ADVANCED HEART FAILURE WITH SEVERE FUNCTIONAL MITRAL REGURGITATION: TOO LATE FOR MITRACLIP OR TOO EARLY FOR LVAD?

Let's try mitralclip first

Giuseppe Musumeci
SC Cardiologia
AO Santa Croce e Carle Cuneo

L'insufficienza Mitralica (IM) trattamenti e outcomes

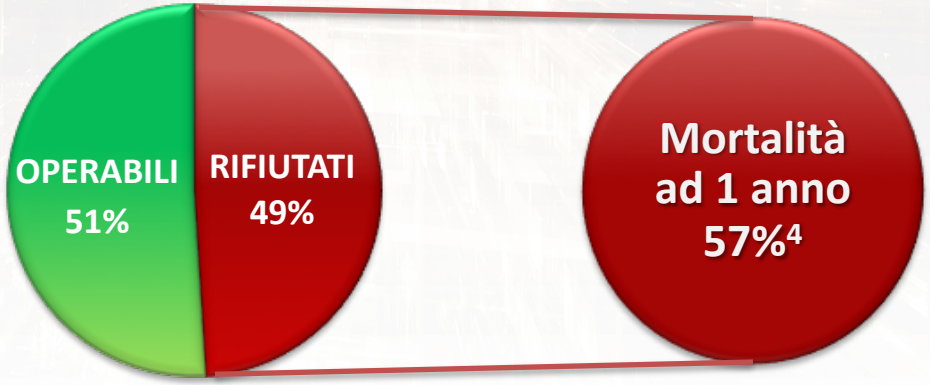
600.000 Pazienti <u>in Italia</u> con Insufficienza Mitralica (Moderata/Severa)[1,2]

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]

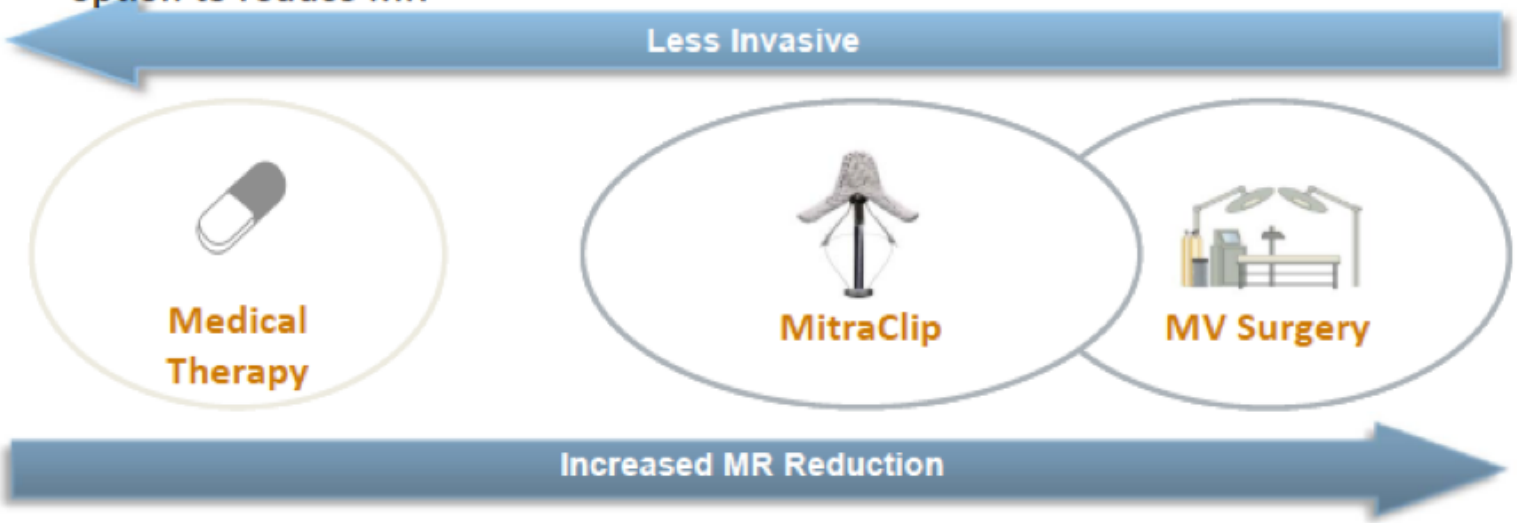
[1] Cioffi G, et al. **Functional mitral regurgitation predicts 1-year mortality in elderly patients with systolic chronic heart failure**. European Journal of Heart Failure 2005 Dec;7(7):1112-7

[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

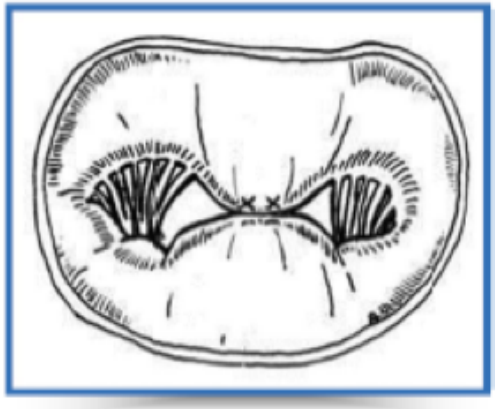
[3] Enriquez-Sarano M, et al. **Quantitative determinants of the outcome of asymptomatic mitral regurgitation**. N Engl J Med. 2005 Mar 3;352(9):875-83

MitraClip Therapy Filling a Treatment Gap

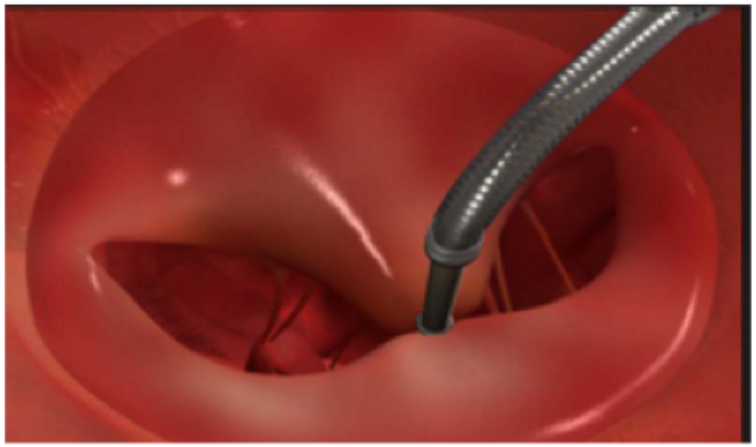
- Medical therapy is limited to symptom management
- MV surgery has been the only option that reliably reduces MR
- **A significant gap exists between patients who receive medical and surgical options, based on risk-benefit profile**
- MitraClip therapy is a first-in-class, minimally invasive catheter-based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



Concept: Percutaneous Mitral Valve Repair (PMVR)

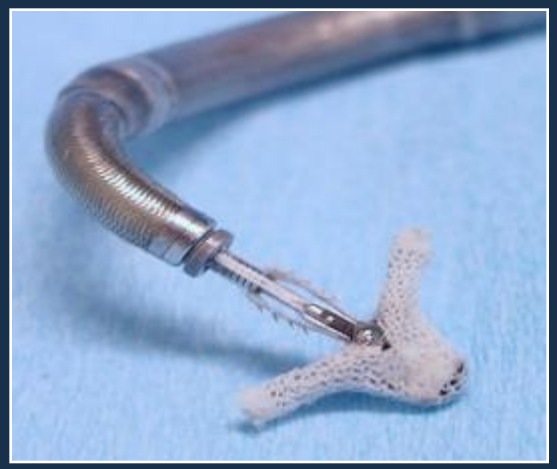


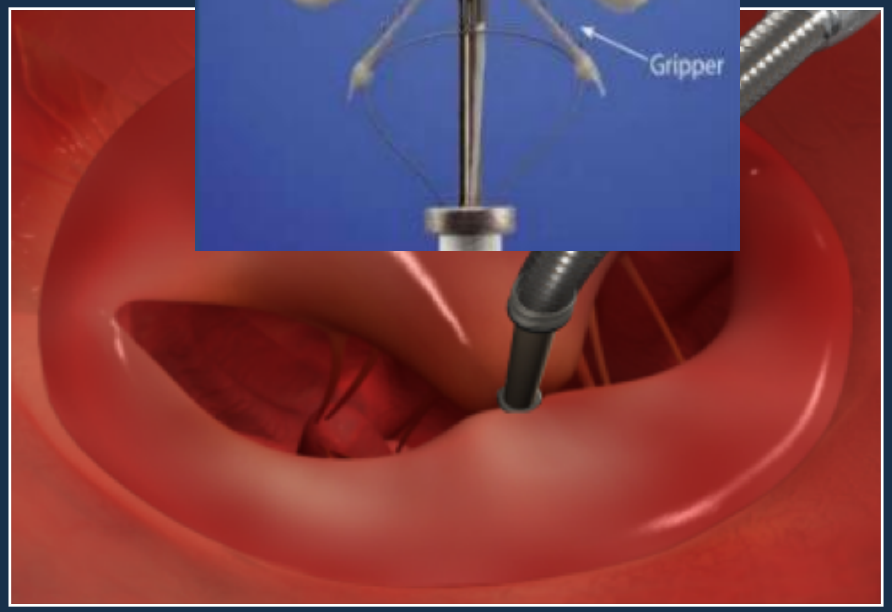
- Double-orifice suture technique developed by Prof. Ottavio Alfieri
- First published results in 1998 illustrated proven benefit
- Suggested procedure best suited for minimally invasive approach

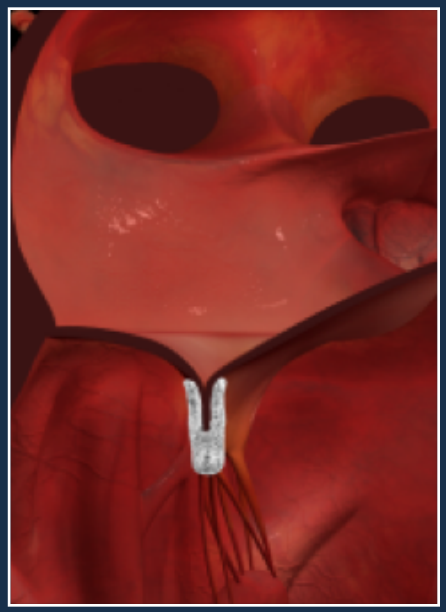


Catheter-Based Mitral Valve Repair

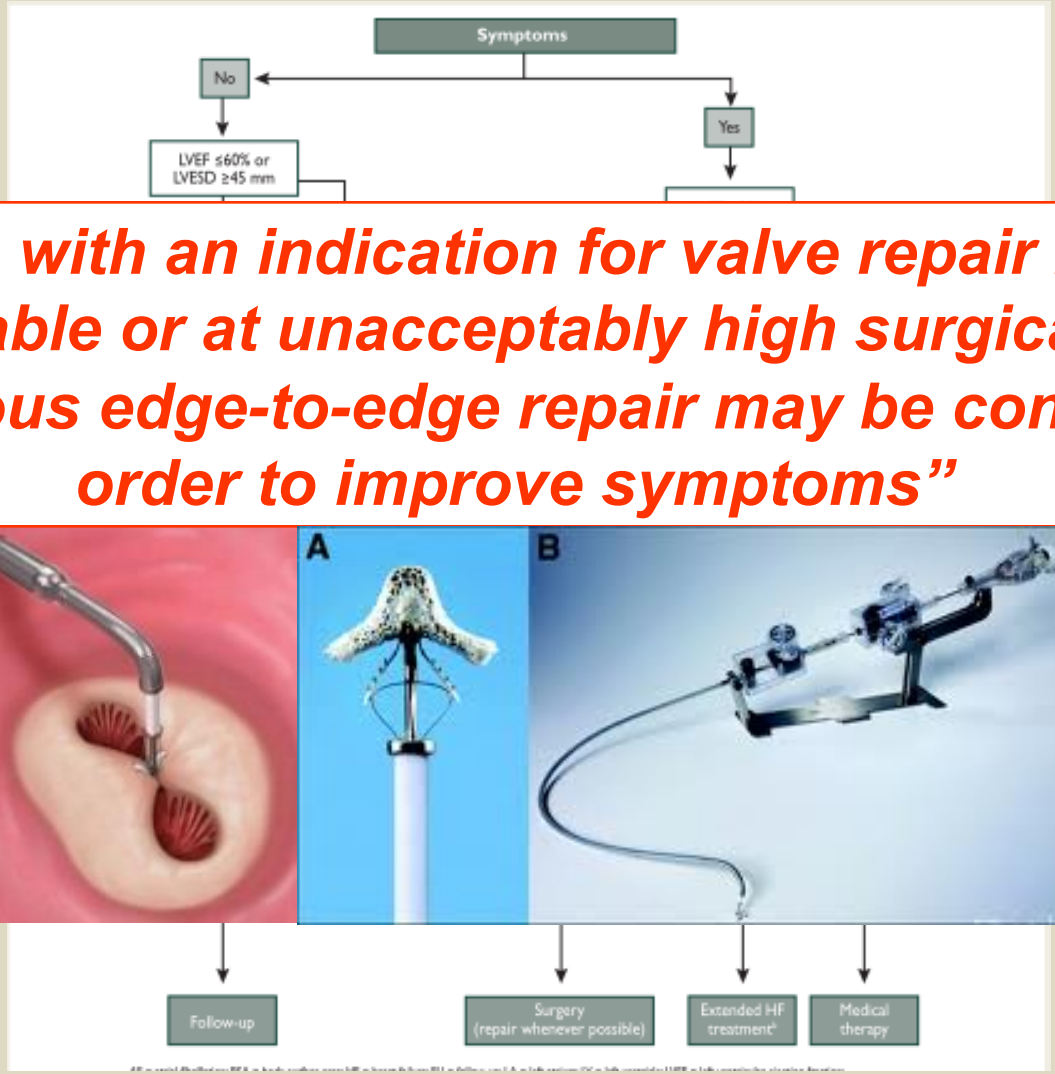
MitraClip® System







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

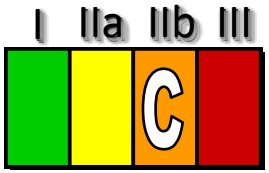


patients with an indication for valve repair but judged inoperable or at unacceptably high surgical risk, percutaneous edge-to-edge repair may be considered in order to improve symptoms"

ESC/EACTS GUIDELINES
Tanscatheter treatment for FMR

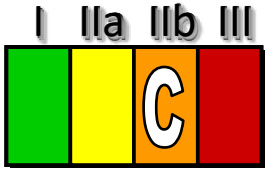
When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and LVEF >30%, who remain symptomatic despite optimal medical management (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility.

ESC '17



In patients with HF with moderate-severe secondary mitral regurgitation who are judged inoperable or at high surgical risk, percutaneous mitral valve intervention (percutaneous edge-to-edge repair) may be considered in order to improve symptoms and quality of life, although no RCT evidence of improvement has been published, only registry studies.

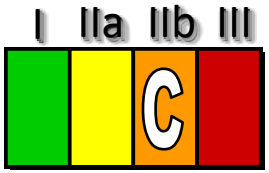
ESC '16



ESC/EACTS GUIDELINES
Tanscatheter treatment for FMR

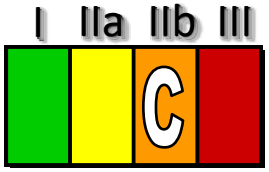
In patients with severe secondary MR and LVEF <30% who remain symptomatic despite OMT (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplant according to individual patient characteristics.

ESC '17



In most patients with severe functional MR and LVEF<30% who cannot be revascularized or have non-ischaemic cardiomyopathy conventional medical and device therapy are preferred. In selected cases, repair may be considered in order to avoid or postpone transplantation based on comprehensive evaluation and discussed within the 'heart team'.

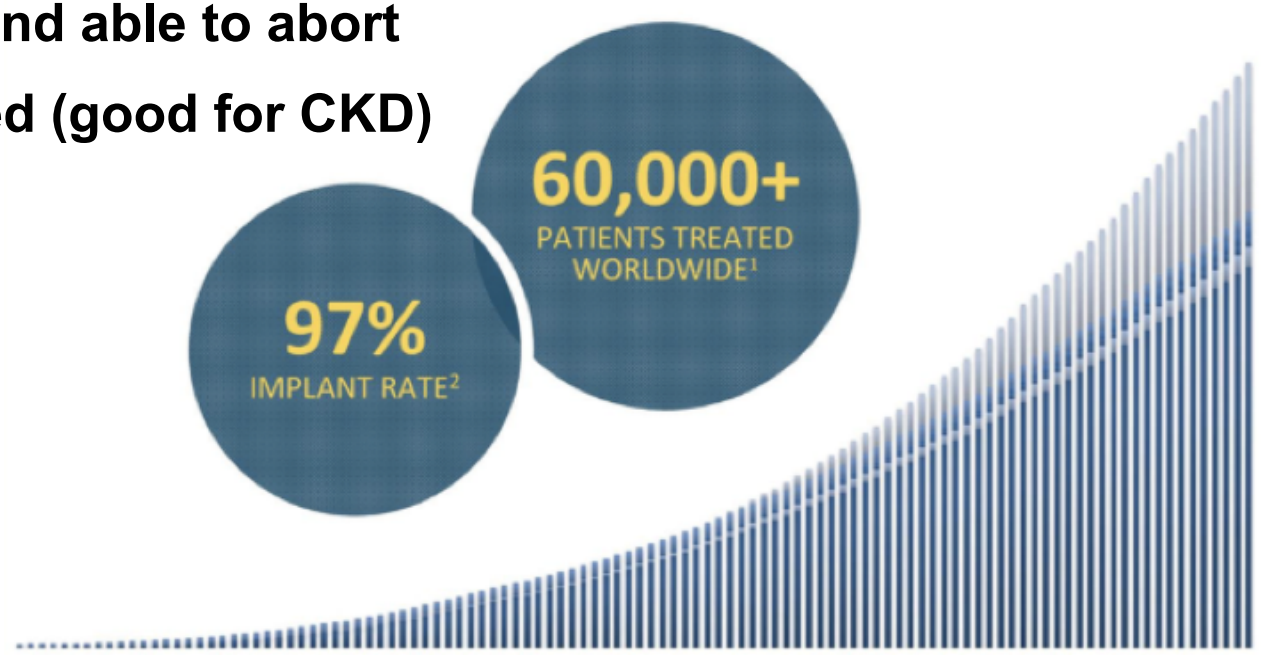
ESC '16



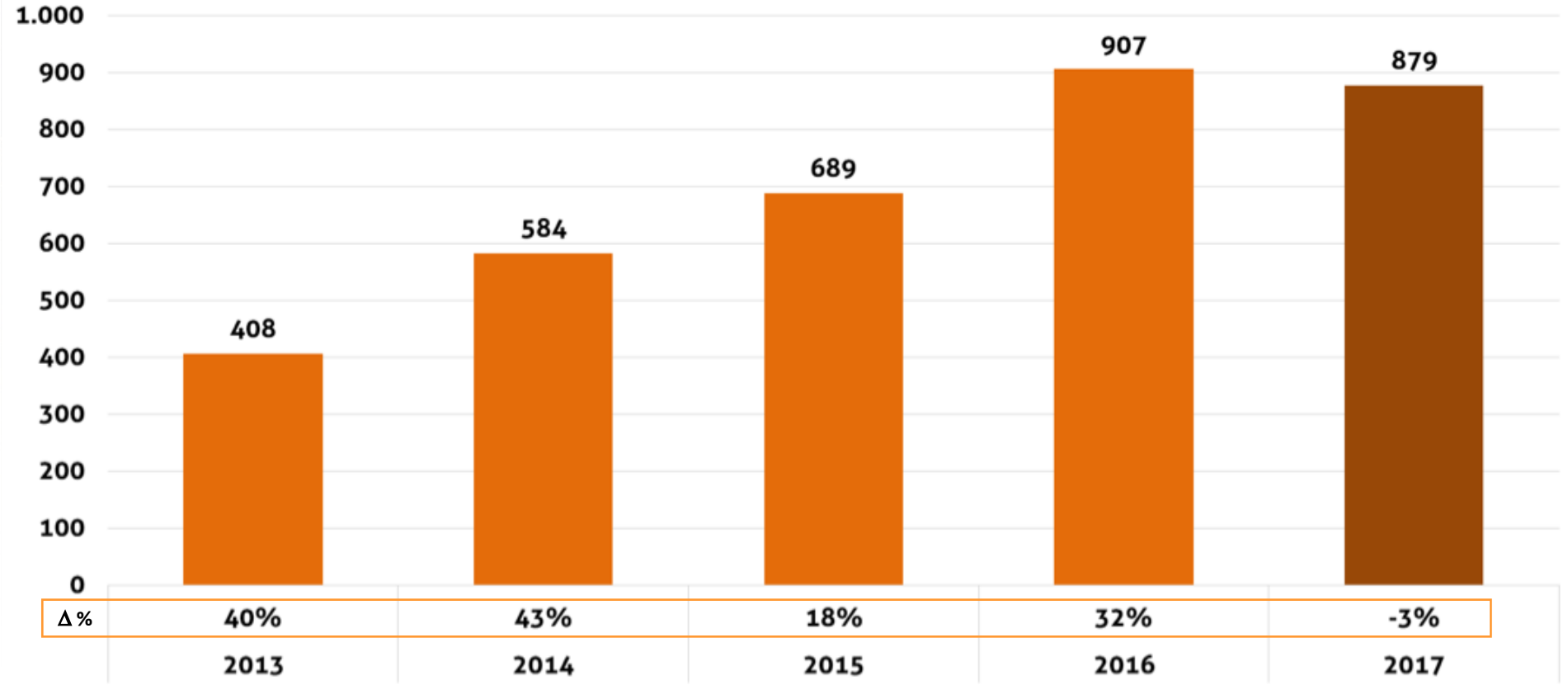
2017 ESC/EACTS Valvular Heart Disease Guidelines
2016 ESC/EACTS Acute and Chronic Heart Failure Guidelines

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)

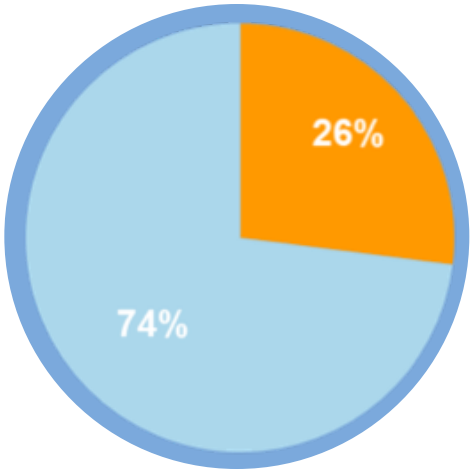


CLIP MITRALICA
ITALIA SERIE STORICA



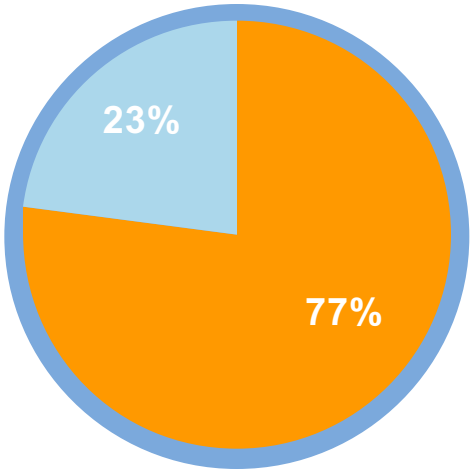
MitraClip Therapy
Broad Spectrum of Experience

EVEREST II
(Randomized Controlled Trial)



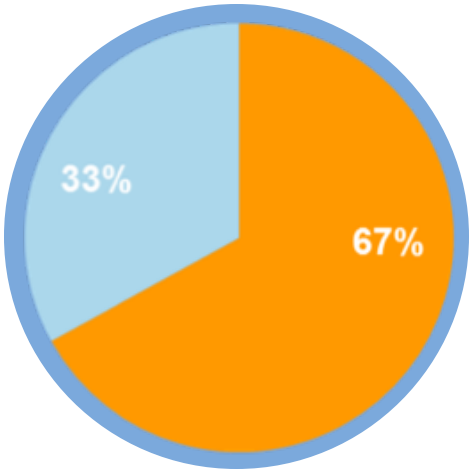
- 178 patients
- Device time – 146 minutes
- Implant rate – 89%

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 RCT

- Positive Safety Profile

Major Adverse Events at 30 Days

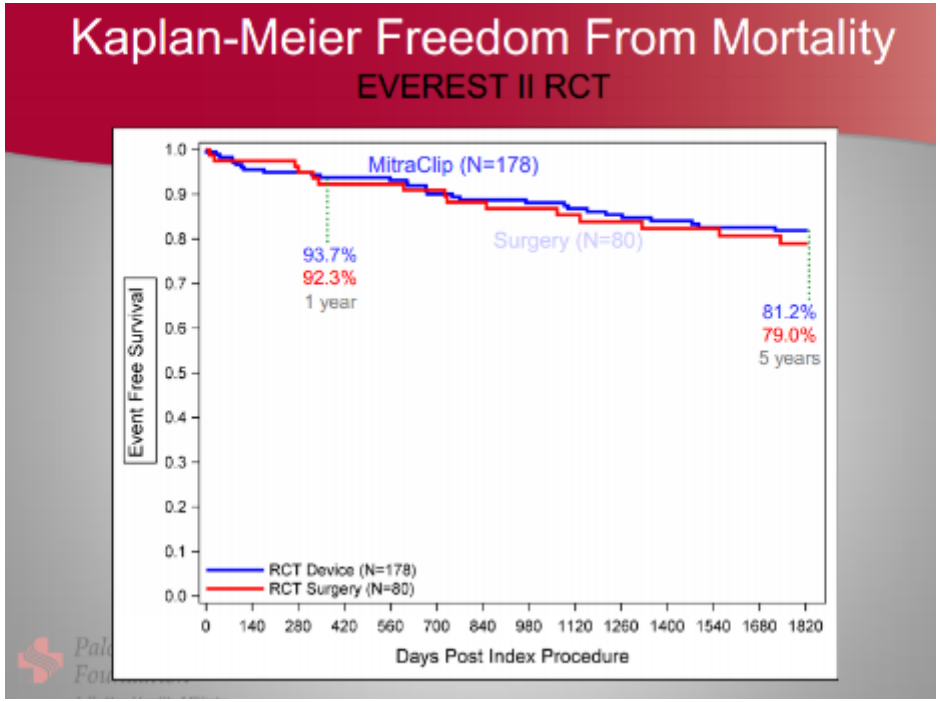
All Treated Patients (N=258)

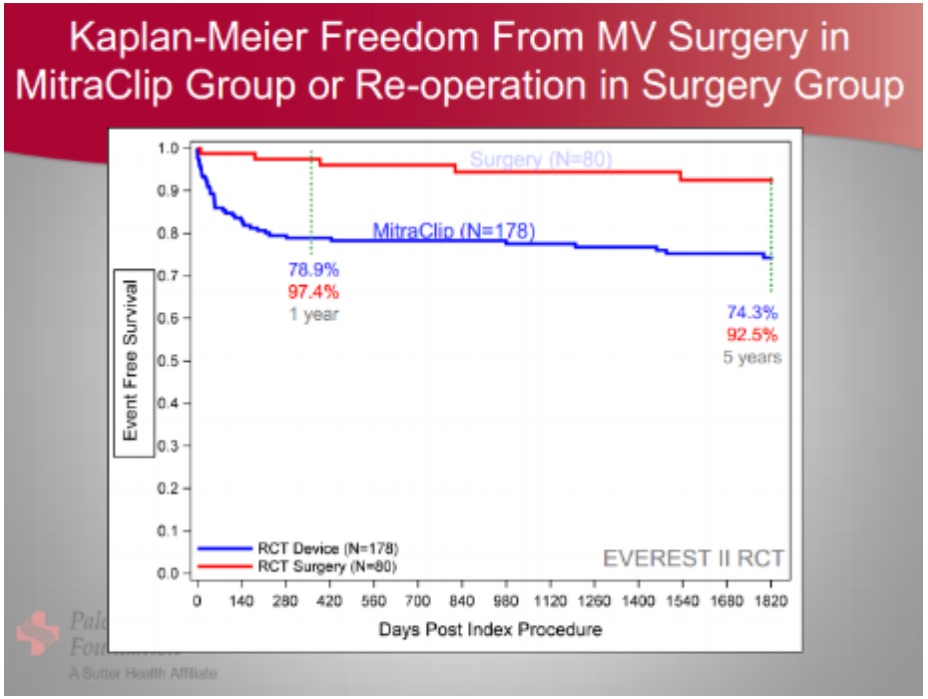
Description of Event	# (%) Patients experiencing event	
	MitraClip (N=178)	Surgery (N=80)
Death	2 (1.1%)	2 (2.5%)
Myocardial Infarction	0	0
Re-operation of Mitral Valve	0	1 (1.3%)
Urgent / Emergent CV Surgery	4 (2.2%)	4 (5.0%)
Stroke	1 (0.6%)	2 (2.5%)
Renal Failure	1 (0.6%)	0
Deep Wound Infection	0	0
Ventilation > 48 hrs	0	4 (5.0%)
GI Complication Requiring Surgery	2 (1.1%)	0
New Onset Permanent AFib	2 (1.1%)	0
Septicemia	0	0
MAE Major Bleeding Complication*	9 (5.1%)	37 (46.3%)
TOTAL % of Patients with MAE	**7.9%**	**50.0%**

Source: Feldman T, Foster E, Qureshi M, et al. The EVEREST II Randomized Controlled Trial: Three Year Outcomes Transcatheter Cardiovascular Therapeutics; October 22-26, 2012; Miami, FL.

*Major Bleeding Complications included in this table required surgery or transfusions ≥ 2 units of blood; does not include bleeding events already reported in other categories in this table.

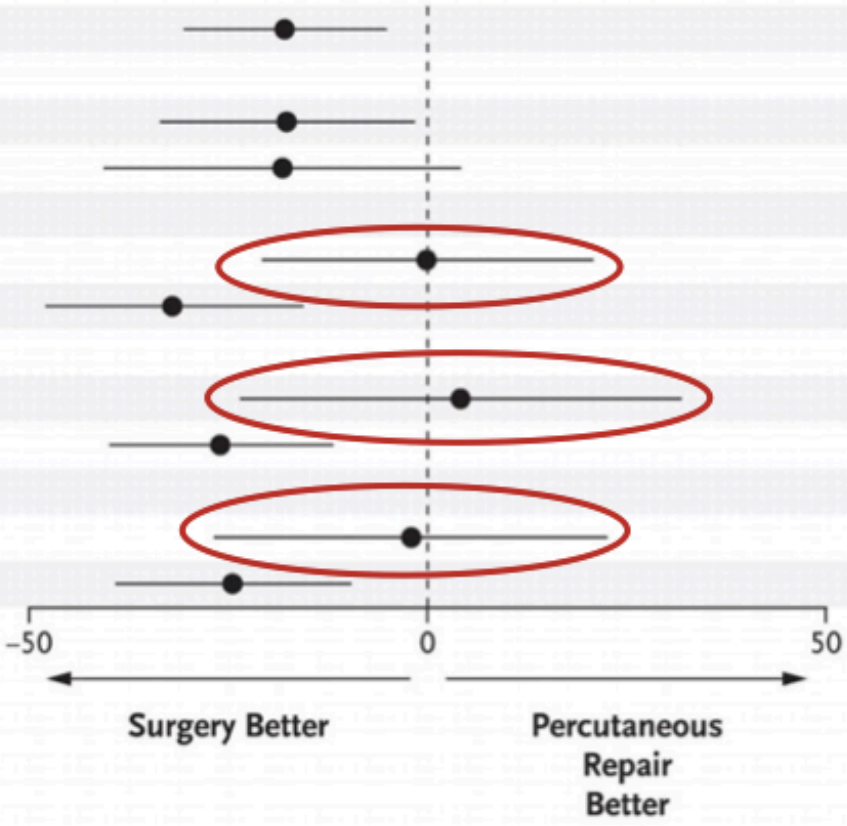
MitraClip vs Chirurgia a 5 anni
Stessa mortalità più reinterventi





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

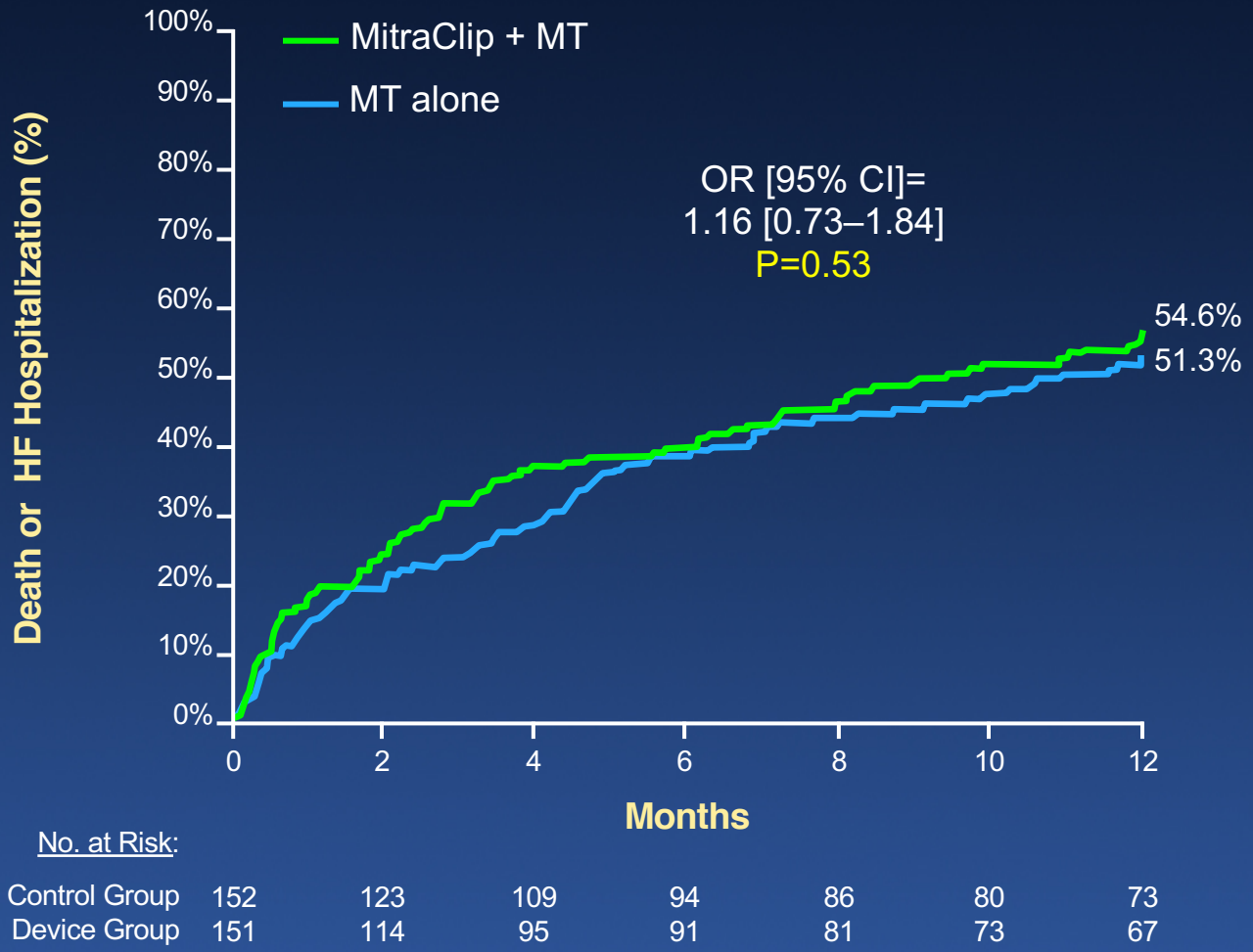
Subgroup	Percutaneous Repair	Surgery	P Value for Interaction
	no. of events/total no. (%)		
All patients	100/181 (55)	65/89 (73)	
Sex			0.97
Male	63/114 (55)	43/59 (73)	
Female	37/67 (55)	22/30 (73)	
Age			0.009
≥70 yr	52/86 (60)	23/38 (61)	
<70 yr	48/95 (51)	42/51 (82)	
MR			
Functional	26/48 (54)	12/24 (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).*

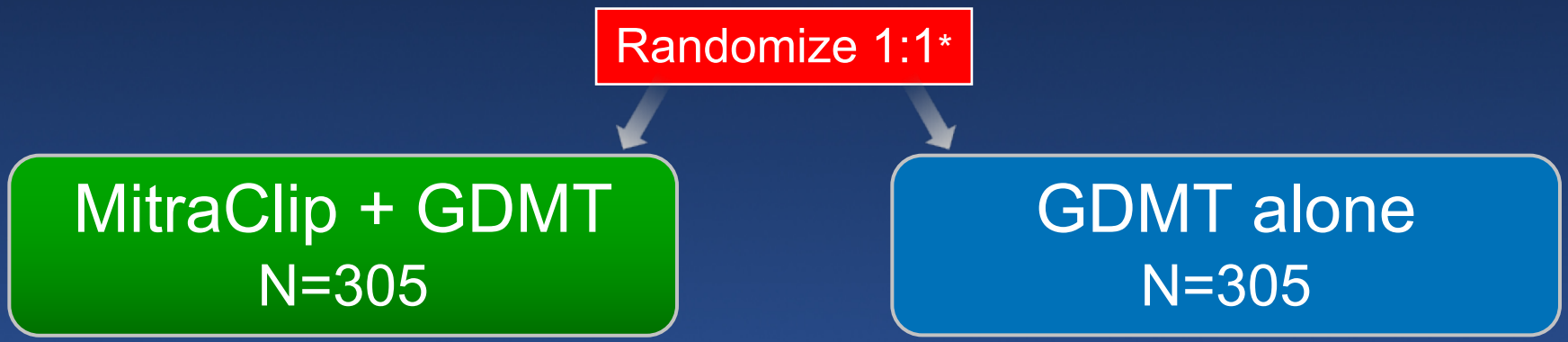
Variable	Intervention Group (N=152)	Control Group (N=152)
Periprocedural complications during device implantation — no./total no. (%)†	21/144 (14.6)	NA
Device-implantation failure	6/144 (4.2)‡	NA
Hemorrhage resulting in transfusion or vascular complication resulting in surgical intervention	5/144 (3.5)	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

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

A parallel-controlled, open-label, multicenter trial in ~610 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated GDMT



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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

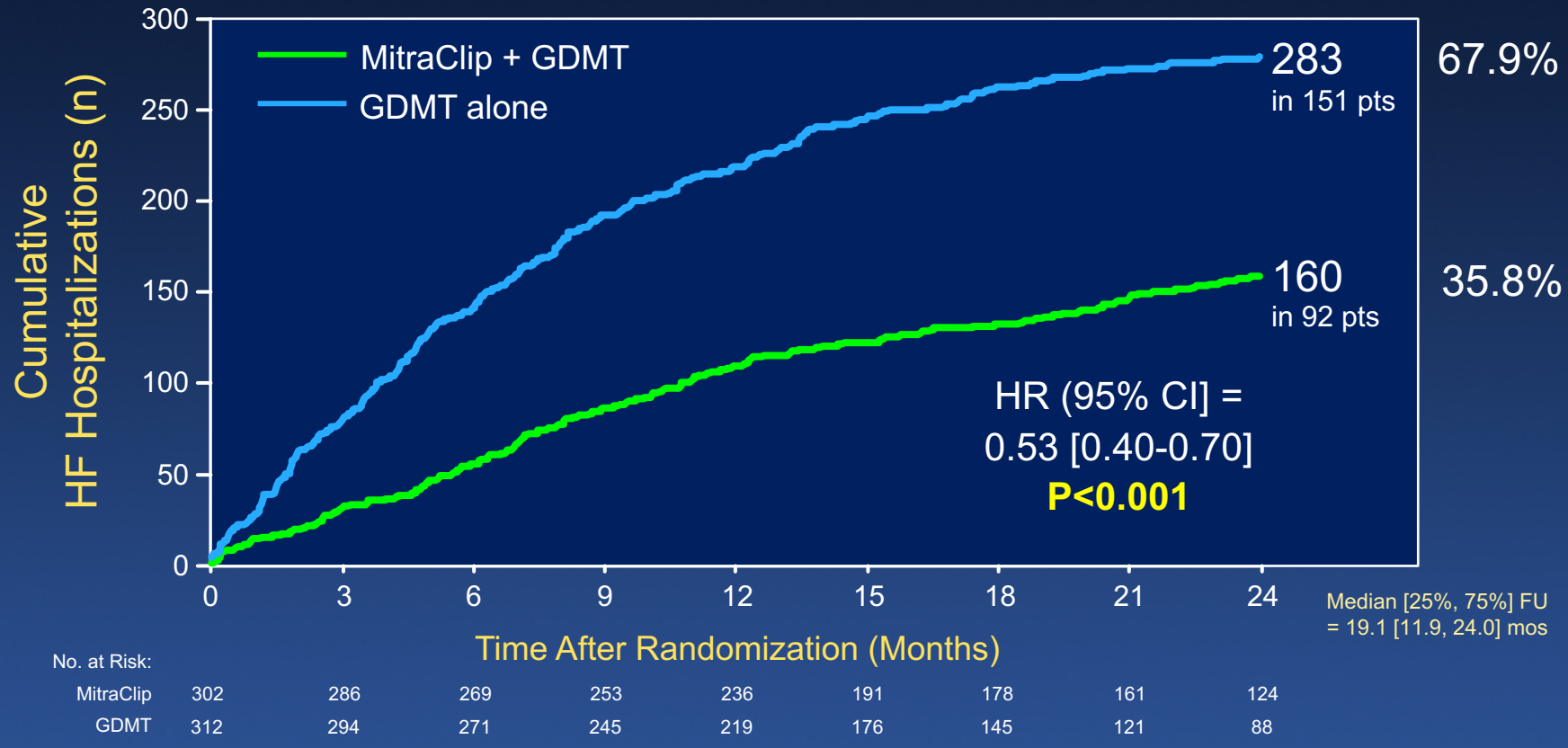
Transcatheter Mitral-Valve Repair in Patients with Heart Failure

G.W. Stone, J.A. Lindenfeld, W.T. Abraham, S. Kar, D.S. Lim, J.M. Mishell, B. Whisenant, P.A. Grayburn, M. Rinaldi, S.R. Kapadia, V. Rajagopal, I.J. Sarembock, A. Brieke, S.O. Marx, D.J. Cohen, N.J. Weissman, and M.J. Mack, for the COAPT Investigators*

COAPT TRIAL

Primary Effectiveness Endpoint

All Hospitalizations for HF within 24 months



COAPT TRIAL

Key Inclusion Criteria

1. Ischemic or non-ischemic cardiomyopathy with LVEF 20%-50% and LVESD ≤70 mm
2. Moderate-to-severe (3+) or severe (4+) secondary MR confirmed by an independent echo core laboratory prior to enrollment (US ASE criteria)
3. NYHA functional class II-IVa (ambulatory) despite a stable maximally-tolerated GDMT regimen and CRT (if appropriate) per societal guidelines
4. Pt has had at least one HF hospitalization within 12 months and/or a BNP ≥300 pg/ml* or a NT-proBNP ≥1500 pg/ml*
5. Not appropriate for mitral valve surgery by local heart team assessment
6. IC believes secondary MR can be successfully treated by the MitraClip

Adjusted by a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m^2 in BMI >20 kg/m^2

COAPT TRIAL

Baseline Characteristics (i)

	MitraClip + GDMT (N=302)	GDMT alone (N=312)
Age (years)	71.7 ± 11.8	72.8 ± 10.5
Male	66.6%	61.5%
Diabetes	35.1%	39.4%
Hypertension	80.5%	80.4%
Hyperchol.	55.0%	52.2%
Prior MI	51.7%	51.3%
Prior PCI	43.0%	49.0%
Prior CABG	40.1%	40.4%
Prior stroke or TIA	18.5%	15.7%
PVD	17.2%	18.3%
COPD	23.5%	23.1%
H/o atrial fibr	57.3%	53.2%

	MitraClip + GDMT (N=302)	GDMT alone (N=312)
BMI (kg/m^2)	27.0 ± 5.8	27.1 ± 5.9
CrCl (ml/min)	50.9 ± 28.5	47.8 ± 25.0
- ≤60 ml/min	71.6%	75.2%
Anemia (WHO)	59.8%	62.7%
BNP (pg/mL)	1015 ± 1086	1017 ± 1219
NT-proBNP (pg/mL)	5174 ± 6567	5944 ± 8438
STS replacement sc	7.8 ± 5.5	8.5 ± 6.2
- ≥8	41.7%	43.6%
Surgical risk (central eligibility committee)		
- High*	68.6%	69.9%
- Not-high	31.4%	30.1%

* STS repl score ≥8% or one or more factors present predicting extremely high surgical risk

COAPT TRIAL

Baseline Characteristics (ii)

HF parameters	MitraClip + GDMT (N=302)	GDMT alone (N=312)	Echo core lab	MitraClip + GDMT (N=302)	GDMT alone (N=312)
Etiology of HF			MR severity		
- Ischemic	60.9%	60.6%	- Mod-to-sev (3+)	49.0%	55.3%
- Non-ischemic	39.1%	39.4%	- Severe (4+)	51.0%	44.7%
NYHA class			EROA, cm^2	0.41 ± 0.15	0.40 ± 0.15
- I	0.3%	0%	LVESD, cm	5.3 ± 0.9	5.3 ± 0.9
- II	42.7%	35.4%	LVEDD, cm	6.2 ± 0.7	6.2 ± 0.8
- III	51.0%	54.0%	LVESV, mL	135.5 ± 56.1	134.3 ± 60.3
- IV	6.0%	10.6%	LVEDV, mL	194.4 ± 69.2	191.0 ± 72.9
HF hosp w/i 1 year	58.3%	56.1%	LVEF, %	31.3 ± 9.1	31.3 ± 9.6
Prior CRT	38.1%	34.9%	- ≤40%	82.2%	82.0%
Prior defibrillator	30.1%	32.4%	RVSP, mmHg	44.0 ± 13.4	44.6 ± 14.0

COAPT TRIAL

Medication Use at Baseline

Maximally-tolerated doses	MitraClip + GDMT (n=302)	GDMT alone (n=312)
Beta-blocker	91.1%	89.7%
ACEI, ARB or ARNI	71.5%	62.8%
Mineralocorticoid receptor antagonist	50.7%	49.7%
Nitrates	6.3%	8.0%
Hydralazine	16.6%	17.6%
Diuretic	89.4%	88.8%
Chronic oral anticoagulant	46.4%	40.1%
Aspirin	57.6%	64.7%
P2Y12 receptor inhibitor	25.2%	22.8%
Statin	62.6%	60.6%

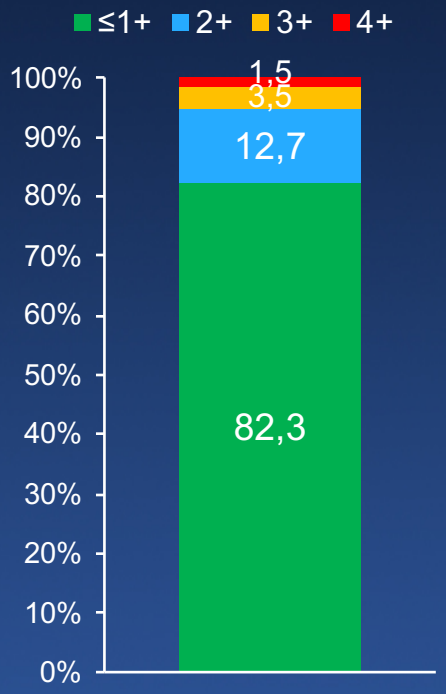
COAPT TRIAL

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

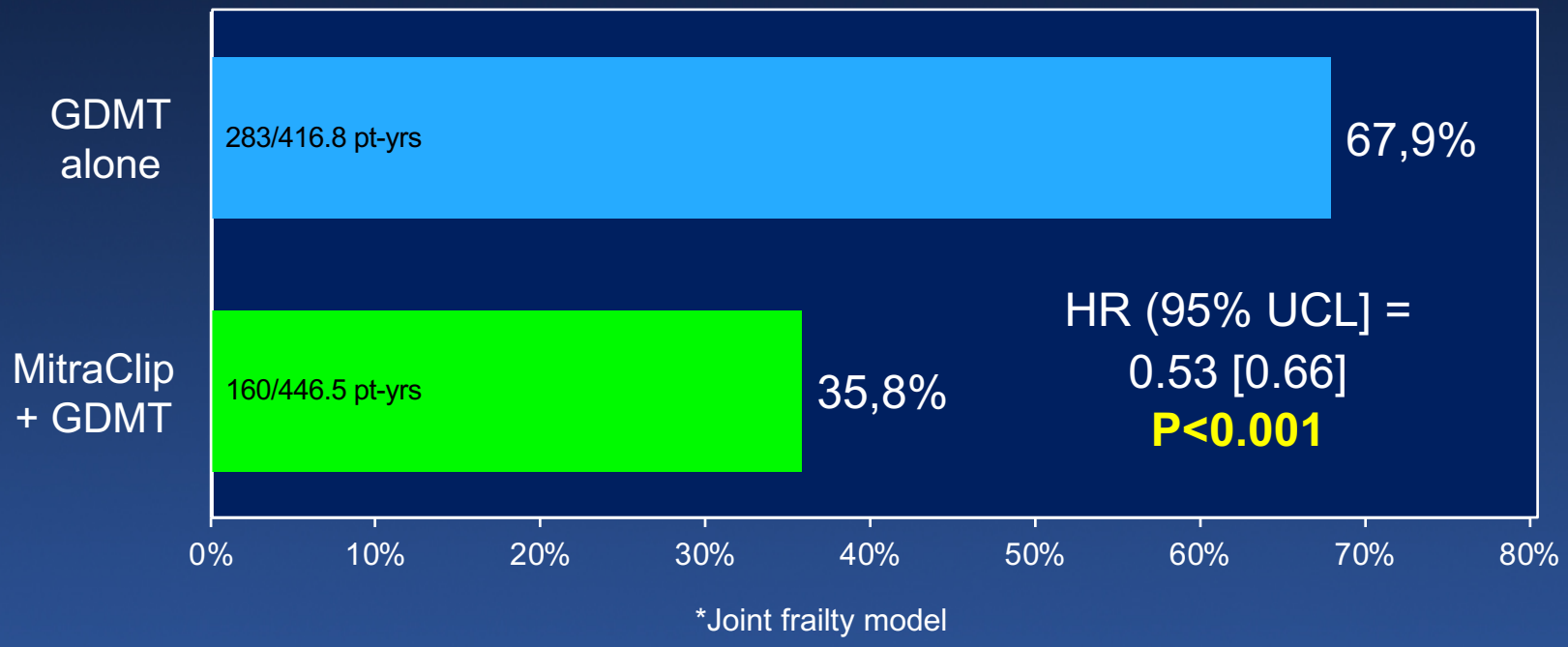


Primary Effectiveness Endpoint

Hospitalizations for HF within 24 months

Annualized rates of HF hospitalization*

NNT (24 mo) = 3.1 [95% CI 1.9, 8.2]



*Joint frailty model

COAPT TRIAL

Powered Secondary Endpoints

- Tested in hierarchical order[1] -

	P-value
1. MR grade ≤2+ at 12 months	
2. All-cause mortality at 12 months[2]	
3. Death and all HF hospitalization through 24 months (Finkelstein-Schoenfeld)	
4. Change in QOL (KCCQ) from baseline to 12 months	
5. Change in 6MWD from baseline to 12 months	
6. All-cause hospitalizations through 24 months	
7. NYHA class I or II at 12 months	
8. Change in LVEDV from baseline to 12 months	
9. All-cause mortality at 24 months	
10. Death, stroke, MI, or non-elective CV surgery for device-related compls at 30 days[3]	

[1]All powered for superiority unless otherwise noted; [2]Powered for noninferiority of the device vs. the control group; [3]Powered for noninferiority against an objective performance goal

COAPT TRIAL

Powered Secondary Endpoints

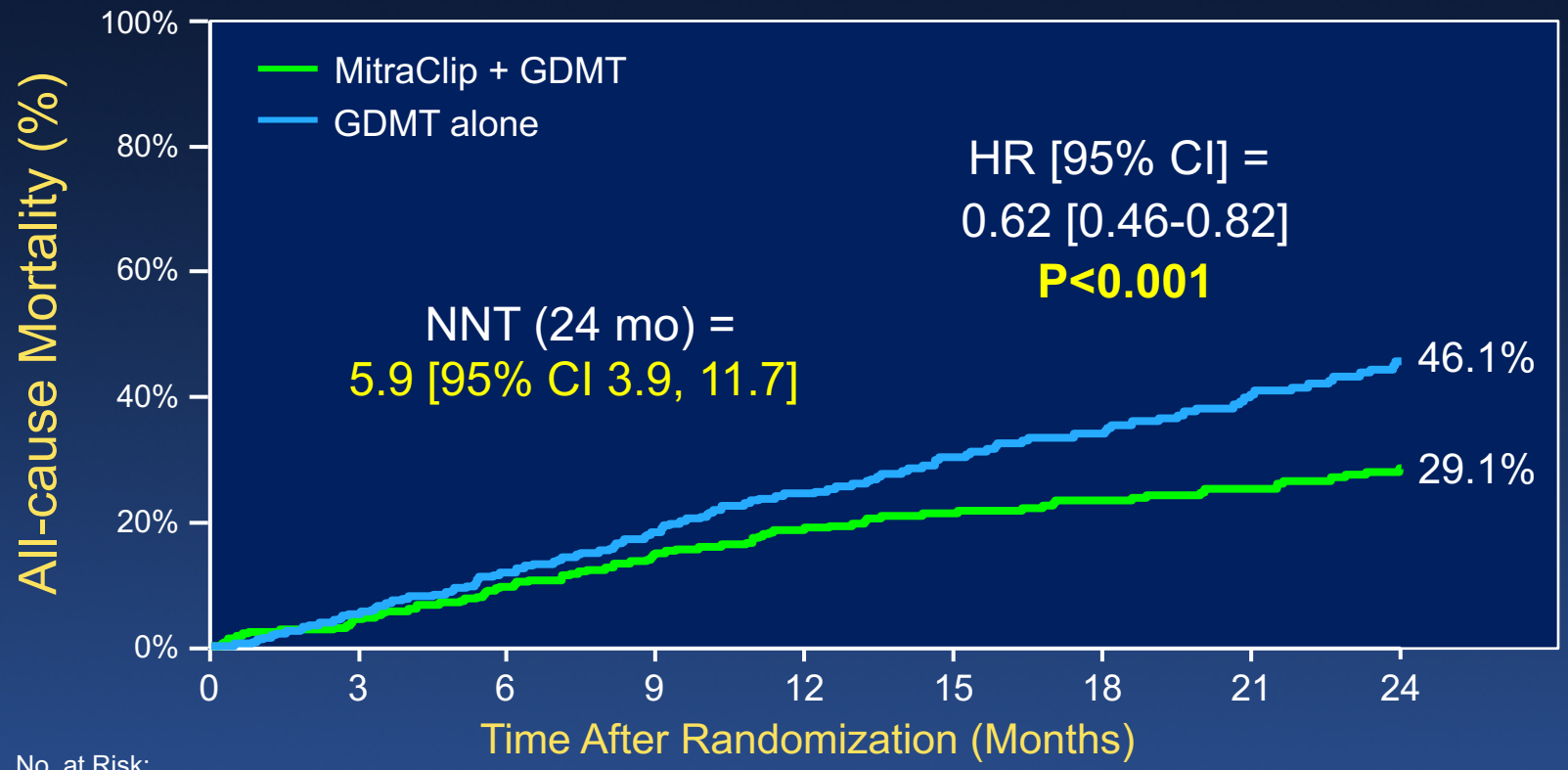
- Tested in hierarchical order[1] -

	P-value
1. MR grade ≤2+ at 12 months	<0.001
2. All-cause mortality at 12 months[2]	<0.001
3. Death and all HF hospitalization through 24 months (Finkelstein-Schoenfeld)	<0.001
4. Change in QOL (KCCQ) from baseline to 12 months	<0.001
5. Change in 6MWD from baseline to 12 months	<0.001
6. All-cause hospitalizations through 24 months	0.03
7. NYHA class I or II at 12 months	<0.001
8. Change in LVEDV from baseline to 12 months	0.003
9. All-cause mortality at 24 months	<0.001
10. Death, stroke, MI, or non-elective CV surgery for device-related compls at 30 days[3]	<0.001

[1]All powered for superiority unless otherwise noted; [2]Powered for noninferiority of the device vs. the control group; [3]Powered for noninferiority against an objective performance goal

COAPT TRIAL

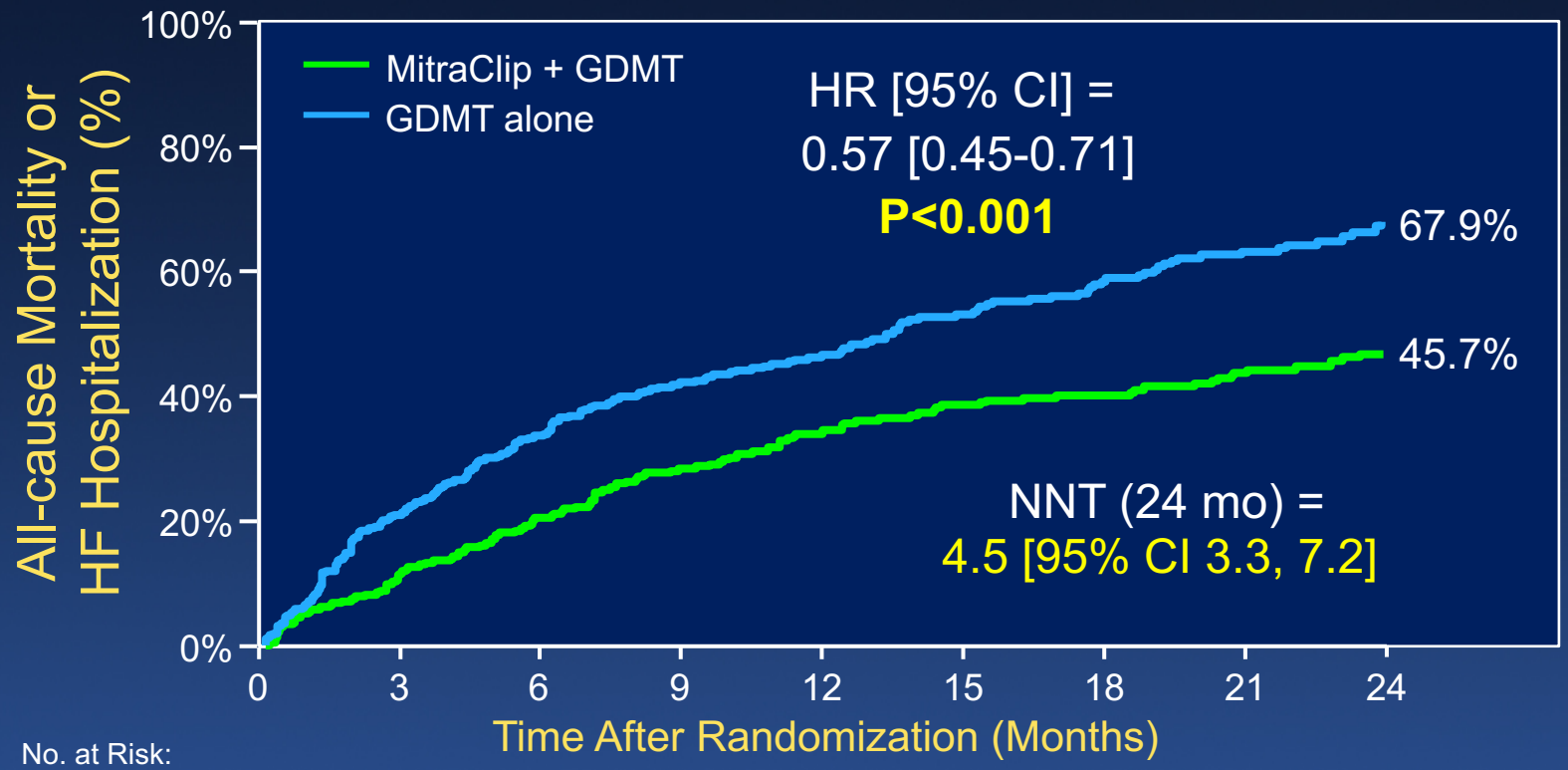
All-cause Mortality



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

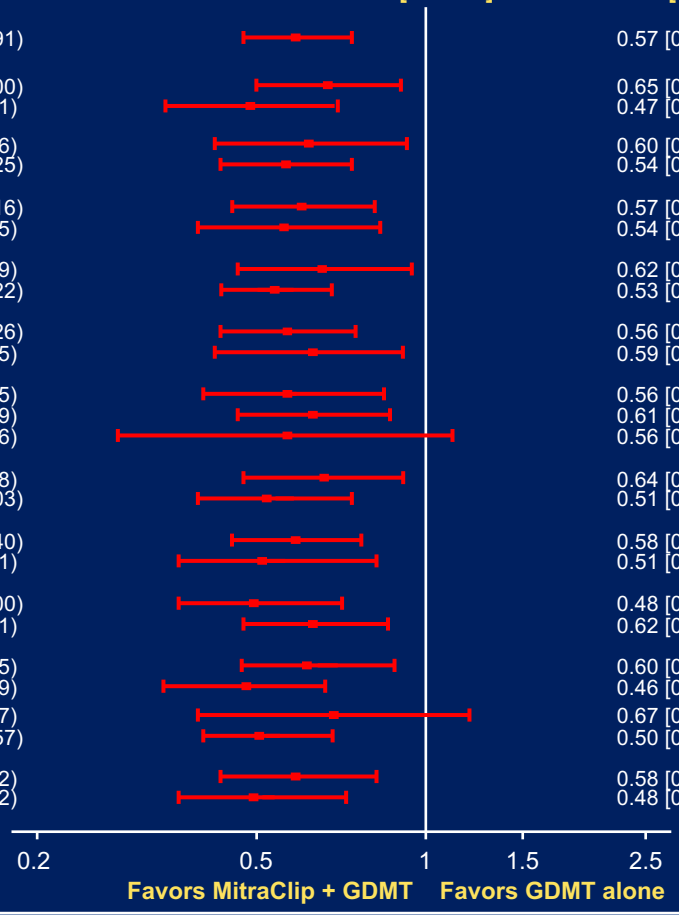


No. at Risk:

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

24-Month Death or HF Hospitalization

Subgroup	MitraClip + GDMT	GDMT alone	HR [95% CI]	P [Int]
All patients	45.7% (129)	67.9% (191)	0.57 [0.45, 0.71]	
Age (median)				
≥74 years (n=317)	52.1% (78)	70.2% (100)	0.65 [0.48, 0.88]	0.13
<74 years (n=297)	37.8% (51)	65.3% (91)	0.47 [0.33, 0.66]	
Sex				
Female (n=221)	43.2% (39)	59.4% (66)	0.60 [0.40, 0.89]	0.76
Male (n=393)	47.1% (90)	73.0% (125)	0.54 [0.41, 0.71]	
Etiology of cardiomyopathy				
Ischemic (n=373)	48.1% (84)	70.0% (116)	0.57 [0.43, 0.76]	0.79
Non-ischemic (n=241)	41.1% (45)	65.2% (75)	0.54 [0.37, 0.78]	
Prior CRT				
Yes (n=224)	50.2% (55)	68.4% (69)	0.62 [0.44, 0.89]	0.54
No (n=390)	42.9% (74)	67.4% (122)	0.53 [0.39, 0.71]	
HF hospitalization within the prior year				
Yes (n=407)	44.7% (86)	67.9% (126)	0.56 [0.42, 0.73]	0.79
No (n=207)	47.6% (43)	67.8% (65)	0.59 [0.40, 0.86]	
Baseline NYHA class				
I or II (n=240)	41.1% (50)	66.9% (65)	0.56 [0.39, 0.81]	0.92
III (n=322)	46.6% (67)	65.3% (99)	0.61 [0.44, 0.83]	
IV (n=51)	68.3% (12)	84.4% (26)	0.56 [0.28, 1.12]	
STS replacement score				
≥8% (n=262)	54.1% (65)	71.4% (88)	0.64 [0.46, 0.88]	0.41
<8% (n=352)	39.2% (64)	65.0% (103)	0.51 [0.37, 0.70]	
Surgical risk status*				
High (n=423)	49.7% (95)	71.5% (140)	0.58 [0.45, 0.75]	0.69
Not high (n=188)	35.8% (32)	58.7% (51)	0.51 [0.33, 0.80]	
Baseline MR grade				
3+ (n=320)	37.5% (51)	65.3% (100)	0.48 [0.34, 0.67]	0.29
4+ (n=293)	53.4% (78)	71.4% (91)	0.62 [0.45, 0.83]	
Baseline LVEF				
≥30% (median; n=301)	44.1% (62)	61.2% (85)	0.60 [0.43, 0.84]	0.32
<30% (median; n=274)	46.4% (56)	77.8% (99)	0.46 [0.33, 0.64]	
>40% (n=103)	49.7% (22)	56.2% (27)	0.67 [0.38, 1.17]	0.31
≤40% (n=472)	44.2% (96)	71.9% (157)	0.50 [0.39, 0.65]	
Baseline LVEDV (median)				
≥181 mL (n=288)	48.9% (43)	68.0% (92)	0.58 [0.42, 0.80]	0.42
<181 mL (n=287)	41.5% (54)	69.5% (92)	0.48 [0.34, 0.67]	



KM time-to-first event rates
*Central eligibility committee assessment

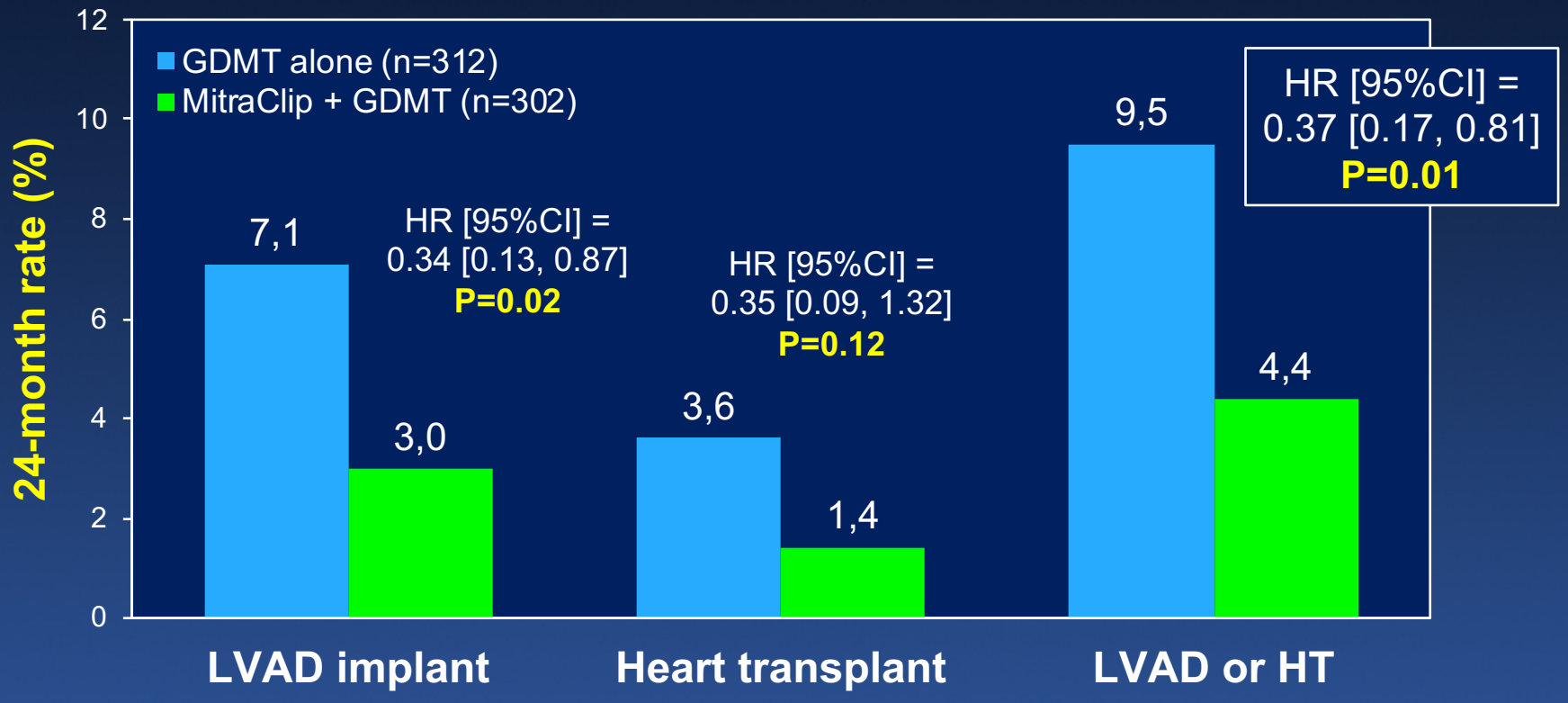
COAPT TRIAL

NYHA Functional Class

NYHA class	I	II	III	IV	HF death	P_{trend}	I or II	P-value
Baseline								
MitraClip (n=302)	0.3%	42.7%	51.0%	6.0%	-	-	43.0%	-
GDMT (n=311)	0%	35.4%	54.0%	10.6%	-		35.4%	
30 days								
MitraClip (n=283)	15.5%	60.8%	19.4%	3.5%	0.7%	<0.001	76.3%	<0.001
GDMT (n=281)	5.0%	42.7%	41.6%	9.6%	1.1%		47.7%	
6 months								
MitraClip (n=263)	19.4%	52.9%	21.3%	2.7%	3.8%	<0.001	72.2%	<0.001
GDMT (n=261)	5.4%	44.8%	38.3%	2.7%	8.8%		50.2%	
12 months								
MitraClip (n=237)	16.9%	55.3%	17.7%	2.5%	7.6%	<0.001	72.2%	<0.001
GDMT (n=232)	7.8%	41.8%	28.0%	4.7%	17.7%		49.6%	
24 months								
MitraClip (n=157)	12.1%	42.7%	21.7%	5.7%	17.8%	<0.001	54.8%	<0.001
GDMT (n=153)	5.2%	28.1%	23.5%	3.3%	39.3%		33.3%	

COAPT TRIAL

LVAD or Heart Transplant Within 24 Months



Stone GW et al. NEJM. 2018 Sept 23.

MR Severity (Core Lab)

MR grade	≤1+	2+	3+	4+	P_{trend}	≤2+	P-value
Baseline							
MitraClip (n=302)	-	-	49.0%	51.0%	-	-	-
GDMT (n=311)	-	-	55.3%	44.7%		-	
30 days							
MitraClip (n=273)	72.9%	19.8%	5.9%	1.5%	<0.001	92.7%	<0.001
GDMT (n=257)	8.2%	26.1%	37.4%	28.4%		34.2%	
6 months							
MitraClip (n=240)	66.7%	27.1%	4.6%	1.7%	<0.001	93.8%	<0.001
GDMT (n=218)	9.2%	28.9%	42.2%	19.7%		38.1%	
12 months							
MitraClip (n=210)	69.1%	25.7%	4.3%	1.0%	<0.001	94.8%	<0.001
GDMT (n=175)	11.4%	35.4%	34.3%	18.9%		46.9%	
24 months							
MitraClip (n=114)	77.2%	21.9%	0%	0.9%	<0.001	99.1%	<0.001
GDMT (n=76)	15.8%	27.6%	40.8%	15.8%		43.4%	

MR Severity (Core Lab)

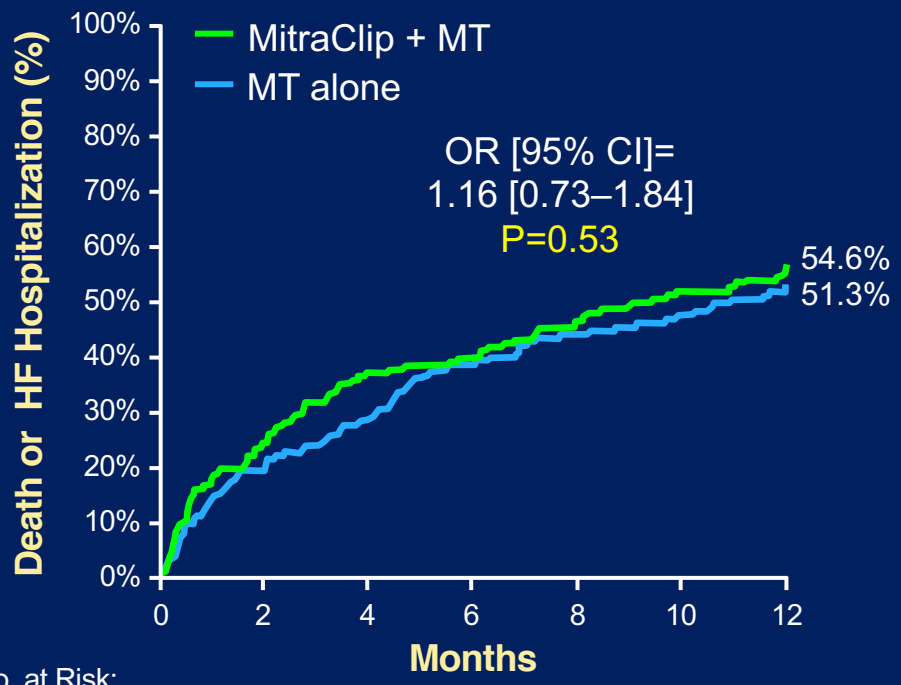
MR grade	≤1+	2+	3+	4+	P_{trend}	≤2+	P-value
Baseline							
MitraClip (n=302)	-	-	49.0%	51.0%	-	-	-
GDMT (n=311)	-	-	55.3%	44.7%		-	
30 days							
MitraClip (n=273)	72.9%	19.8%	5.9%	1.5%	<0.001	92.7%	<0.001
GDMT (n=257)	8.2%	26.1%	37.4%	28.4%		34.2%	
6 months							
MitraClip (n=240)	66.7%	27.1%	4.6%	1.7%	<0.001	93.8%	<0.001
GDMT (n=218)	9.2%	28.9%	42.2%	19.7%		38.1%	
12 months							
MitraClip (n=210)	69.1%	25.7%	4.3%	1.0%	<0.001	94.8%	<0.001
GDMT (n=175)	11.4%	35.4%	34.3%	18.9%		46.9%	
24 months							
MitraClip (n=114)	77.2%	21.9%	0%	0.9%	<0.001	99.1%	<0.001
GDMT (n=76)	15.8%	27.6%	40.8%	15.8%		43.4%	

MR Severity (Core Lab)

MR grade	≤1+	2+	3+	4+	P_{trend}	≤2+	P-value
Baseline			3+-4+				
MitraClip (n=302)	-	-	49.0%	51.0%	-	-	-
GDMT (n=311)	-	-	55.3%	44.7%		-	
30 days			7.4%				
MitraClip (n=273)	72.9%	19.8%	5.9%	1.5%	<0.001	92.7%	<0.001
GDMT (n=257)	8.2%	26.1%	37.4%	28.4%		34.2%	
6 months			6.3%				
MitraClip (n=240)	66.7%	27.1%	4.6%	1.7%	<0.001	93.8%	<0.001
GDMT (n=218)	9.2%	28.9%	42.2%	19.7%		38.1%	
12 months			5.3%				
MitraClip (n=210)	69.1%	25.7%	4.3%	1.0%	<0.001	94.8%	<0.001
GDMT (n=175)	11.4%	35.4%	34.3%	18.9%		46.9%	
24 months			0.9%				
MitraClip (n=114)	77.2%	21.9%	0%	0.9%	<0.001	99.1%	<0.001
GDMT (n=76)	15.8%	27.6%	40.8%	15.8%		43.4%	

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

MITRA-FR

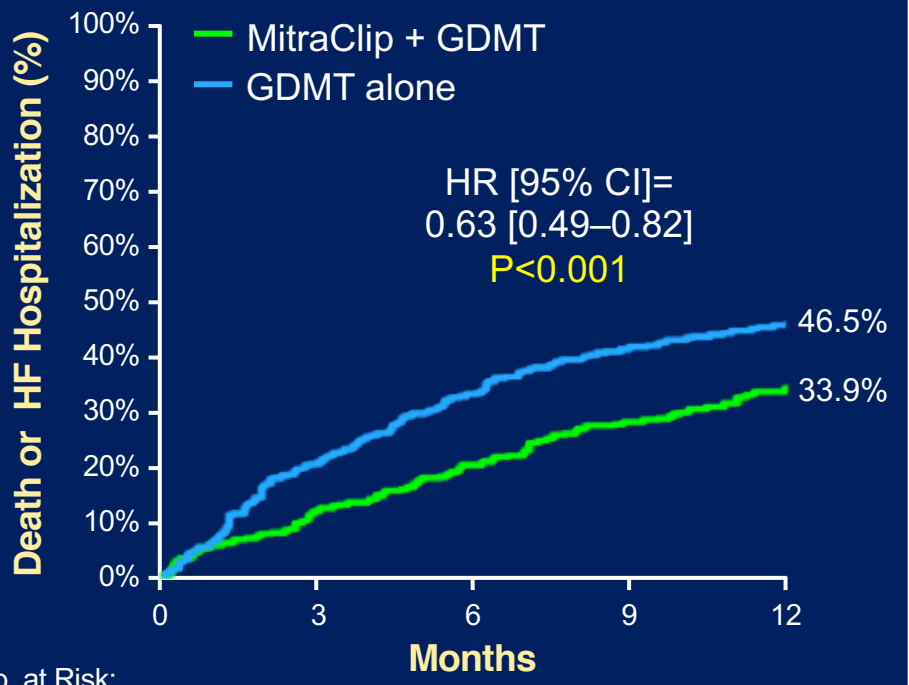


No. at Risk:

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

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

COAPT



No. at Risk:

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

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

COAPT vs. MITRA-FR: MitraClip Outcomes

	COAPT (n=302)	MITRA-FR (n=152)
MitraClip attempted	293 (97.0%)	144 (94.7%)
≥1 Clip implanted	287 (95.0%)	138 (90.8%)
Procedural complications	25/293 (8.5%)	21/144 (14.6%)
- Device implant failure	6 (2.0%)	6 (4.2%)
- Transfusion or vasc compl requiring surgery	16 (5.5%)	5 (3.5%)
- ASD	2 (0.7%)	4 (2.8%)
- Cardiogenic shock	1 (0.3%)	4 (2.8%)
- Cardiac embolism/stroke	1 (0.3%)	2 (1.4%)
- Tamponade	1 (0.3%)	2 (1.5%)
- Urgent cardiac surgery	1 (0.3%)	0 (0%)
Acute result: MR ≥3+	5%	9%
12-month result: MR ≥3+	5%	17%

Stone GW et al. NEJM. 2018 Sept 23; Obadia JF et al. NEJM. 2018 Aug 27. doi: 10.1056/NEJMoa1805374

RESHAPE-HF: Trial design

~800 patients enrolled at up to 50 EU sites

Significant FMR (≥3+ by core lab)

Chronic heart failure despite optimal medical therapy

Specific anatomical criteria

Randomize 1:1

MitraClip
N=400

Control group
Standard of care
N=400

Clinical and TTE follow-up:
1, 6, 12, 18, 24 months

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

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

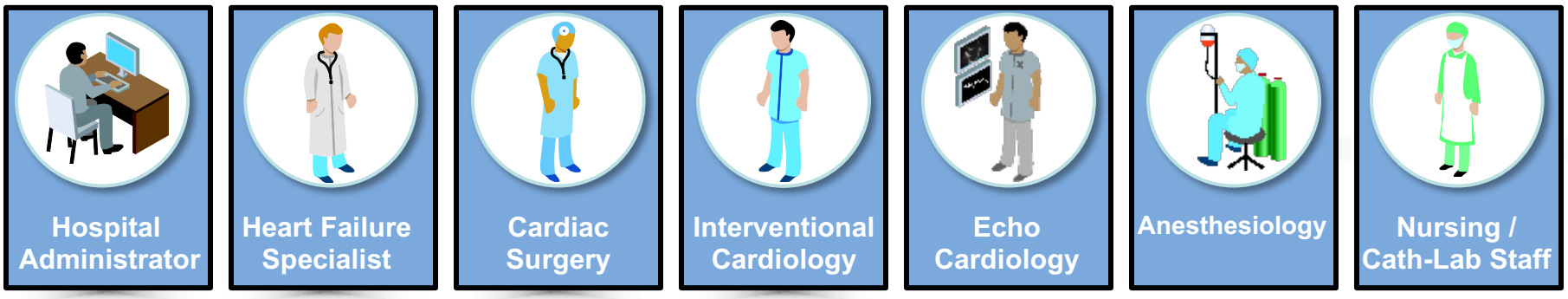
1. **Inoperable/high surgical risk pts + No CABG planned + FE>30%**
2. **Low likelyhood of durable repair**
3. **CRT non-responders**
4. **End-stage heart failure/Severe LV disfunction**
4. **Bridge to LVAD or Transplant**

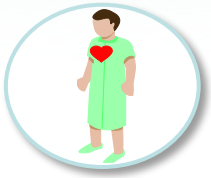
Franzen o. EJ Heart Fail 2011; 13 (5): 569-76

How to improve long-term outcomes?

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

Role of a multidisciplinary Heart-Team





Optimal Patient Care

How to improve long-term outcomes?

- **Patients selection: clinical and anatomical criteria**
  - **Timing of ir**
  - **Device imp** **es**

MitraClip I gen

2008

Carillon + MitraClip

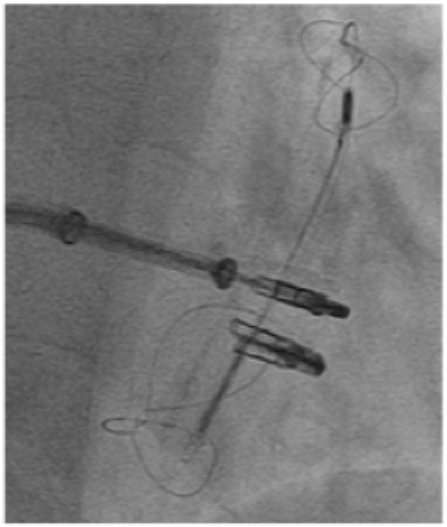
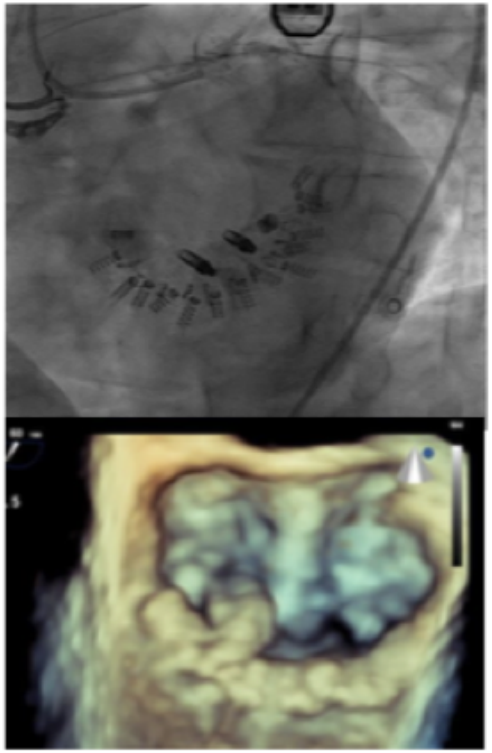


Image courtesy of R.S. von Bardeleben

EMO GVM CENTRO CUORE COLUMBUS s.r.l.

- Migliore navigabilità

Cardioband + MitraClip



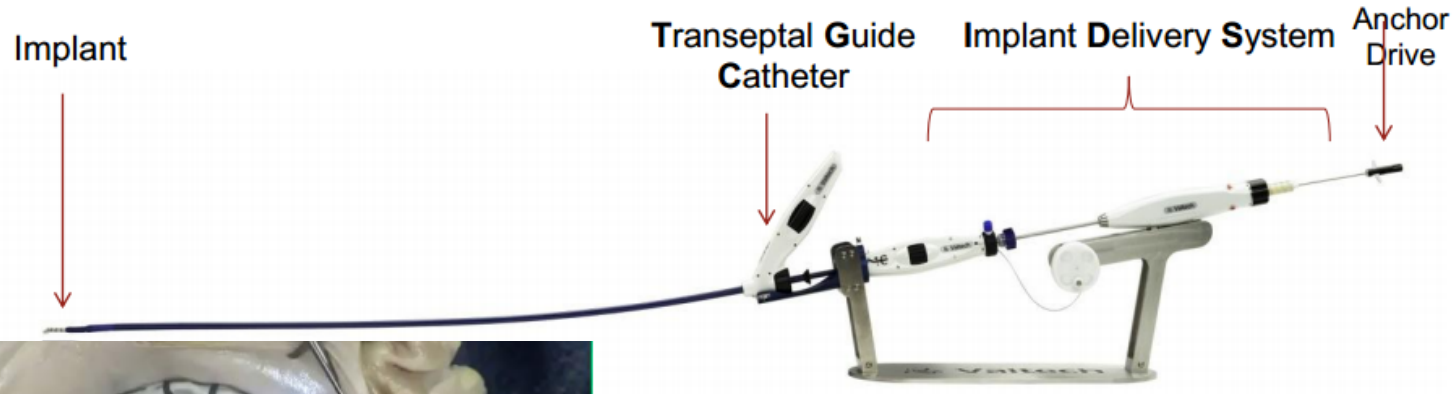
Latib - Agricola

- Migliore navigabilità

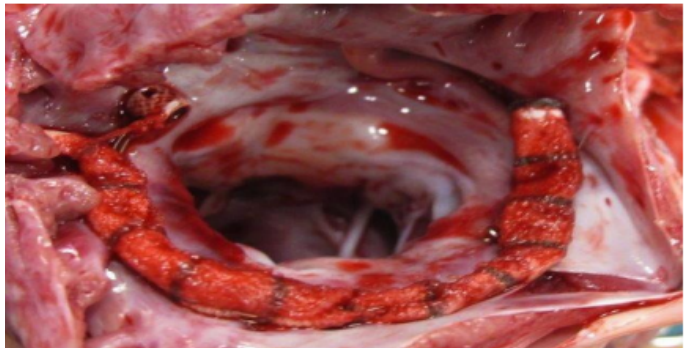
TriClip

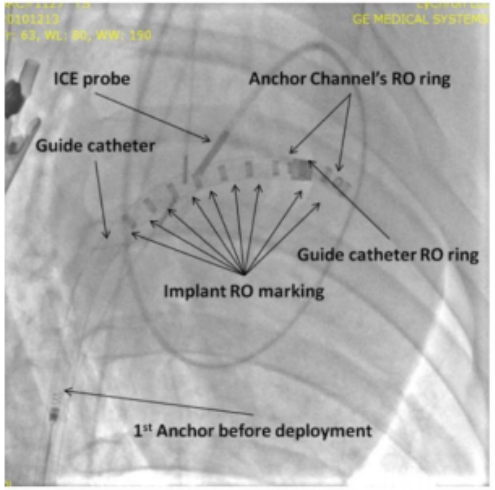
2019

Valtech Cardio: Percutaneous Annuloplasty Device Without Open-Heart Surgery



Cardioband Implant

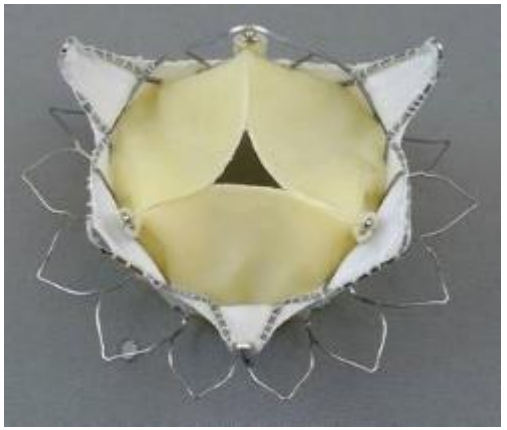




Sostituzione valvola mitrale transcatetere: dispositivi già impiantati nell'uomo

CARDIAQ

EDWARDS FORTIS



NEOVASC TIARA

TENDYNE

Gen 2 CardiAQ™ TMVI System (Edwards)

MULTIPLE ACCESS ROUTES

- TF – femoral vein and trans-septal
- TA – trans-apical, retrograde approach

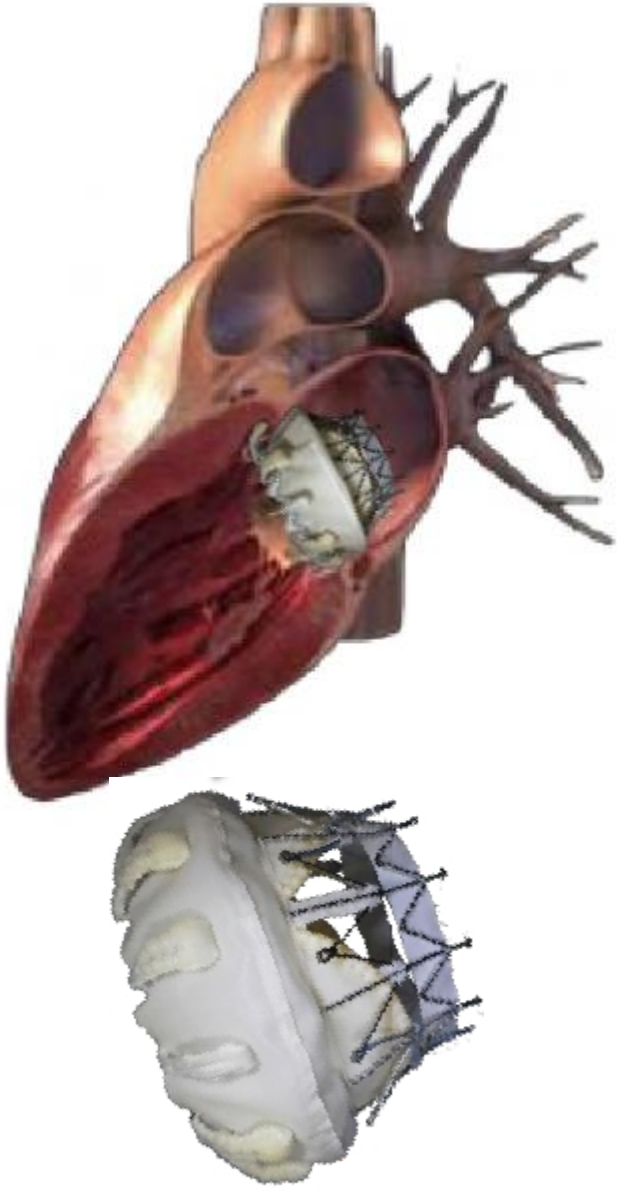
PRECISE, CONTROLLED POSITIONING

- Intra/Supra annular placement
- Multi-stage controlled deployment
- Self-positioning within native valve annulus

SECURE ANCHORING

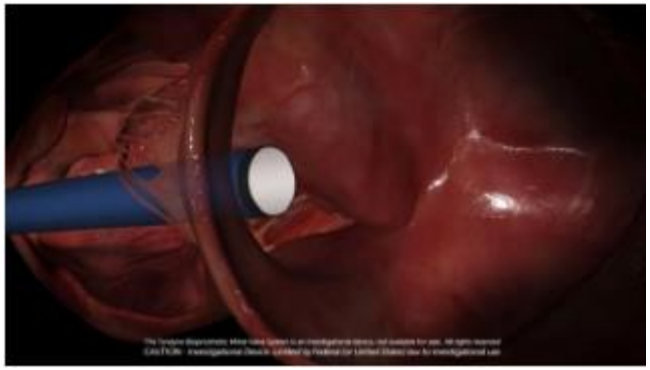
- Engages leaflets and preserves chords
- Balances load between chords and annulus

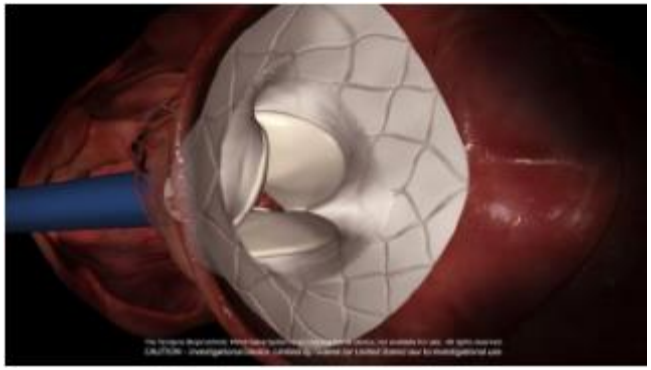
8 Human cases success in 7
In H death 4 cases

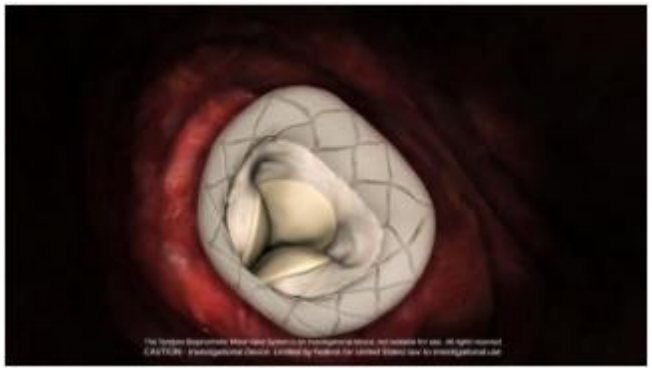


Tendyne Transcatheter Mitral Valve (Abbott)

- ✓ Transapical approach
- ✓ Secure Apical Pad
- ✓ Fully Repositionable
- ✓ Fully Retrievable
- ✓ Well tolerated







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**
- **Surgical annuloplasty is effective in short tearm but carries a substantial risk for recurrence of MR, replecement as alternative option**
- **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**