cardiaco



L'IM attiva una cascata di eventi che portano allo scompenso cardiaco ed infine alla morte se non trattata[2,3]

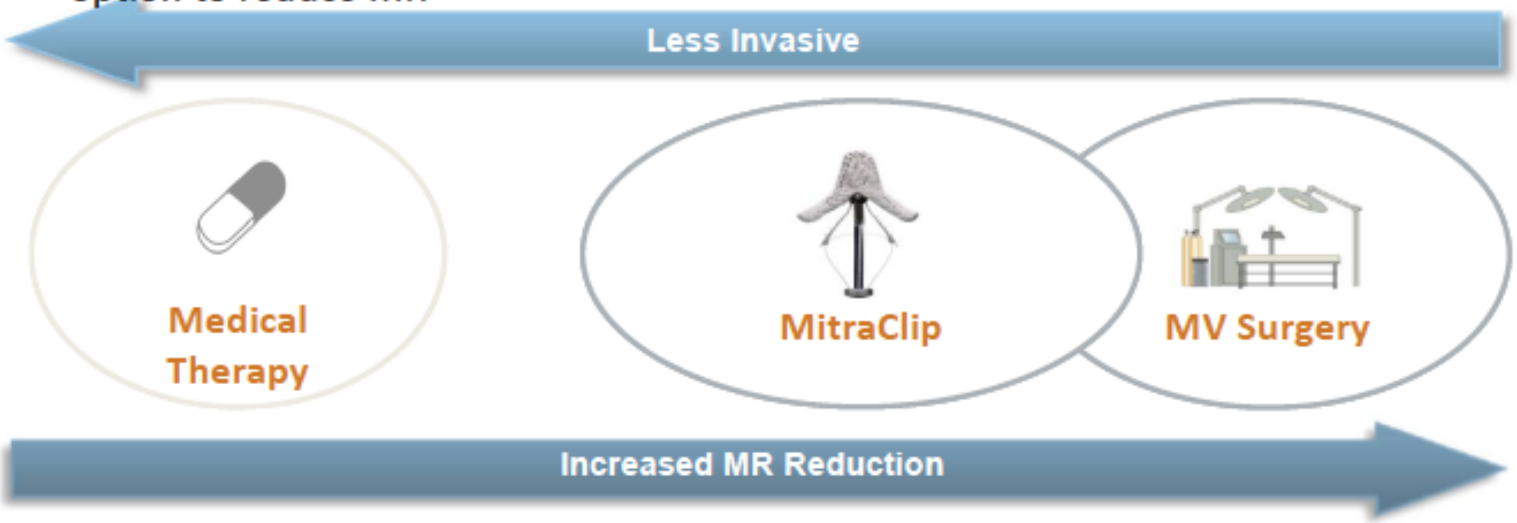
[1] Cioffi G, et al. **Functional mitral regurgitation predicts 1-year mortality in elderly patients with systolic chronic heart failure**. European Journal of Heart Failure 2005 Dec;7(7):1112-7

[2] Grigioni F, et al. **Outcomes in mitral regurgitation due to flail leaflets a multicenter European study**. JACC Cardiovasc Imaging. 2008 Mar;1(2):133-41

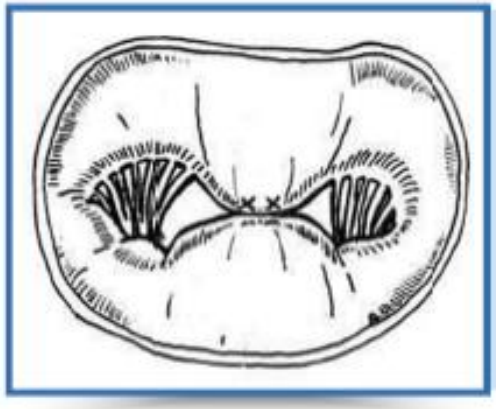
[3] Enriquez-Sarano M, et al. **Quantitative determinants of the outcome of asymptomatic mitral regurgitation**. N Engl J Med. 2005 Mar 3;352(9):875-83

MitraClip Therapy Filling a Treatment Gap

- Medical therapy is limited to symptom management
- MV surgery has been the only option that reliably reduces MR
- **A significant gap exists between patients who receive medical and surgical options, based on risk-benefit profile**
- MitraClip therapy is a first-in-class, minimally invasive catheter-based technology option to reduce MR



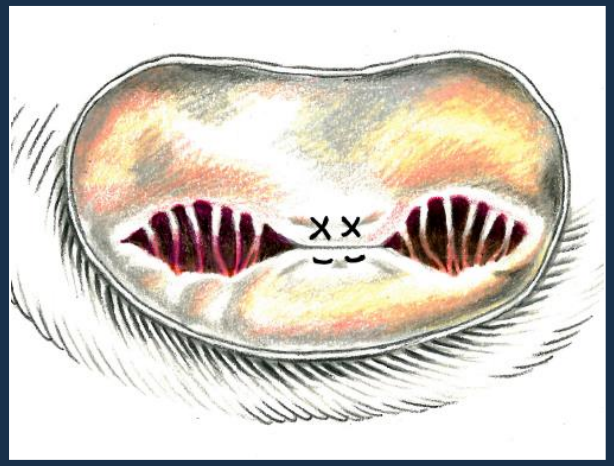
Concept: Percutaneous Mitral Valve Repair (PMVR)

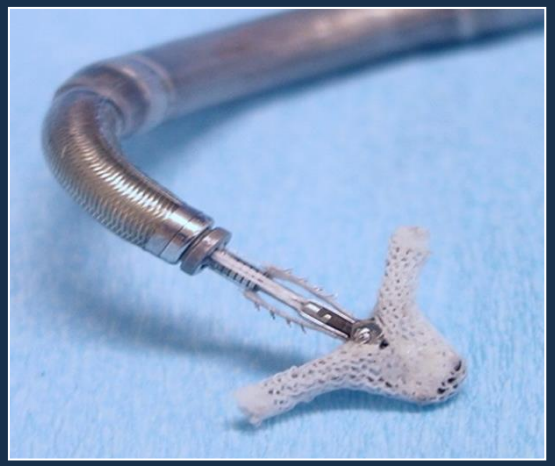


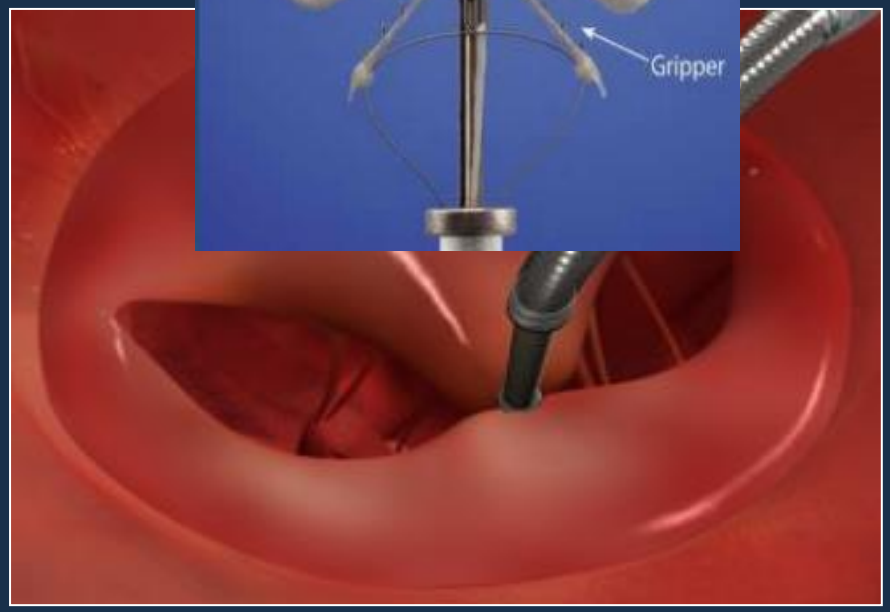
- Double-orifice suture technique developed by Prof. Ottavio Alfieri
- First published results in 1998 illustrated proven benefit
- Suggested procedure best suited for minimally invasive approach

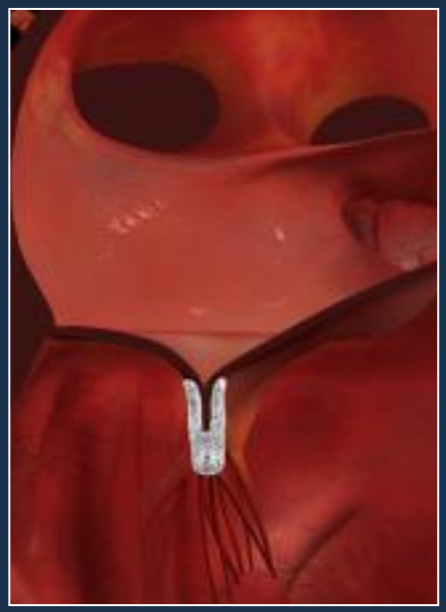
Catheter-Based Mitral Valve Repair

MitraClip® System



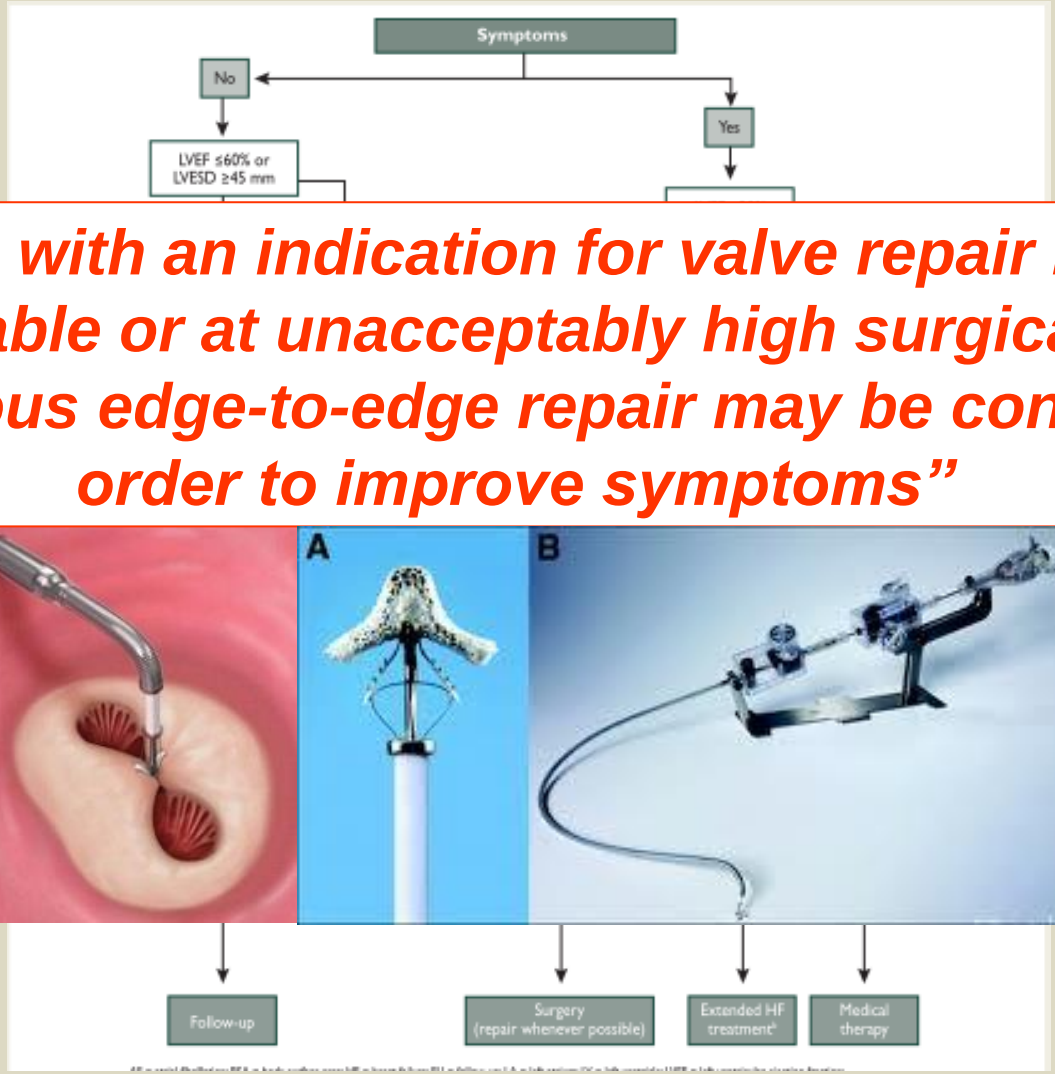






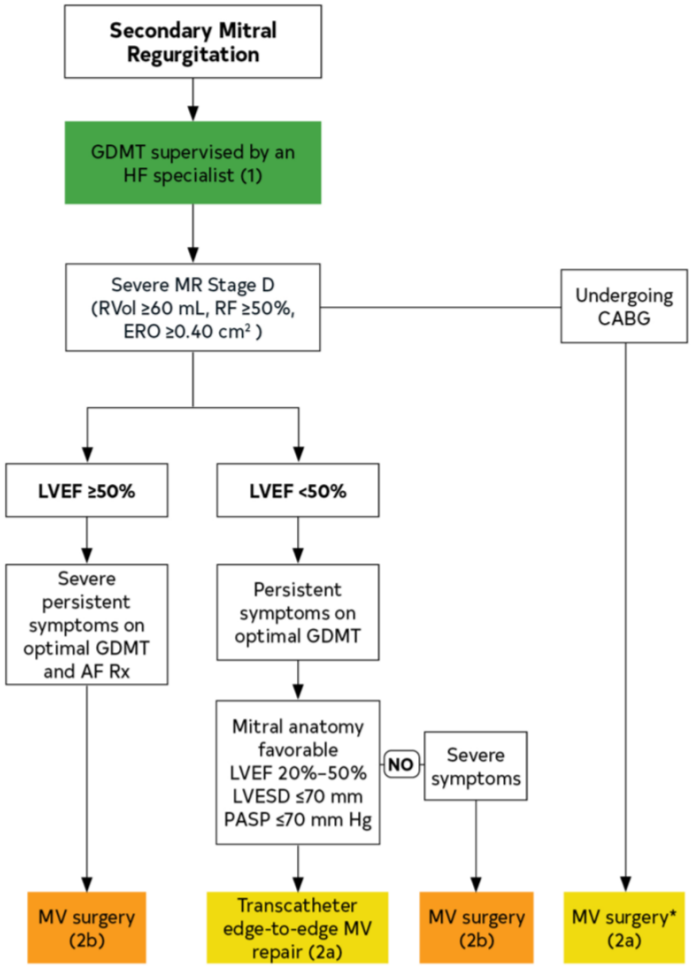
NorthShore University HealthSystem
Evanston Hospital

Guidelines on the management of valvular heart disease (version 2012)



patients with an indication for valve repair but judged inoperable or at unacceptably high surgical risk, percutaneous edge-to-edge repair may be considered in order to improve symptoms"

TEER for FMR: Ready for Prime Time

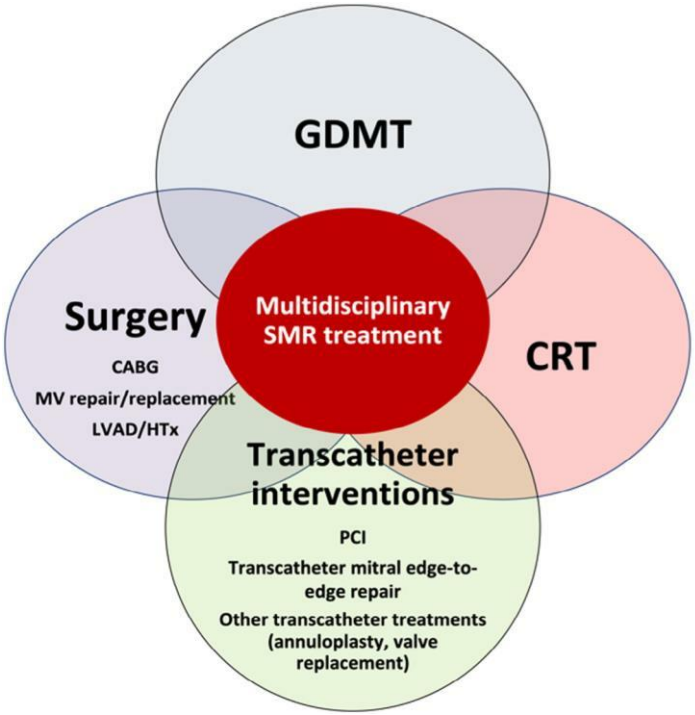


AHA/ACC 2020 Guidelines

TEER for FMR: Ready for Prime Time

Percutaneous edge-to-edge mitral valve repair should be considered in carefully selected patients with secondary mitral regurgitation, not eligible for surgery and not needing coronary revascularization, who are symptomatic despite OMT and who fulfil criteria to achieve a reduction in HF hospitalizations.	IIa
Percutaneous edge-to-edge mitral valve repair may be considered to improve symptoms in carefully selected patients with secondary mitral regurgitation, not eligible for surgery and not needing coronary revascularization, who are highly symptomatic despite OMT and who do not fulfil criteria for reducing HF hospitalization.	IIb

ESC 2021



ESC 2021

Four Generations of MitraClip Built on Robust Clinical Experience

MitraClip Pipeline

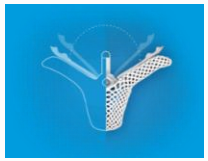
GEN 1

MitraClip

Breakthrough Technology to restore leaflet coaptation with a delivery system specifically designed for the MV

GEN 2

MitraClip NT



Leaflet grasping and steering enhancements

GEN 3

MitraClip NTR & MitraClip XTR

- Improved grasping, Increased coaptation surface area
- Customized repair with 2 Clip sizes
- Enhanced steering accuracy and ease-of-use[1]

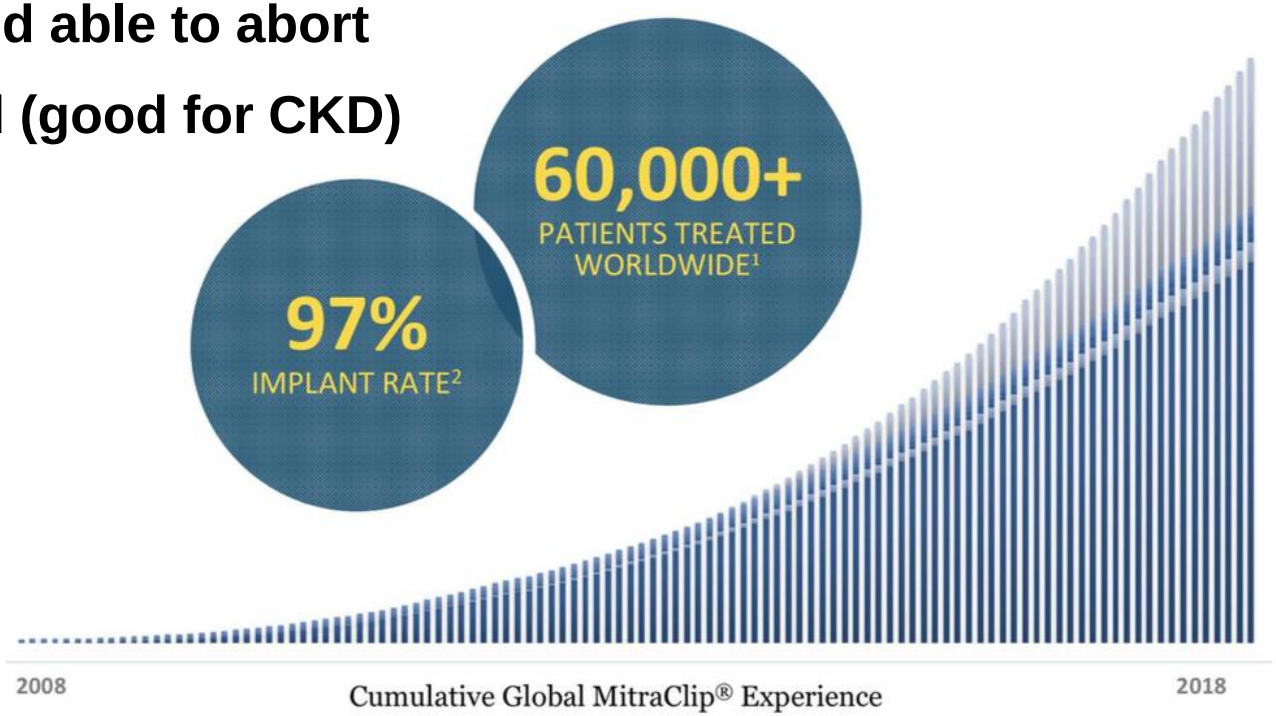
GEN 4

MitraClip G4

- Enable ability to choose Clip size based on MV anatomy with 4 sizes
- Ability to grasp leaflets simultaneously or independently with Controlled Gripper Actuation (CGA)
- Streamlined procedure with simplified system deployment & reduced number of steps

Advantage of mitraClip for FMR

- High procedural safetiness by transvenous approach
- Effective in 90% of patients
- Combination of multiple repair technique will expand indications
- Assessment of MR by beating heart
- Repeat grasping and able to abort
- No contrast needed (good for CKD)

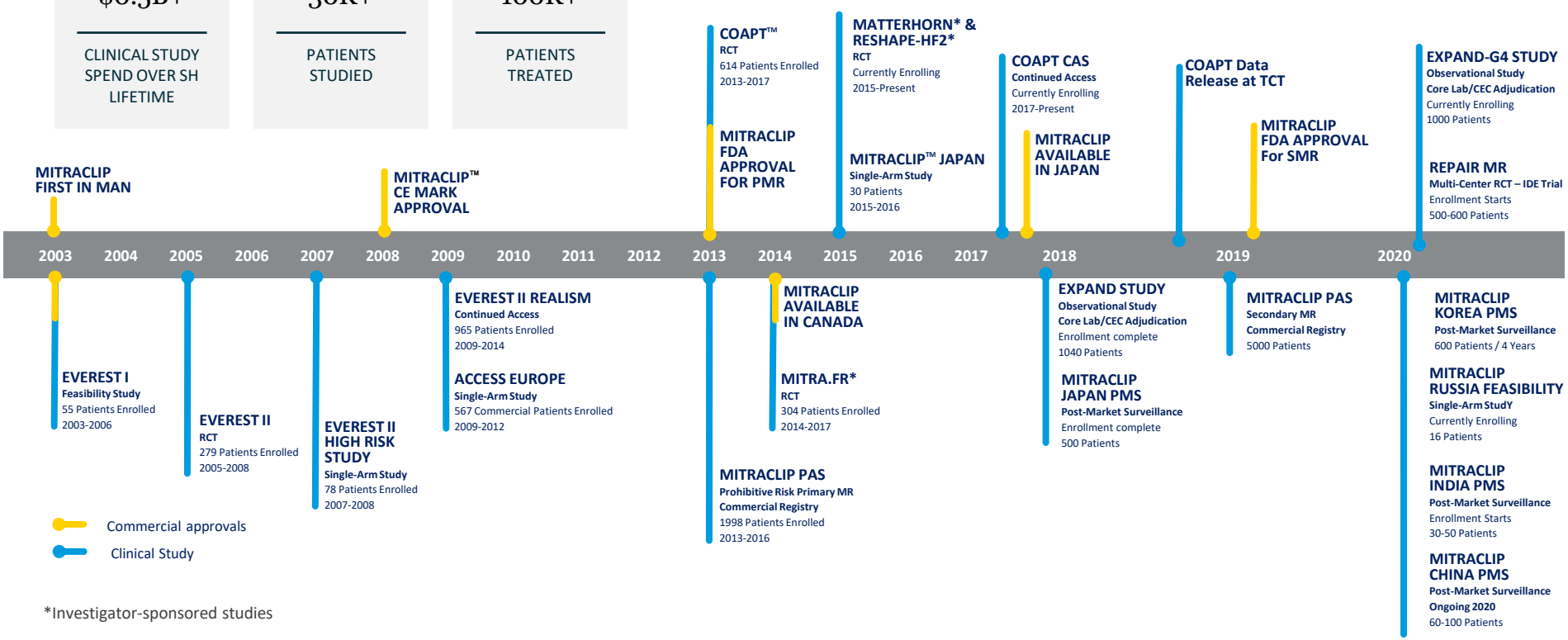


18+ Years Dedicated to the Treatment of Valvular Regurgitation

$0.5B+
CLINICAL STUDY SPEND OVER SH LIFETIME

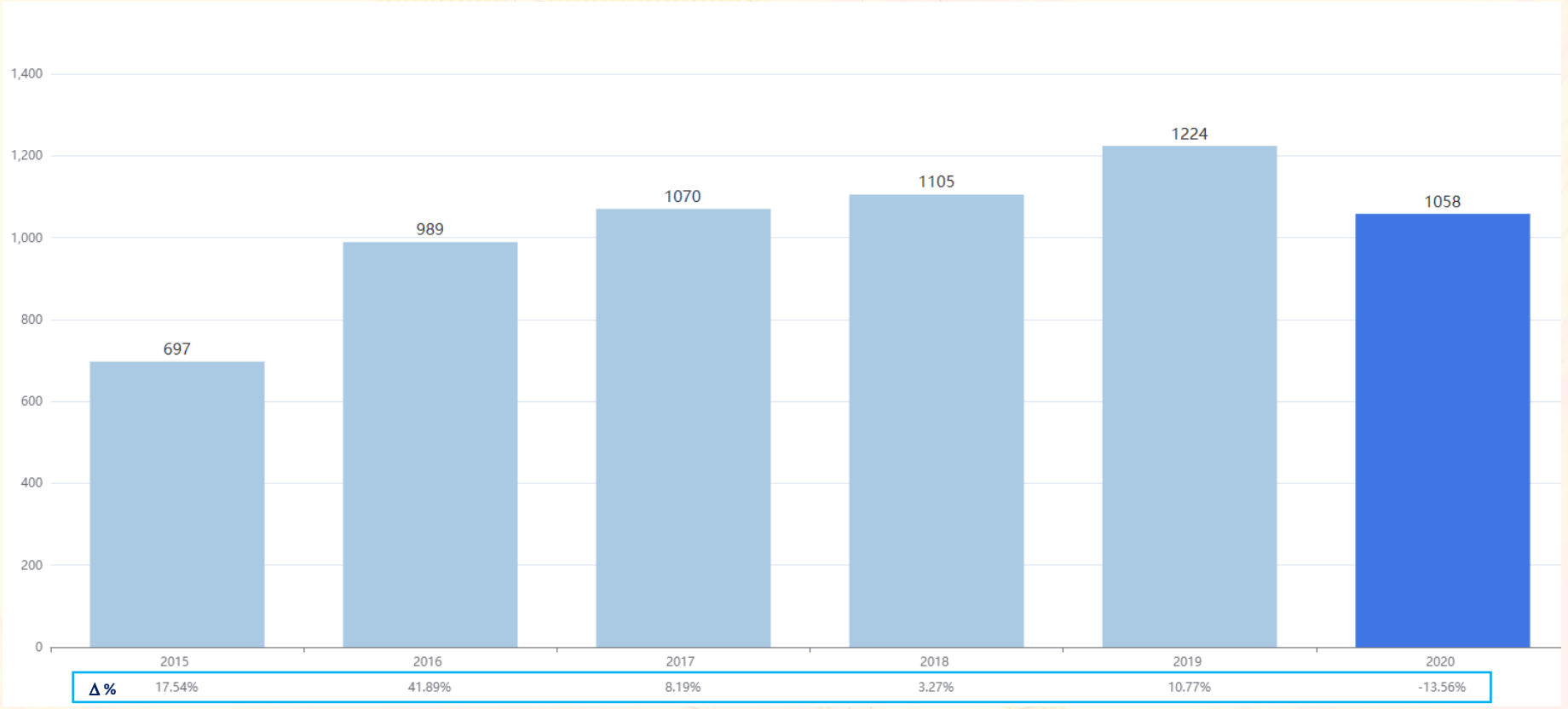
30K+
PATIENTS STUDIED

100K+
PATIENTS TREATED



*Investigator-sponsored studies

Interventistica Mitralica
Serie storica Italia



L'impegno del GISE a oggi

2016
Registro GIOTTO

Impegno della creazione di *evidenze cliniche* grazie alla raccolta di dati real-world. Primo Registro in Europa per numero di pazienti arruolati.

2017
Editoriale Gise


GIORNALE ITALIANO DI CARDIOLOGIA

Trattamento transcatetere dell'insufficienza mitralica per i pazienti non eleggibili all'intervento chirurgico: epidemiologia, diagnosi, equità di accesso ed impatto economico

Francesco Bedogni, Sergio Berti, Giovanni Esposito, Caterina Maria Gandolfo, Alessio Gaetano La Manna, Ugo Limbruno, Alfredo Marchese, Ciro Mauro, Alessandro Salvi, Gennaro Santoro, Giuseppe Tarantini, Fabio Tarantino, Ferdinando Varbella, Roberto Violini, Giuseppe Musumeci

Impegno nell'approfondimento degli aspetti legati *all'accesso alla terapia e all'impatto economico*

2017
Europe South Position Paper


GISE · Sección de Hemodinâmica y Cardiología Intervencionista · apic

International Journal of Cardiology 243 (2017) 169–173

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

ELSEVIER

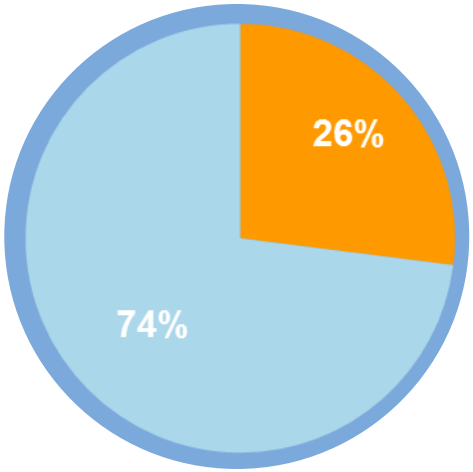
Transcatheter mitral valve interventions for mitral regurgitation, with special focus on MitraClip: The position of Spanish, Portuguese and Italian interventional societies

Rodrigo Estévez-Loureiro [a,*], Xavier Freixa [b], Dabit Arzamendi [c], Armando Perez de Prado [a], Rui Campante-Teles [d], Bruno Melica [e], Giuseppe Tarantini [f], Giuseppe Musumeci [g], Manuel Pan [h]

Impegno nella creazione di evidenze e *awareness* sulla terapia grazie alla condivisione dell'esperienza del Sud Europa

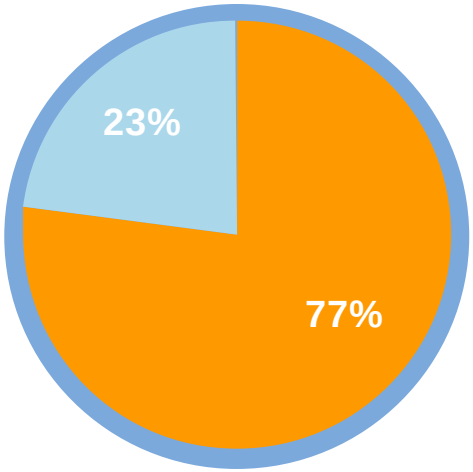
MitraClip Therapy
Broad Spectrum of Experience

EVEREST II
(Randomized Controlled Trial)



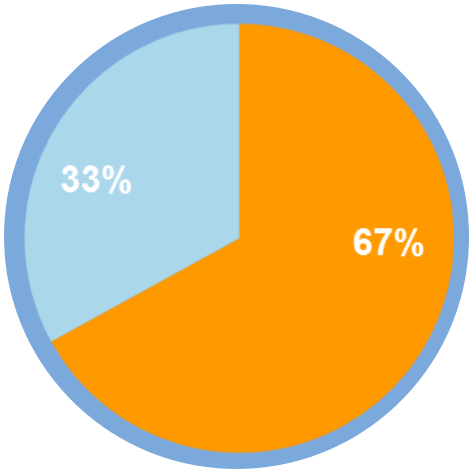
- 178 patients
- Device time – 146 minutes
- Implant rate – 89%

ACCESS EU
(Europe)



- 567 patients
- Procedure time – 117 minutes
- Implant rate – 99%

Commercial
(APJ, CALA, Europe, US)



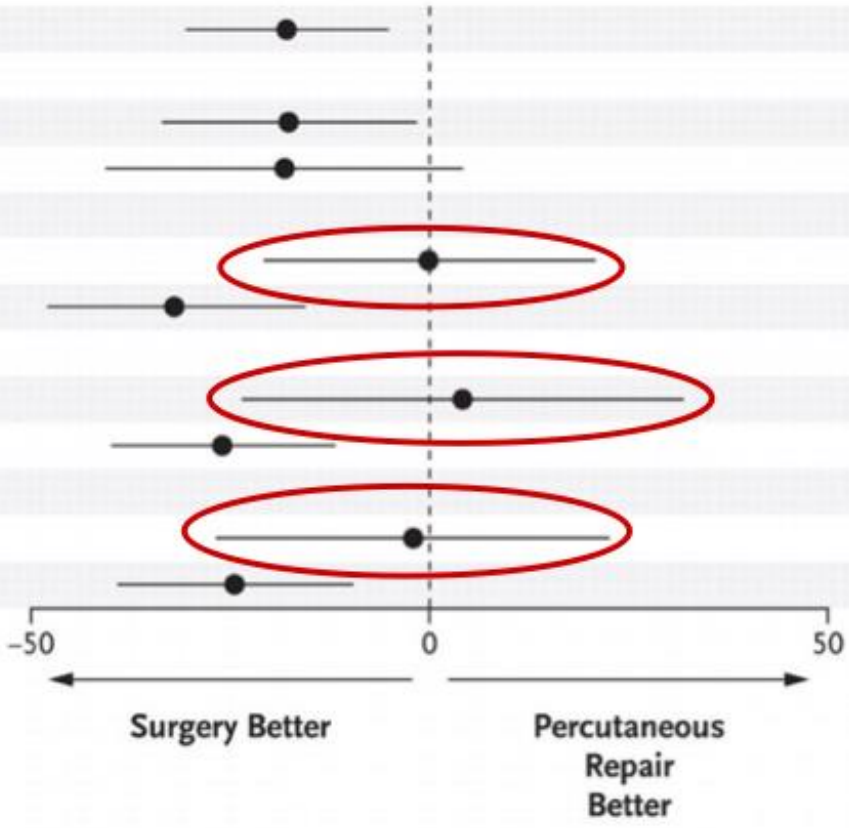
- 50,000 patients
- Device time – 91 minutes
- Implant rate – 96%

= DMR = FMR

Data on file Abbott Vascular, March 2014,
Source: Schillinger, W. ACCESS-EUROPE Phase I: A Post Market Study of the MitraClip System for the Treatment of Significant Mitral Regurgitation in Europe: Analysis of Outcomes at 1 Year. ESC 2012; August 25-29, 2012; Munich, Germany.
Lim, S. The EVEREST II High Surgical Risk Cohort:Effectiveness of Transcatheter Reduction of Significant Mitral Regurgitation in High Surgical Risk Patients. ACC 2013; San Francisco, CA

EVEREST II Subgroup Analyses for the Primary End Point at 12 Months

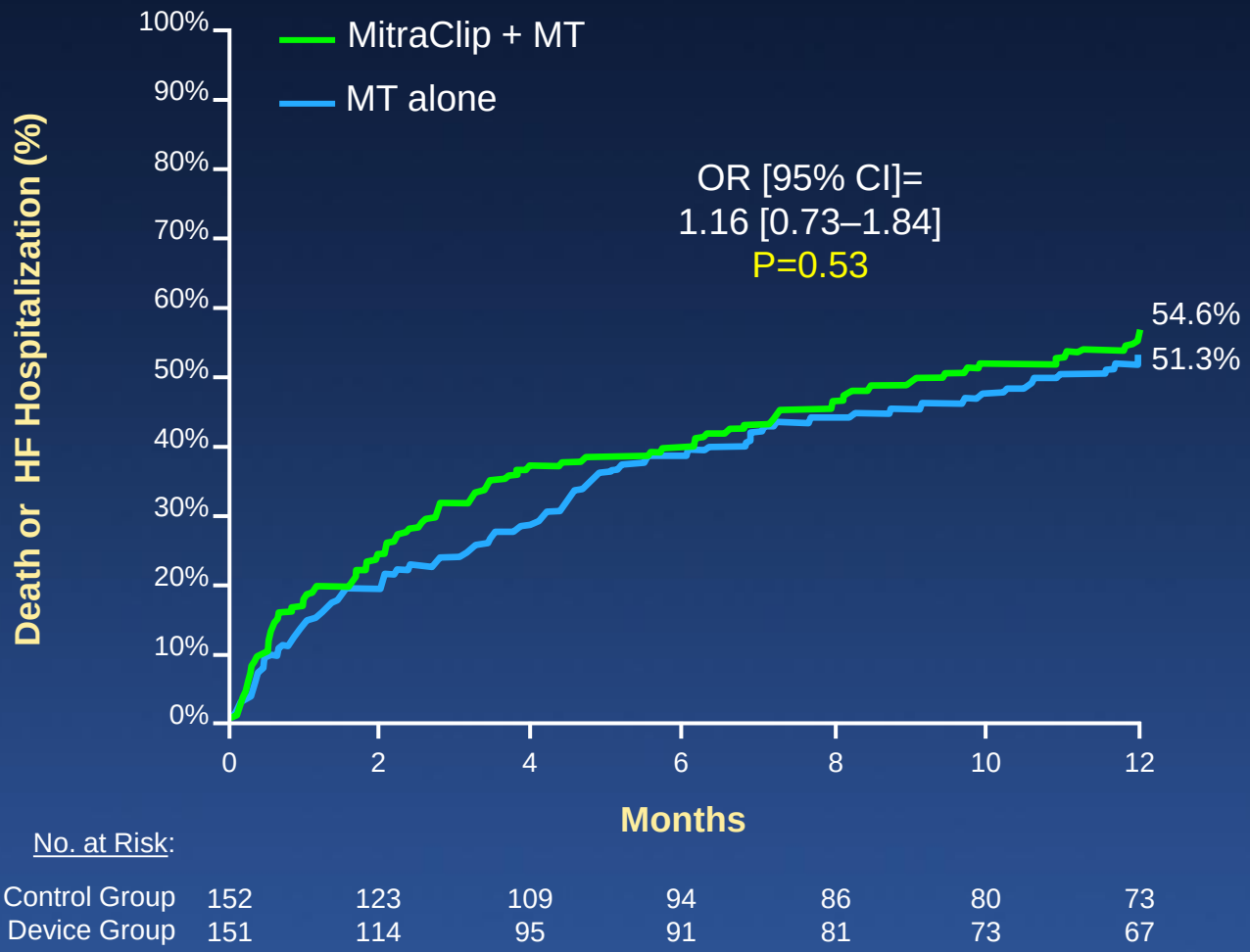
Subgroup	Percutaneous Repair	Surgery	P Value for Interaction
	no. of events/total no. (%)		
All patients	100/181 (55)	65/89 (73)	
Sex			0.97
Male	63/114 (55)	43/59 (73)	
Female	37/67 (55)	22/30 (73)	
Age			0.009
≥70 yr	52/86 (60)	23/38 (61)	
<70 yr	48/95 (51)	42/51 (82)	
MR			
Functional	26/48 (54)	12/24 (50)	0.02
Degenerative	74/133 (56)	53/65 (82)	
LVEF			0.06
<60%	35/68 (51)	15/28 (54)	
≥60%	64/111 (58)	50/61 (82)	



The NEW ENGLAND JOURNAL of MEDICINE

Feldman T et al. N Engl J Med 2011;364:1395-1406.

MITRA-FR: 12-Month Death or HF Hosp



Obadia JF et al. NEJM. 2018 Aug 27. doi: 10.1056/NEJMoa1805374

MITRA-FR: Periprocedural Complications

Table 2. Periprocedural Complications and Prespecified Serious Adverse Events (Intention-to-Treat Population).*

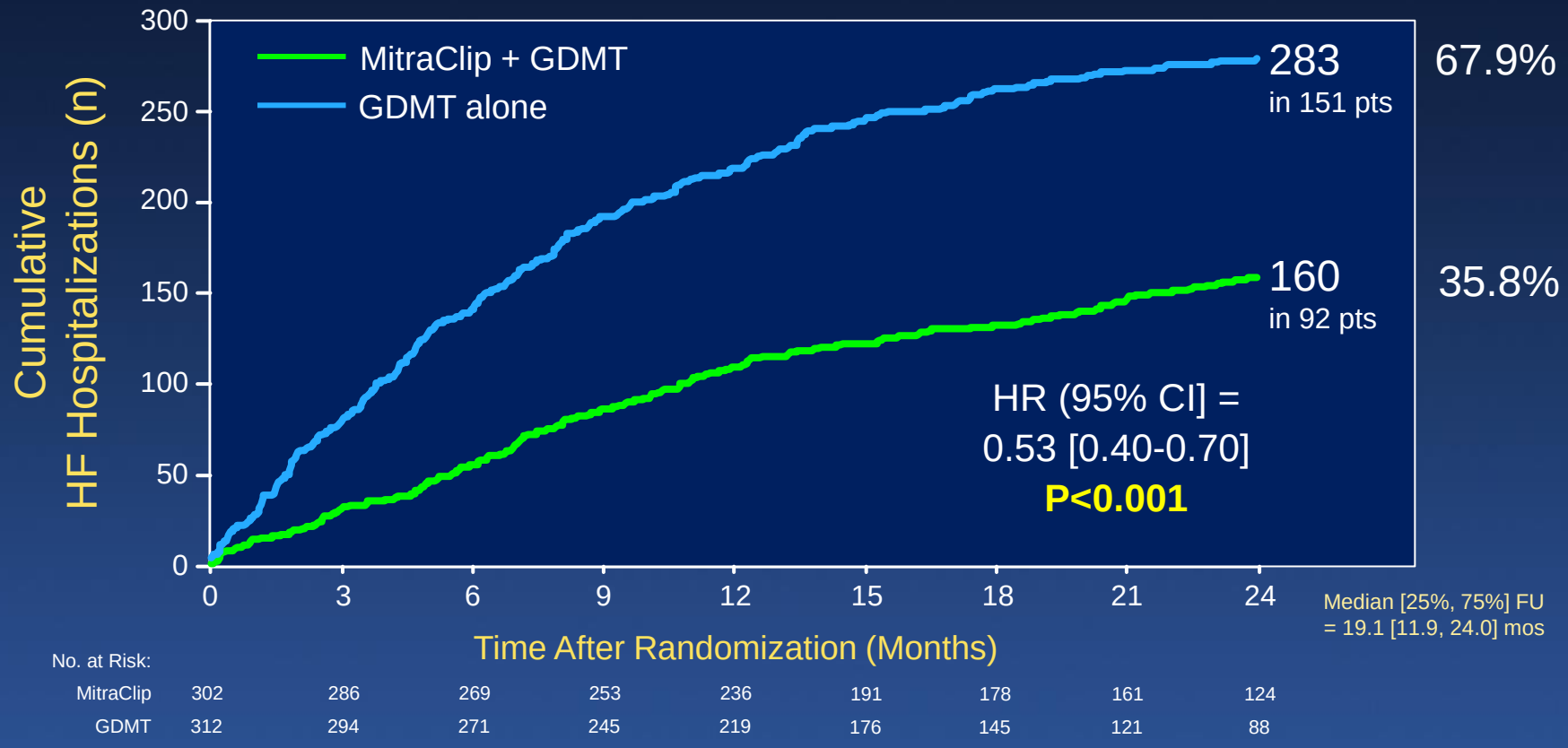
Variable	Intervention Group (N=152)	Control Group (N=152)
Periprocedural complications during device implantation — no./total no. (%)†	21/144 (14.6)	NA
Device-implantation failure	6/144 (4.2)‡	NA
Hemorrhage resulting in transfusion or vascular complication resulting in surgical intervention	5/144 (3.5)	NA
Atrial septum lesion or atrial septal defect	4/144 (2.8)	NA
Cardiogenic shock resulting in intravenous inotropic support	4/144 (2.8)	NA
Cardiac embolism, including gas embolism and stroke	2/144 (1.4)	NA
Tamponade	2/144 (1.4)	NA
Urgent conversion to heart surgery	0	NA

Obadia JF et al. NEJM. 2018 Aug 27. doi: 10.1056/NEJMoa1805374

The COAPT Trial

Primary Effectiveness Endpoint

All Hospitalizations for HF within 24 months



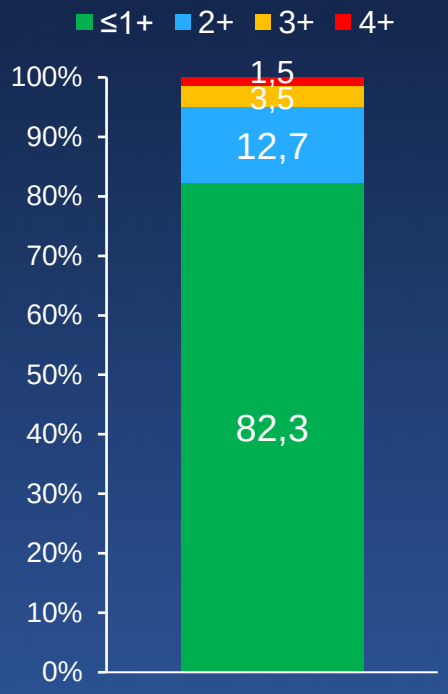
COAPT TRIAL

MitraClip Procedure (n=302)

MitraClip procedure attempted	293/302 (97.0%)
Clip implanted (MitraClip procedure attempted)	287/293 (98.0%)
Clip implanted (all patients)	287/302 (95.0%)
Mean # of clips implanted	1.7 ± 0.7 (n=293)
- 0 clips implanted	6 (2.0%)
- 1 clip implanted	106 (36.2%)
- 2 clips implanted	157 (53.6%)
- 3 clips implanted	23 (7.9%)
- 4 clips implanted	1 (0.3%)
Procedure duration (mins)	162.9 ± 118.1
- Device procedure time (mins)	118.9 ± 63.5
- Device time (mins)	82.7 ± 80.8
- Fluoroscopy time (mins)	33.9 ± 23.2

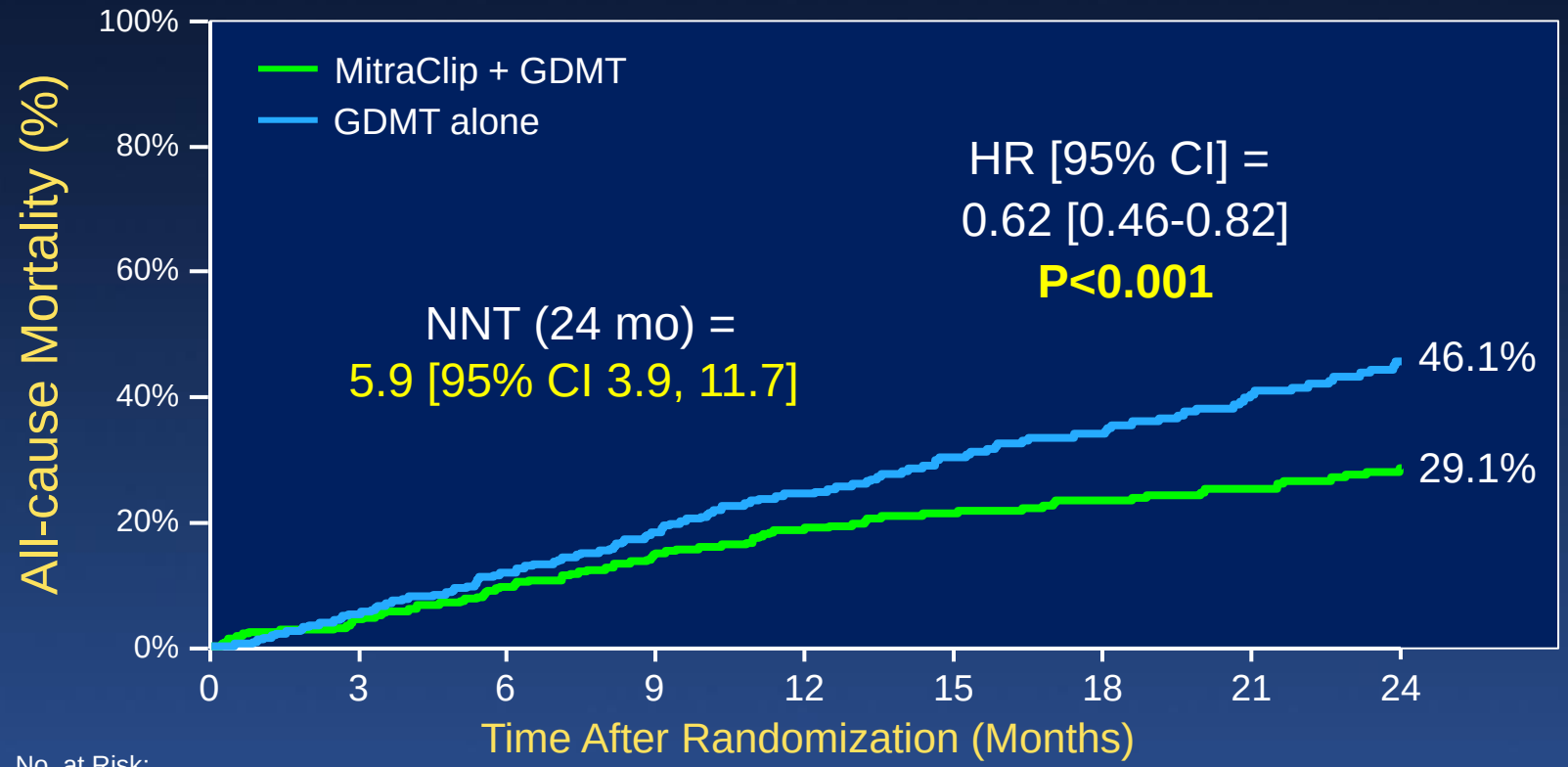
TTE at discharge (n=260)

MR grade



COAPT TRIAL

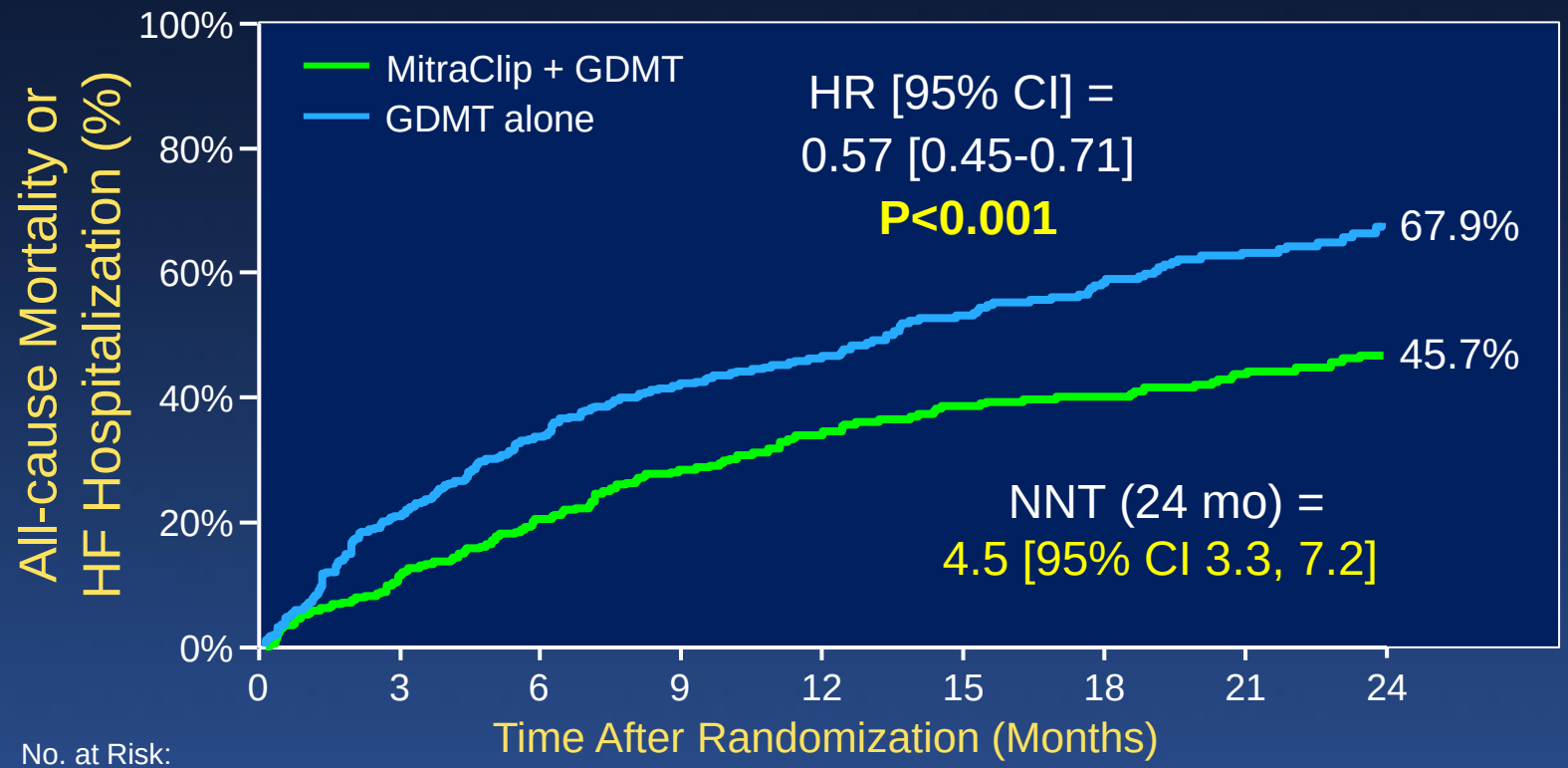
All-cause Mortality



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

COAPT TRIAL

Death or HF Hospitalization

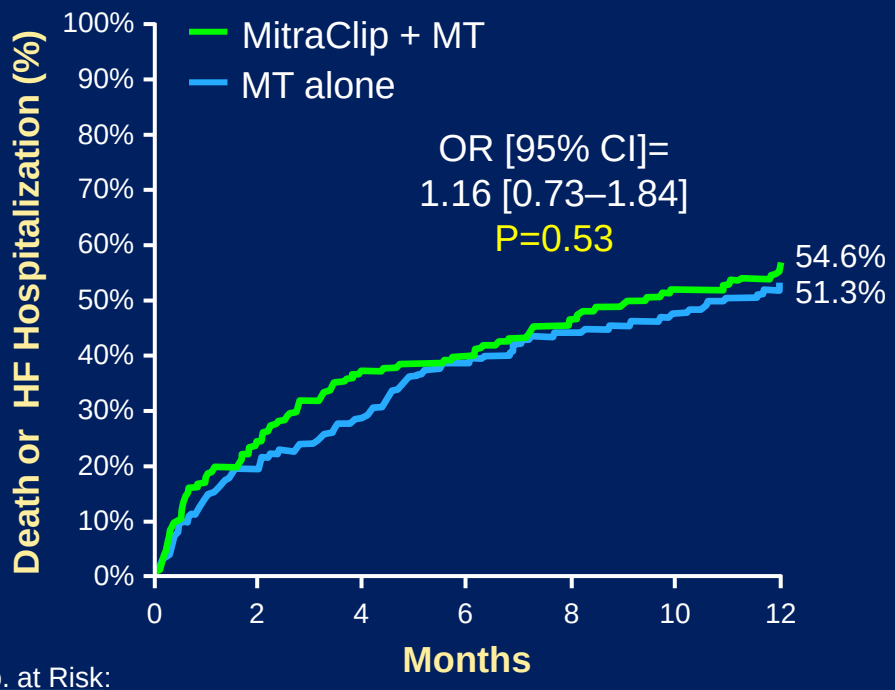


No. at Risk:

MitraClip + GDMT	302	264	238	215	194	154	145	126	97
GDMT alone	312	244	205	174	153	117	90	75	55

COAPT vs. MITRA-FR: 12-Month Death or HF Hosp

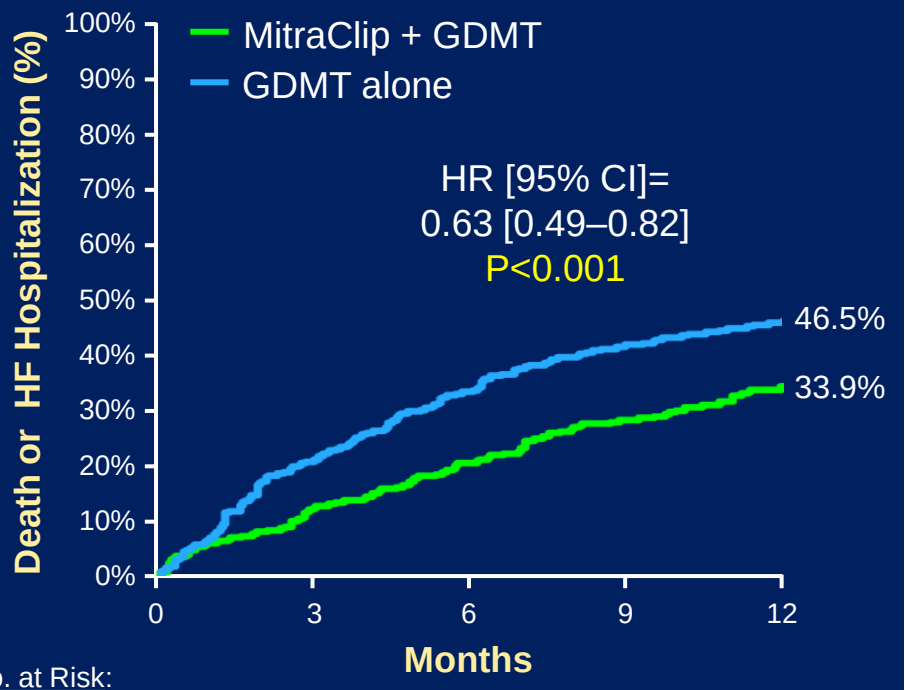
MITRA-FR



No. at Risk:

Control Group	152	123	109	94	86	80	73
Device Group	151	114	95	91	81	73	67

COAPT



No. at Risk:

Control Group	312	244	205	174	153
Device Group	302	264	238	215	194

Obadia JF et al. NEJM. 2018 Aug 27. doi: 10.1056/NEJMoa1805374

Stone GW et al. NEJM. 2018 Sept 23.

Why are the COAPT Results so Different from MITRA-FR?

Possible Reasons

	MITRA-FR (n=304)	COAPT (n=614)
Severe MR entry criteria	Severe FMR by EU guidelines: EROA >20 mm^2 or RV >30 mL/beat	Severe FMR by US guidelines: EROA >30 mm^2 or RV >45 mL/beat
EROA (mean ± SD)	31 ± 10 mm^2	41 ± 15 mm^2
LVEDV (mean ± SD)	135 ± 35 mL/m^2	101 ± 34 mL/m^2
GDMT at baseline and FU	Receiving HF meds at baseline – allowed variable adjustment in each group during follow-up per "real-world" practice	CEC confirmed pts were failing maximally-tolerated GDMT at baseline – few major changes during follow-up
Acute results: No clip / ≥3+ MR	9% / 9%	5% / 5%
Procedural complications*	14.6%	8.5%
12-mo MitraClip ≥3+ MR	17%	5%

*MITRA-FR defn: device implant failure, transf or vasc compl req surg, ASD, card shock, cardiac embolism/stroke, tamponade, urg card surg

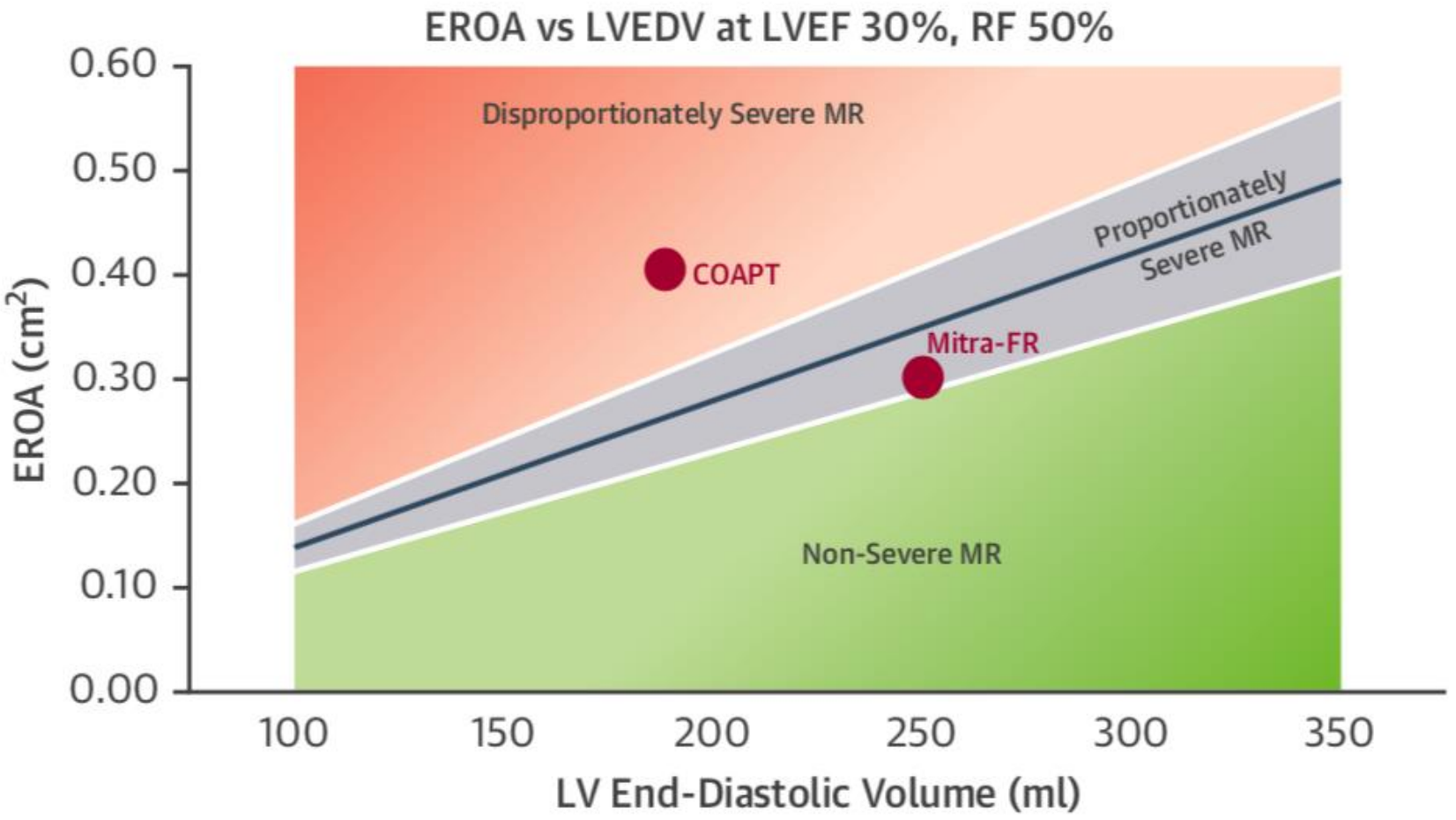
EDITORIAL VIEWPOINT

JACC Cardiovasc Imaging 2018 Dec 6

Proportionate and Disproportionate Functional Mitral Regurgitation

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

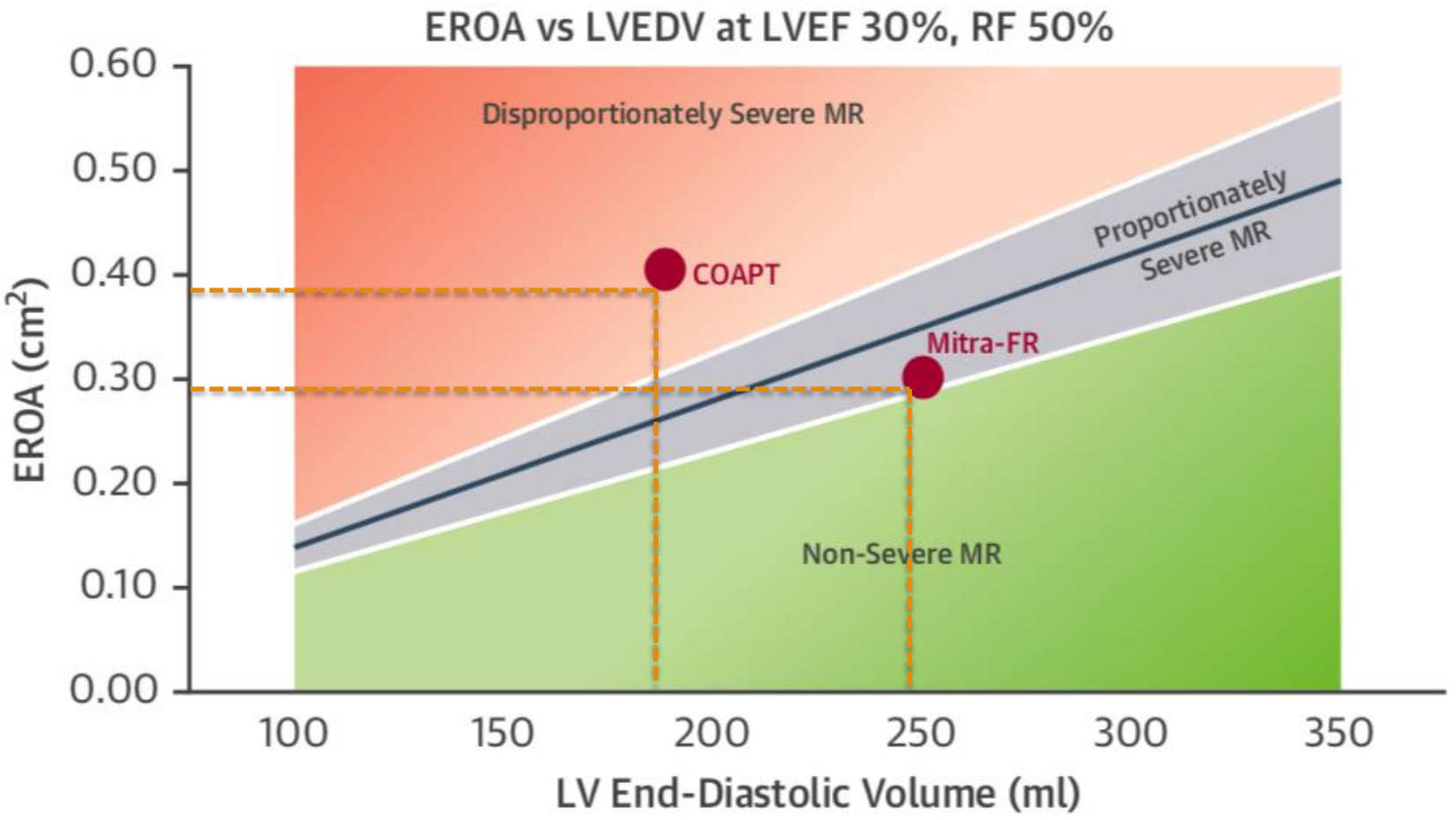
Paul A. Grayburn, MD, Anna Sannino, MD, Milton Packer, MD



Relationship Between EROA and LVEDV

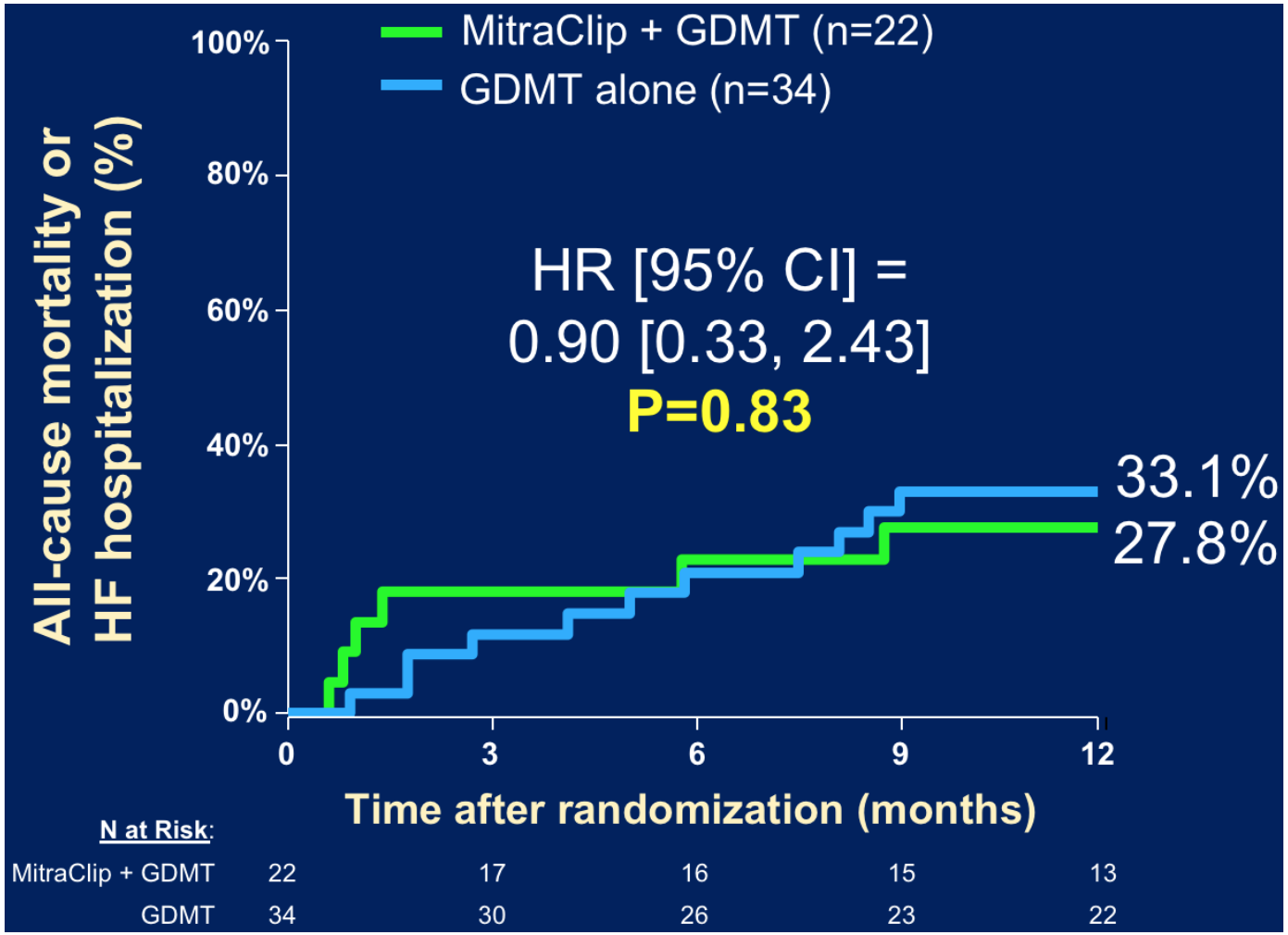
MITRA-FR: 52% pts EROA <0.3 cm2, 70% pts LVEDV>65 mm

COAPT: 14% pts EROA <0.3 cm2, LVEDV>70 mm not eligible

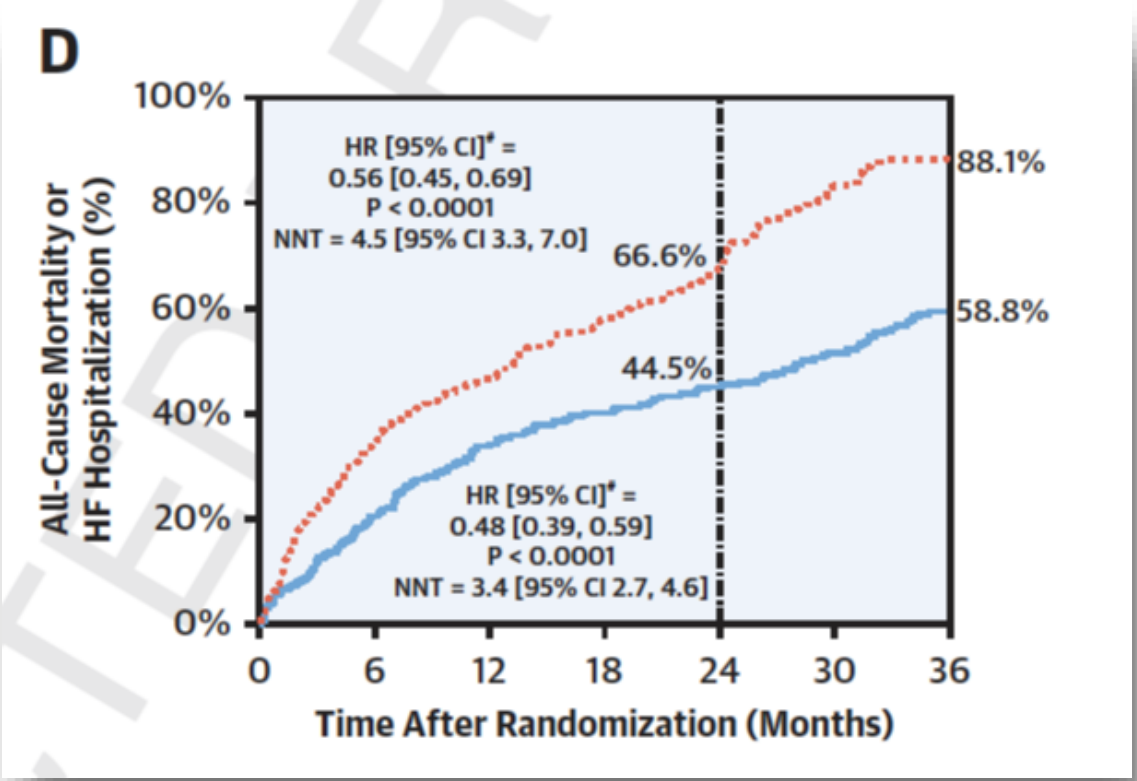


COAPT Trial subgroup analysis: Impact of EROA and LVEDV

EROA ≤30 mm2 + LVEDVI >96 ml/m2 (N=56; 10.2%)



COAPT @ 3 years



Mack, JACC 2021

The 4th Generation of MitraClip

MitraClip G4 Overview:

4 Clip Options
- Two additional Clip sizes G4 NTW and XTW (wider versions of NT and XT) with total of four Clip sizes (NT, XT, NTW and XTW)
- Ability to choose Clip size based on patient MV anatomy

Controlled Gripper Actuation (CGA)
- More options to confirm and optimize leaflet capture with ability to grasp the leaflets independently or simultaneously

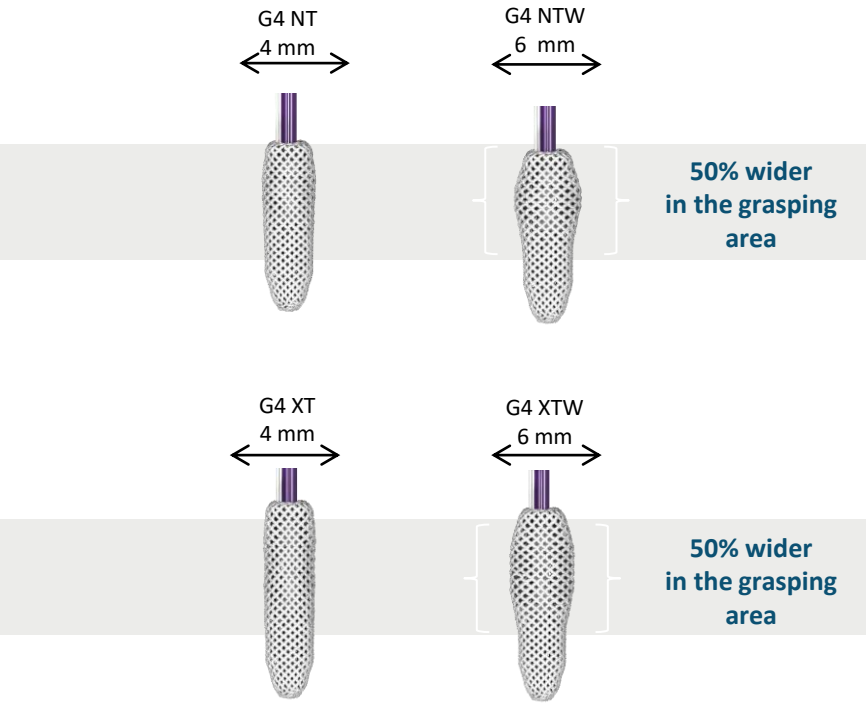
Simplified Procedural Steps*
- 40% reduction in system preparation steps
- Streamlined deployment sequence

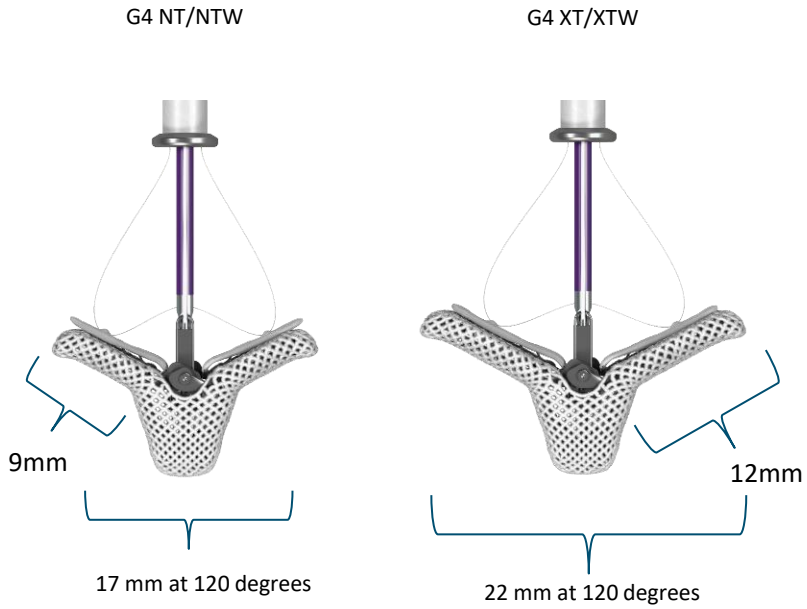
Delivery System Specifically Designed for MV
- Controlled and precise steering

Left Atrial Pressure (LAP) monitoring
- Facilitated assessment of MR reduction

*MitraClip G4 Instructions for Use.

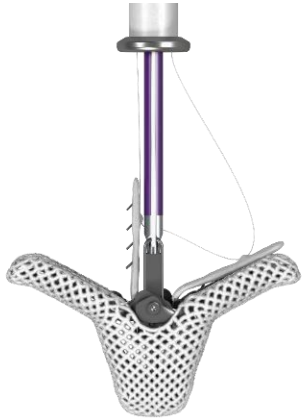
MitraClip G4: Expanded Clip Size to Tailor MV Repair





MitraClip G4: Controlled Gripper Actuation to Confirm and Optimize Leaflet Grasping

Both Grippers Lowered



One Gripper Lowered at a time

Choose MitraClip G4 Clip Sizes Based on Each Patient MV Anatomy

Key Anatomical Consideration to evaluate to ensure adequate MR reduction, clip stability, preservation of MV area:

1. Length of Leaflet
2. Width of the Jet
3. Mitral Valve Area

	Anatomical Considerations		Favors G4 NTW	Favors G4 NT	Favors G4 XTW	Favors G4 XT
1. Leaflet insertion	**Length of mobile leaflet in grasping zone?**	Leaflet Length < 9 mm	+	+		
		Leaflet Length ≥ 9 mm			+	+
2. Jet Width	**Width of jet?**	Broad jet	+		+	
3. MVA	**Area of valve?**	Smaller Valve		+		
		Larger Valve	+		+	+

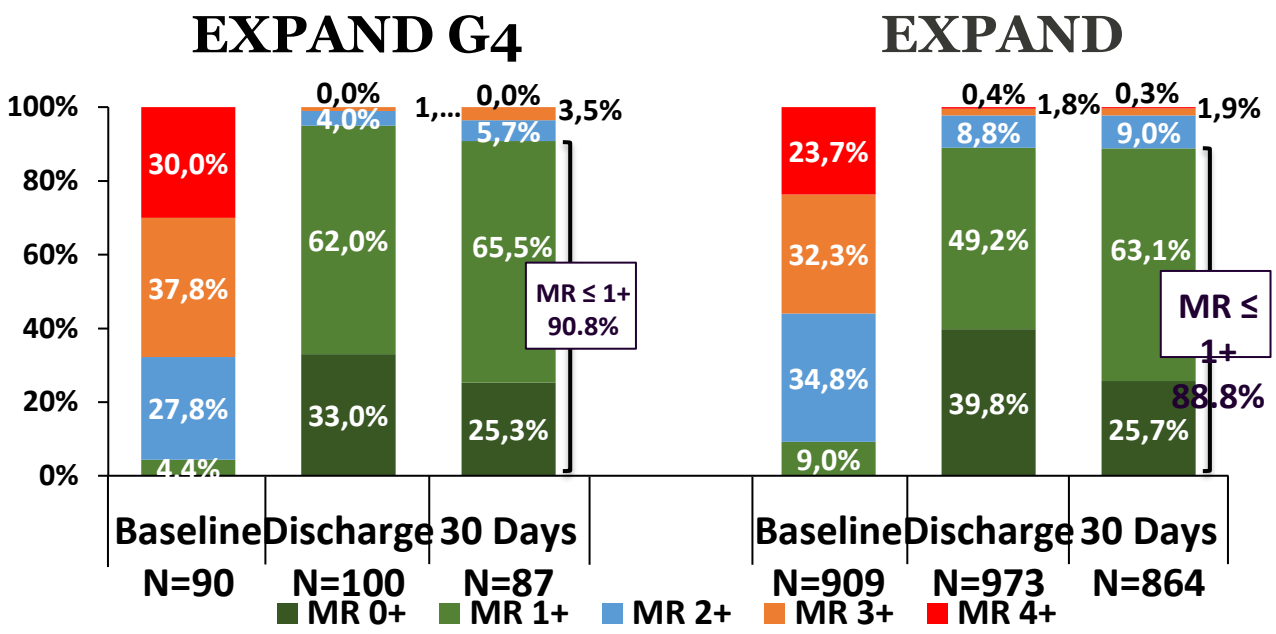
EXPAND G4 Study Procedural Outcome

	EXPAND G4 (N=101)	**EXPAND[1] (N=1040)**	**TVT Registry[2] (N=2,952)**	**ACCESS-EU[3] (N=567)**
Implant Rate % (n/N) [95% Confidence Interval]	**99.0% (100/101)** [94.6%, 100.0%]	98.9% (1030/1041) [98.12%, 99.5%]	NA	99.6%
Acute Procedural Success (APS)* % (n/N) [95% Confidence Interval]	**99.0% (99/100)** [94.6%, 100.0%] (ECL)	95.9% (983/1026) [94.4%, 97.0%] (ECL)	91.8% (2,709/2,952) Site-Reported	91% [514/565) Site-Reported
Device Time (min) Median [Inter-Quartile Range]	**39.0 [24.0-63.0]**	46.0 [30.0-71.0]	NA	NA
Fluoroscopy Time (min) Median [Inter-Quartile Range]	16.2 [11.1 – 22.1]	17.2 [11.1 – 27.0]	NA	25.0 (0.0, 152)
Procedure Time (min) Median [Inter-Quartile Range]	80.0 [57.0-109.0]	80.0 [54.0-115.0]	NA	100.0 (15, 390)
Length of Stay in Hospital for Index Procedure, Mean±SD	3.3±4.2	3.2±4.2 (US only)	NA	7.7±8.2

*APS defined as successful implantation of the MitraClip® device with resulting MR severity of 2+ or less on discharge Echocardiogram (30-day echocardiogram is used if discharge is unavailable or uninterpretable). Subjects who die or undergo mitral valve surgery before discharge are considered to be an APS failure

[1]Rottbauer et al. Primary Outcomes. EuroPCR 2020
[2]Sorajja et al. J Am Coll Cardiol 2017;70:2315–27
[3]Maisano et al. J Am Coll Cardiol 2013;62:1052–61

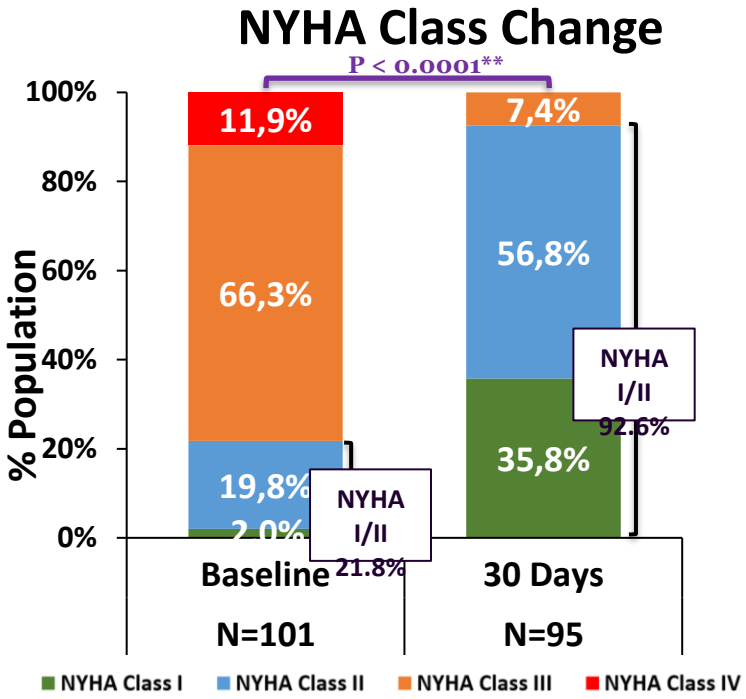
EXPAND G4 ECL Adjudicated MR Severity

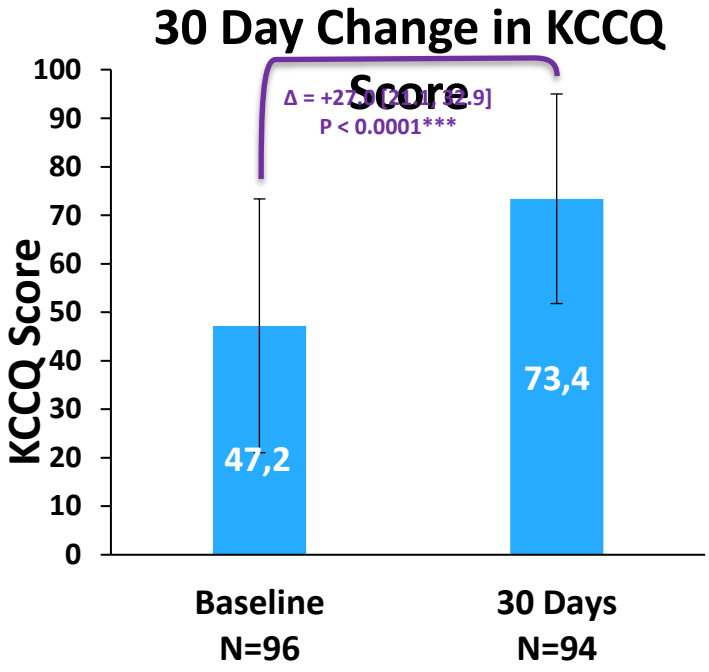


MR Reduction to ≤ mild at 30 days achieved in 90.8% of subjects; 96.5% had MR reduction to ≤ moderate.

** Baseline MR Severity was reported as 3+/4+ for all subjects enrolled in EXPAND G4 and EXPAND per site assessment.*
***ECL assessed MR severity based on ASE Guidelines (Zoghbi et al. J Am Soc Echocardiogr 2003; 16:777-802, 2017;30:303-371, 2019;32:431-475)*

EXPAND G4 Improved Functional Capacity and QoL*





** Quality of Life (QoL) Improvements assessed by Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS)*

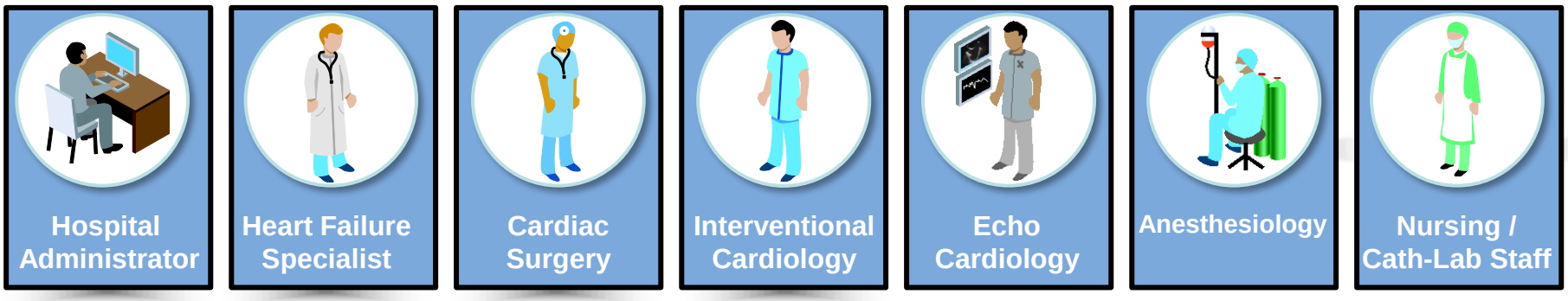
*** Pairwise comparison of improvement from NYHA Class III/IV to Class I/I between Baseline and 30 days (n=95)*

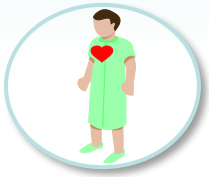
**** Pairwise comparison of KCCQ score between Baseline and 30 Days Year (n=90); 95% CI shown in brackets*

How to improve long-term outcomes?

- **Patients selection: clinical and anatomical criteria**

Role of a multidisciplinary Heart-Team





Optimal Patient Care

Percutaneous edge-to-edge repair: in which patients?

Symptomatic moderate/severe MR DESPITE OMT/CRT + SUITABLE MORPHOLOGY

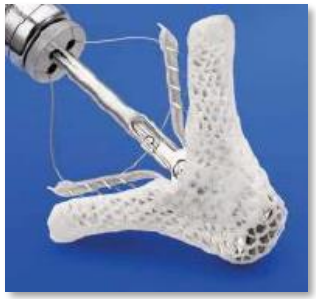
1. **Inoperable/high surgical risk pts + No CABG planned + FE>30%**
2. **Low likelyhood of durable repair**
3. **CRT non-responders**
4. **End-stage heart failure/Severe LV disfunction**
4. **Bridge to LVAD or Transplant**

Franzen o. EJ Heart Fail 2011; 13 (5): 569-76

How to improve long-term outcomes?

- **Patients se[illegible] clinical and anatomical criteria**
  - **Timing of ir**
  - **Device imp[illegible]es**

MitraClip I gen



2008

Carillon + MitraClip

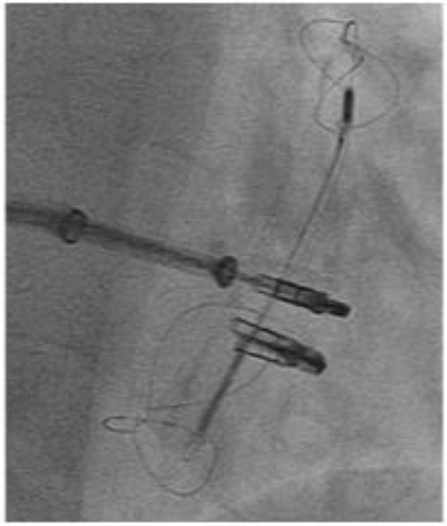
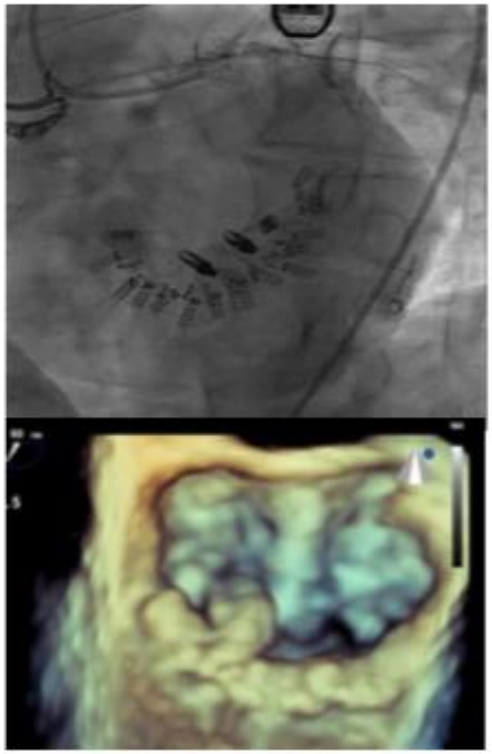


Image courtesy of R.S. von Bardeleben

EMO GVM CENTRO CUORE COLUMBUS s.r.l.

- Migliore navigabilità

Cardioband + MitraClip



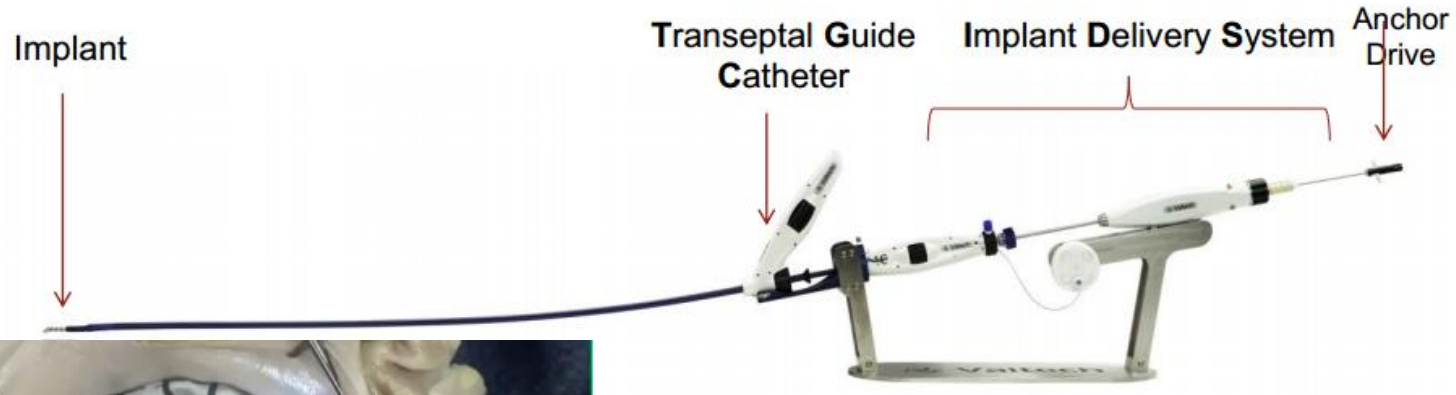
Latib - Agricola

- Migliore navigabilità

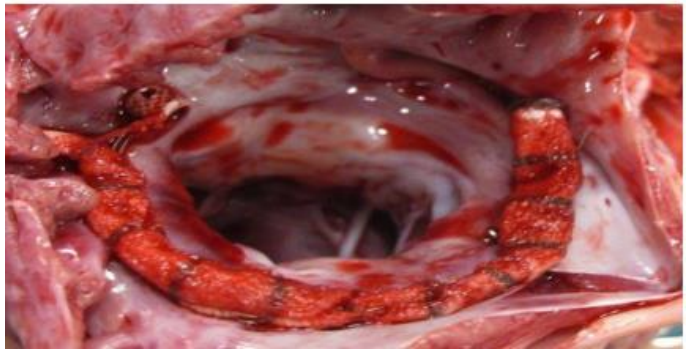
TriClip

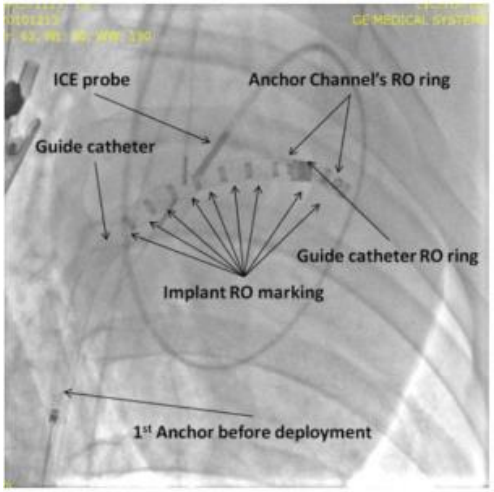
2019

Percutaneous Annuloplasty Device Without Open-Heart Surgery

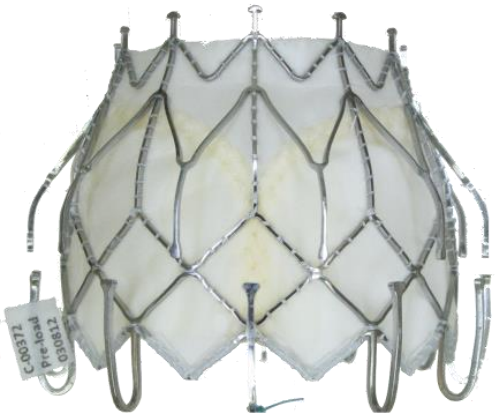


Cardioband Implant



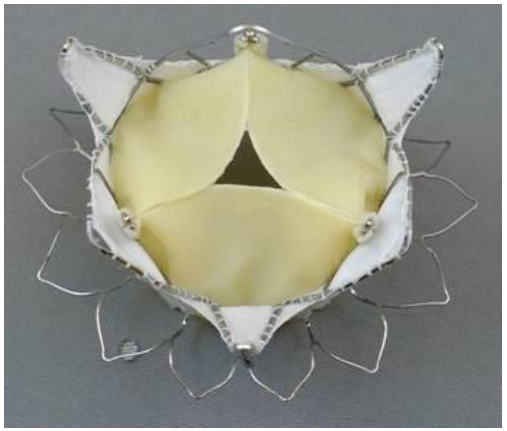


Sostituzione valvola mitrale transcatetere: dispositivi già impiantati nell'uomo



CARDIAQ

EDWARDS FORTIS



NEOVASC TIARA

TENDYNE

CONCLUSIONS

- **Severe FMR carries poorer outcomes**
- **Secondary FMR is a ventricular disease and needs different approaches than primary MR**
- **Optimal medical therapy is mandatory**
- **Surgery is indicated if concomitant disease requiring intervention**
- **In pts with HF and moderate-to-severe or severe secondary MR who remained symptomatic despite maximally-tolerated GDMT, transcatheter mitral leaflet approximation with the MitraClip was safe, provided durable reduction in MR, reduced the rate of HF hospitalizations, and improved survival, quality-of-life and functional capacity during 24-month follow-up**
- **As such, the MitraClip is the first therapy shown to improve the prognosis of patients with HF by reducing secondary MR due to LV dysfunction**
- **Patients selection is crucial**