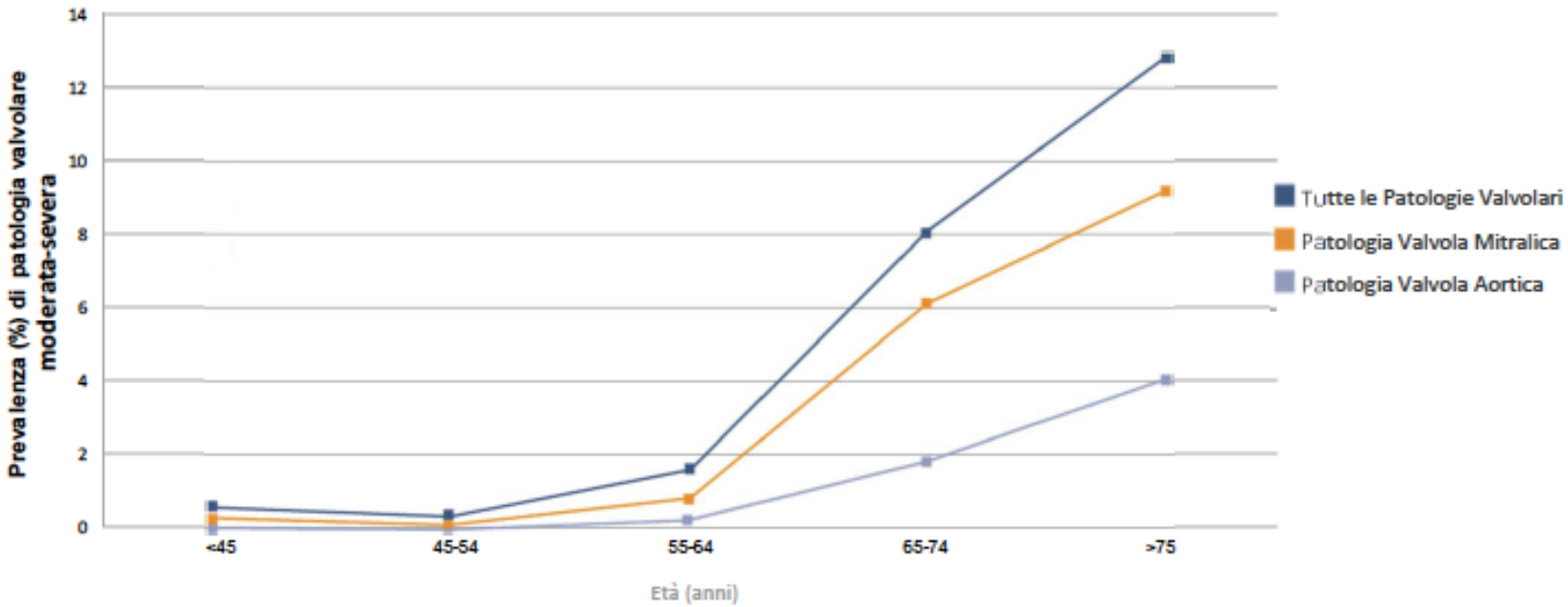
Trattamento interventistico della valvulopatia mitralica: dati attuali e prospettive future

Giuseppe Musumeci
SC Cardiologia
AO Santa Croce e Carle Cuneo

Prevalenza dell'IM: una patologia che aumenta con l'Età[1,2]

Quasi 1 persona su 10 con 75 anni di età o più è affetta da IM ≥ 2+



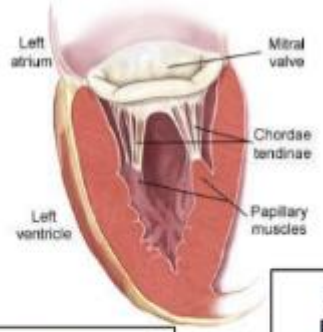
[1] **Heart Disease and Stroke Statistics 2010 Update: A Report From the American Heart Association.** *Circulation*. 2010;121:e46-e215

[2] Nkomo et al. Burden of Valvular Heart Diseases: A Population-based Study, Lancet, 2006; 368: 1005-11

Mechanism of FMR

Type IIIb

Mitral Regurgitation



63%
1

Functional Mitral Regurgitation (FMR)

LV Dysfunction
Dilated Annulus
(Non-ischemic or ischemic dilated cardiomyopathy)

Etiologies

LA Dysfunction
Dilated Annulus
(Chronic atrial fibrillation, hypertension)

Loss of leaflet coapation due to:

- Annular enlargement
- Papillary muscle displacement causing leaflet tethering/tenting

37%
1

Degenerative Mitral Regurgitation (DMR)

Etiologies:

- Advanced Barlow's Disease
- Fibroelastic deficiency

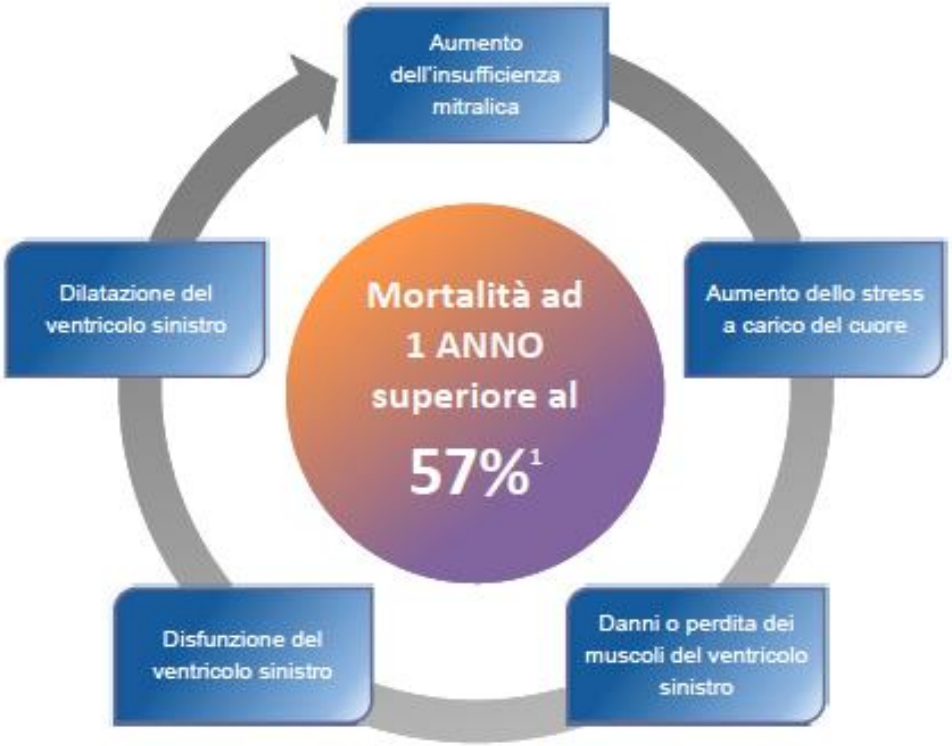
Leaflet prolapse due to:

- Leaflet deformities or lesions
- Ruptured/ elongated chordae
- Papillary muscle rupture

Type II

Bach et al, JACC; 54 (9), 2009

L'Insufficienza Mitralica porta allo Scompenso Cardiaco



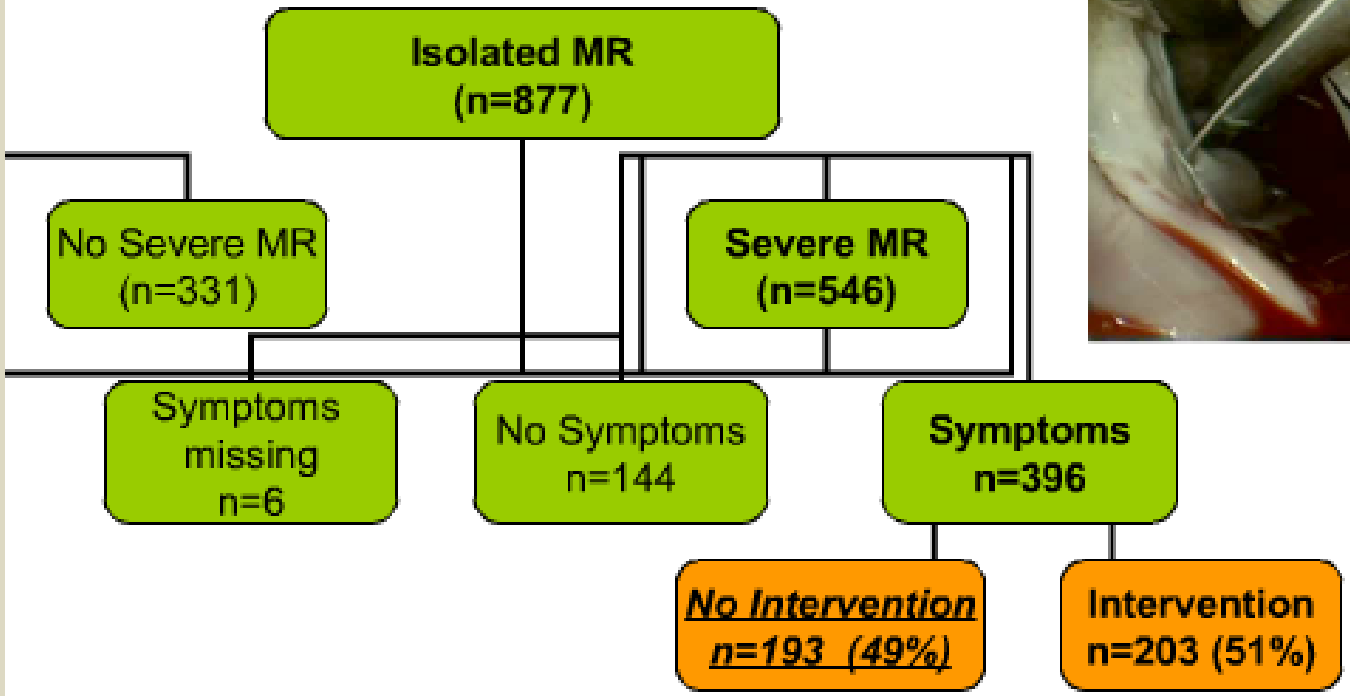
L'IM attiva una cascata di eventi che portano allo scompenso cardiaco ed infine alla morte se non trattata[2,3]

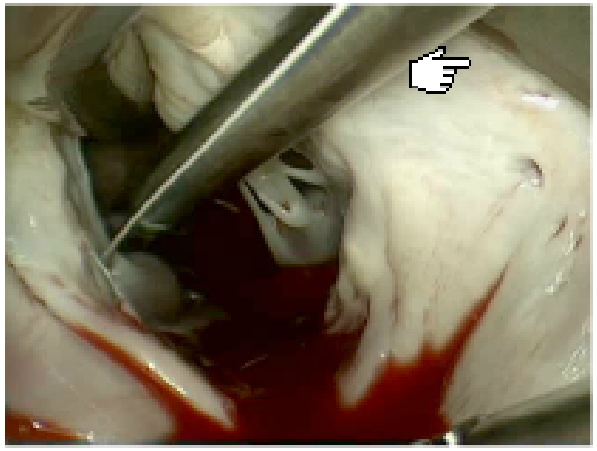
[1] Cioffi G, et al. **Functional mitral regurgitation predicts 1-year mortality in elderly patients with systolic chronic heart failure**. European Journal of Heart Failure 2005 Dec;7(7):1112-7

[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

Molti pazienti con insufficienza mitralica non possono essere operati





(Mirabel et al. Eur Heart J 2007;28:1358-65)

thinkheart with GISE

L'insufficienza Mitralica (IM) trattamenti e outcomes

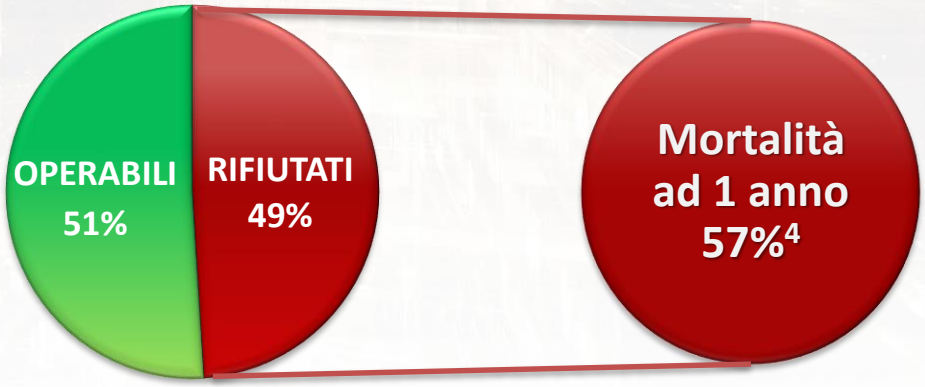
600.000 Pazienti in Italia con Insufficienza Mitralica (Moderata/Severa)[1,2]

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]

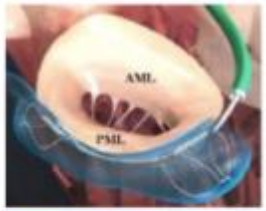
In una popolazione anziana, **se non trattata**, l'IM innesca una cascata di eventi che portano alla **morte[5]**



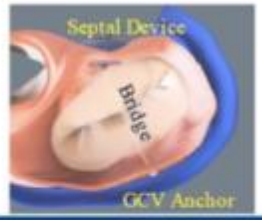
1.Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (The Framingham Heart Study). Am J Cardiol 1999; 83:897–902; Nkomo, Vuyisile T., et al. "Burden of valvular heart diseases: a population-based study." The Lancet 368.9540 (2006): 1005-1011.
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

Transcatheter MV interventions

Indirect Annuloplasty



Carillon*



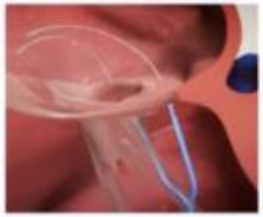
MVRx ARTO

Mitral Loop Cerclage

Direct Annuloplasty

Cardioband*

Millipede



Mitralign*

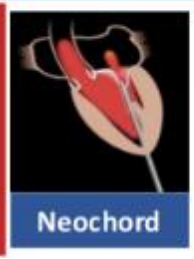
Valcare

Valfix

AccuCinch

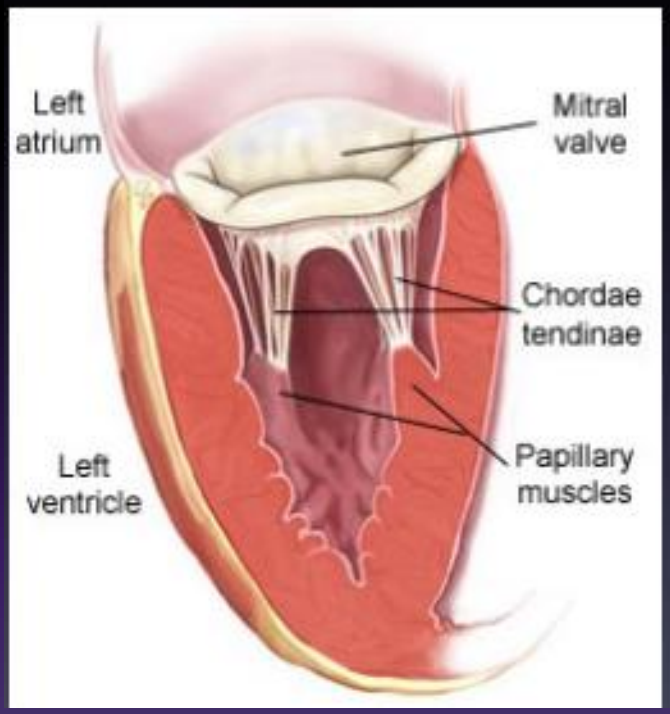
Leaflet Repair

MitraClip



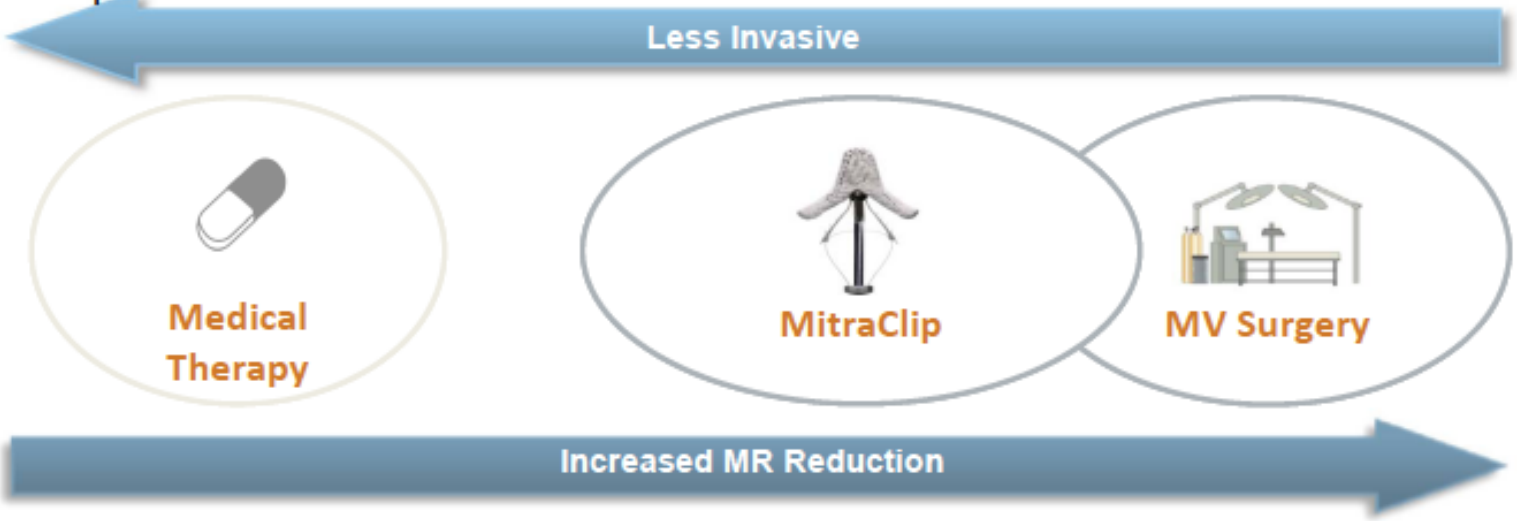
Neochord

Mitral Apparatus and repair opportunities

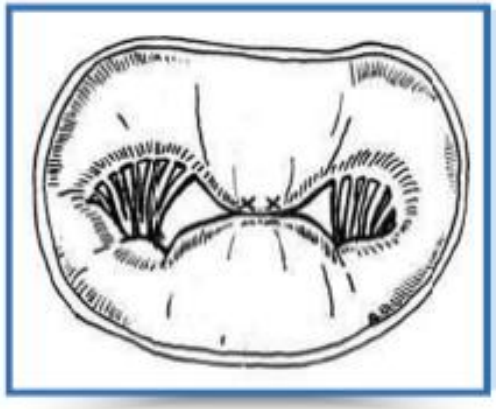


MitraClip Therapy Filling a Treatment Gap

- 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



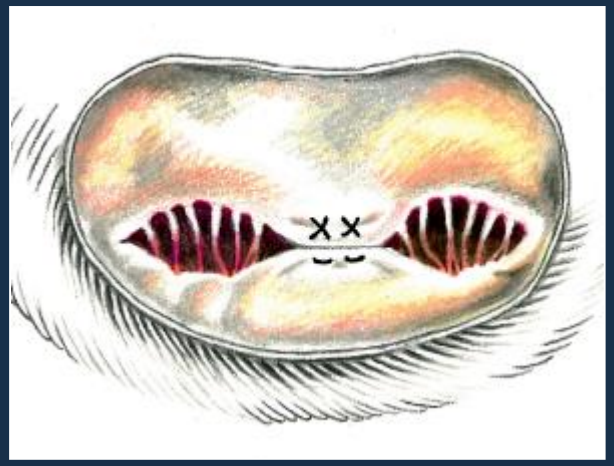
Concept: Percutaneous Mitral Valve Repair (PMVR)

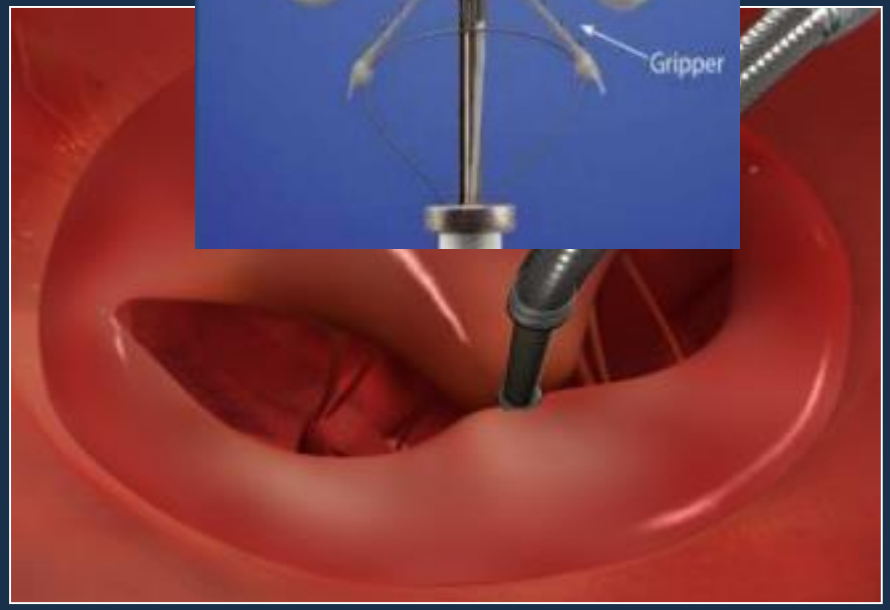


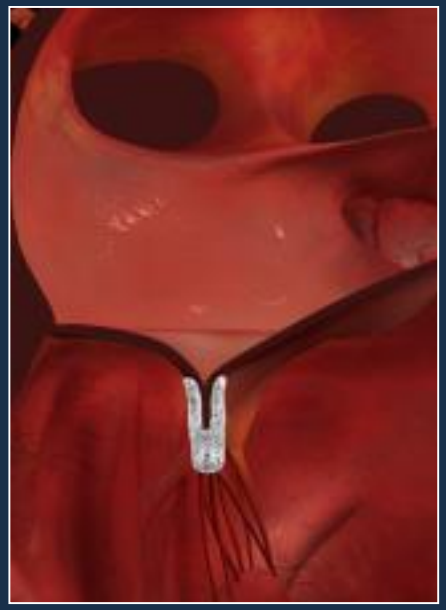
- Double-orifice suture technique developed by Prof. Ottavio Alfieri
- First published results in 1998 illustrated proven benefit
- Suggested procedure best suited for minimally invasive approach

Catheter-Based Mitral Valve Repair

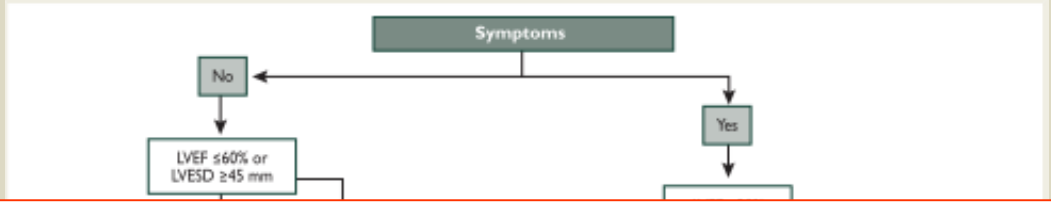
MitraClip® System



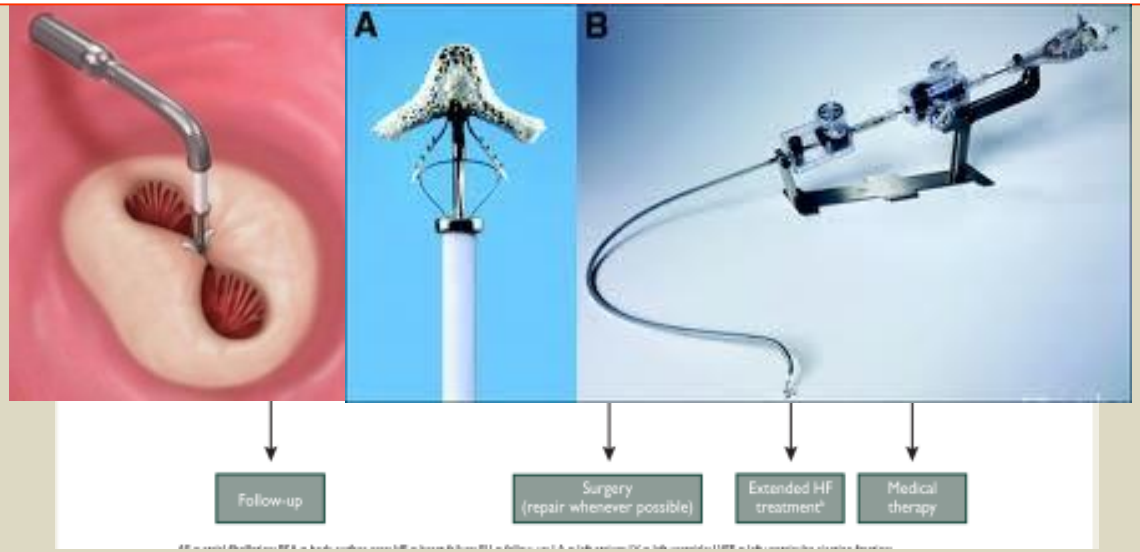




Guidelines on the management of valvular heart disease (version 2012)



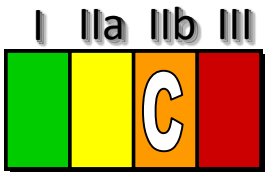
patients with an indication for valve repair but judged inoperable or at unacceptably high surgical risk, percutaneous edge-to-edge repair may be considered in order to improve symptoms"



ESC/EACTS GUIDELINES
Tanscatheter treatment for FMR

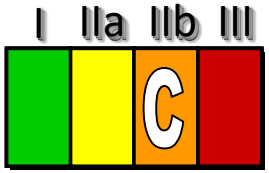
When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and LVEF >30%, who remain symptomatic despite optimal medical management (including CRT if indicated) and who have a suitable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

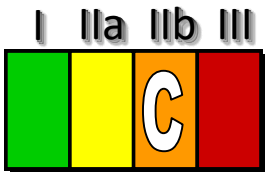


2017 ESC/EACTS Valvular Heart Disease Guidelines
2016 ESC/EACTS Acute and Chronic Heart Failure Guidelines

ESC/EACTS GUIDELINES
Tanscatheter treatment for FMR

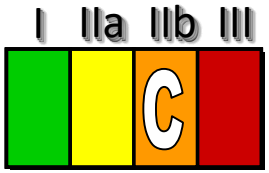
In patients with severe secondary MR and LVEF <30% who remain symptomatic despite OMT (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device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

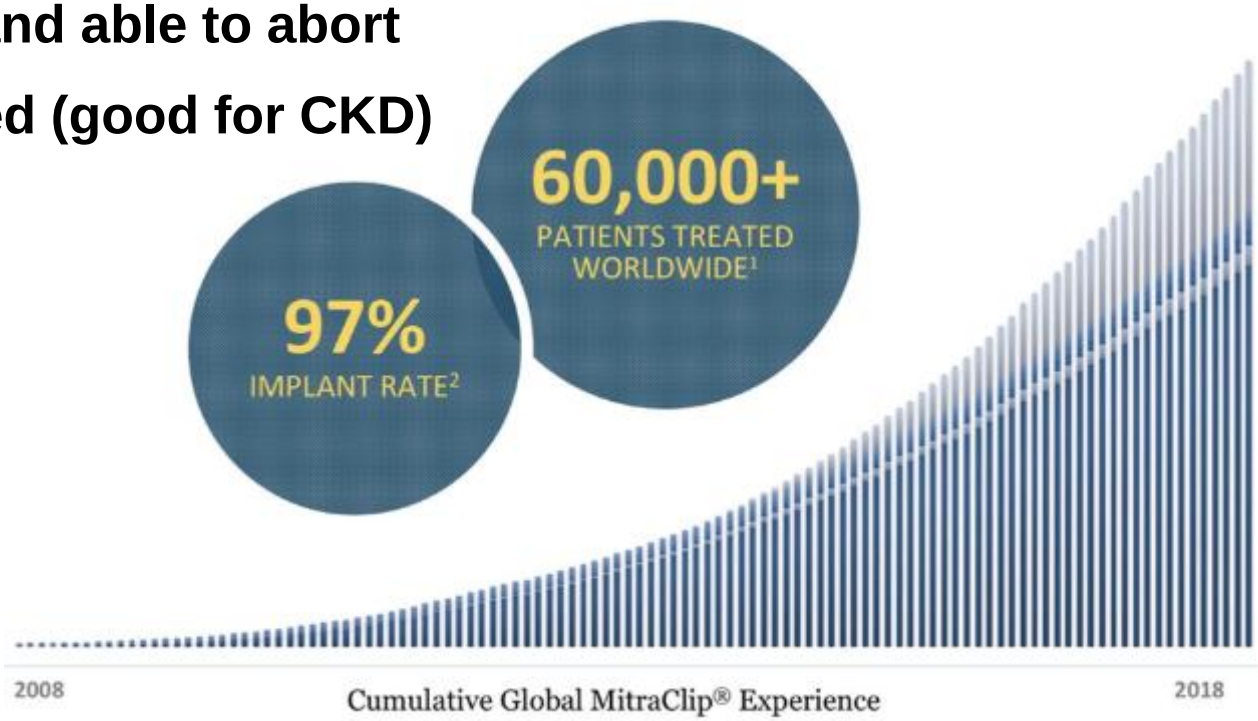
ESC '16



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

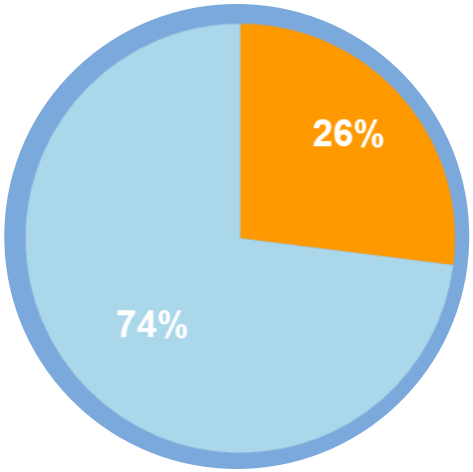
Advantage of mitraClip for FMR

- 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)



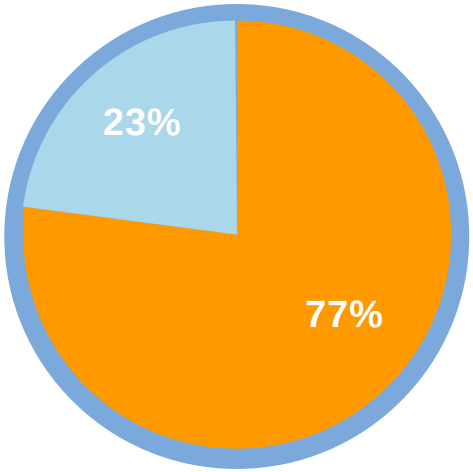
MitraClip Therapy
Broad Spectrum of Experience

EVEREST II
(Randomized Controlled Trial)



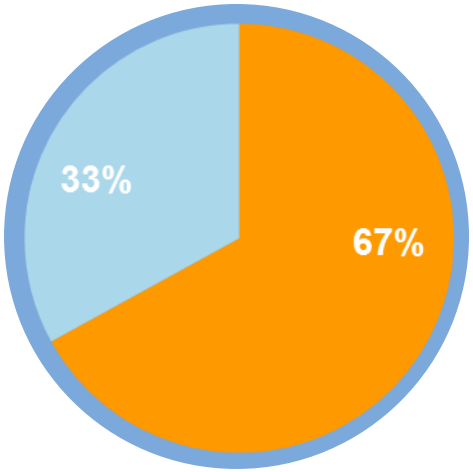
- 178 patients
- Device time – 146 minutes
- Implant rate – 89%

ACCESS EU
(Europe)



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

Commercial
(APJ, CALA, Europe, US)

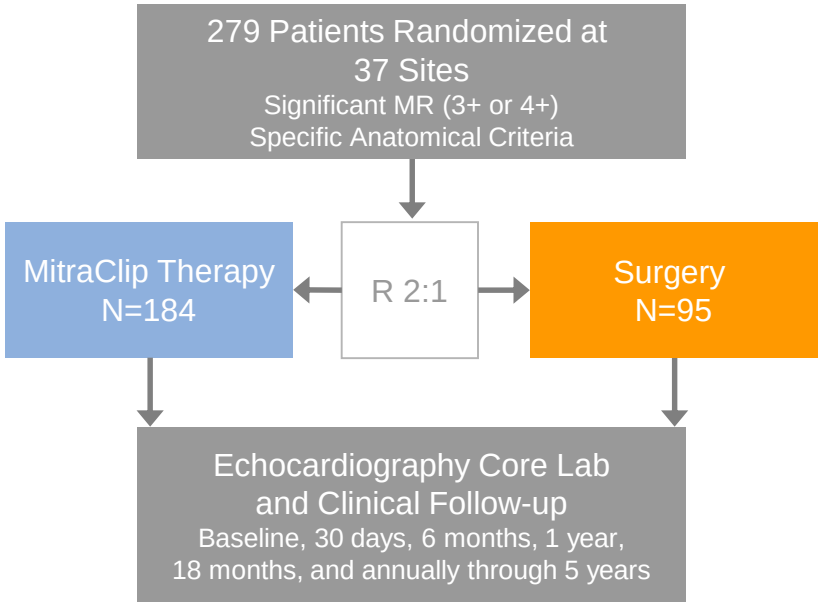


- 50,000 patients
- Device time – 91 minutes
- Implant rate – 96%

= 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
Randomized Controlled Trial Design



Patient Demographics	MitraClip Therapy (n=184)	Surgery (n=95)	P-value
Age (mean)	67 years	66 years	0.32
Male	63%	66%	0.60
History of CHF	91%	78%	0.005
Degenerative MR Etiology	74%	73%	0.81
Functional MR Etiology	26%	27%	0.81
Mean Ejection Fraction	60%	61%	0.65
Previous Coronary Artery Bypass Grafting (CBAG)	21%	19%	0.54
NYHA Functional Class III/IV	51%	48%	0.61
Atrial Fibrillation	34%	39%	0.42

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.

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.

Dueling Adverse Events

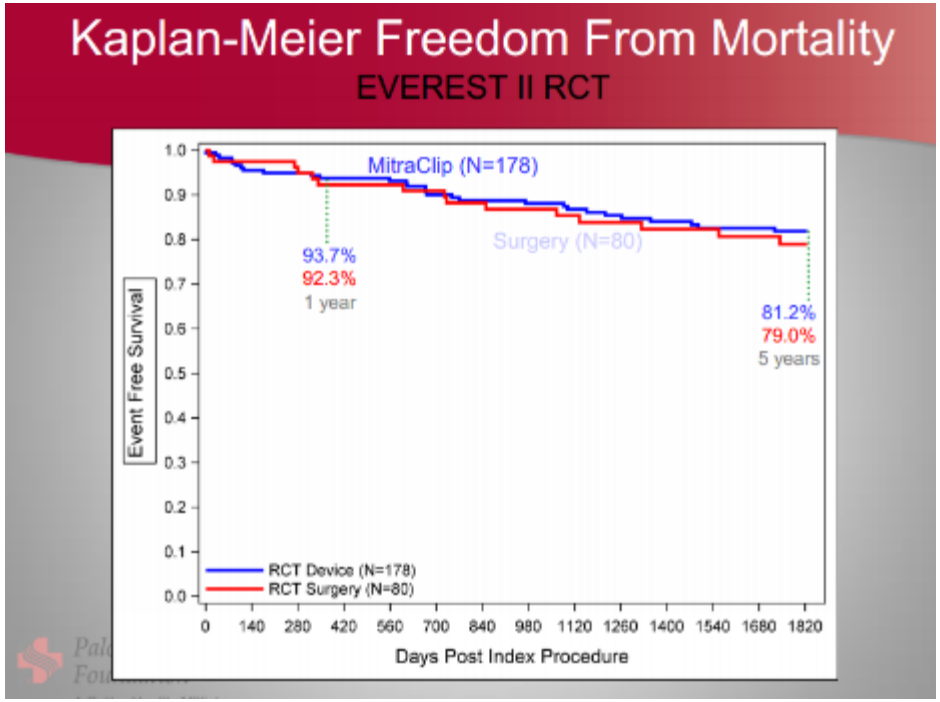
Commenting on the trial, J. Scott Millikan, MD, a cardiovascular surgeon at the Deaconess Billings Clinic (Billings, MT), pointed out that with regard to the study definition of major adverse events,

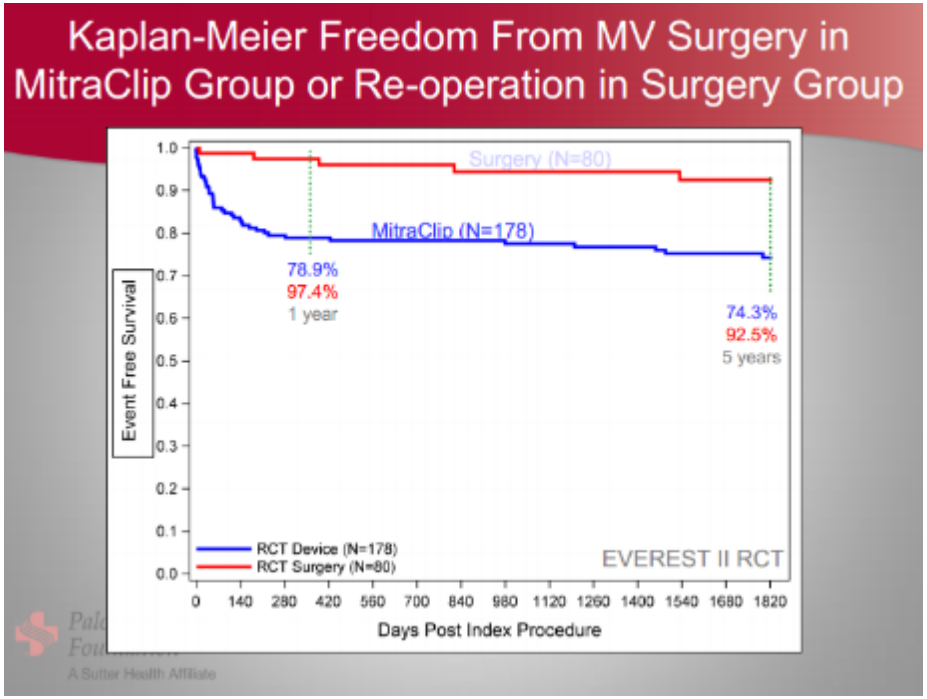
"weighing blood transfusion the same as death or stroke just doesn't make sense,"

adding that "if blood transfusion in cardiac surgery is a major adverse event, maybe we should consider radiation exposure [during percutaneous repair] similarly."

To which Dr. Feldman responded, "in that spirit, I would say sternotomy might be considered an adverse event as well."

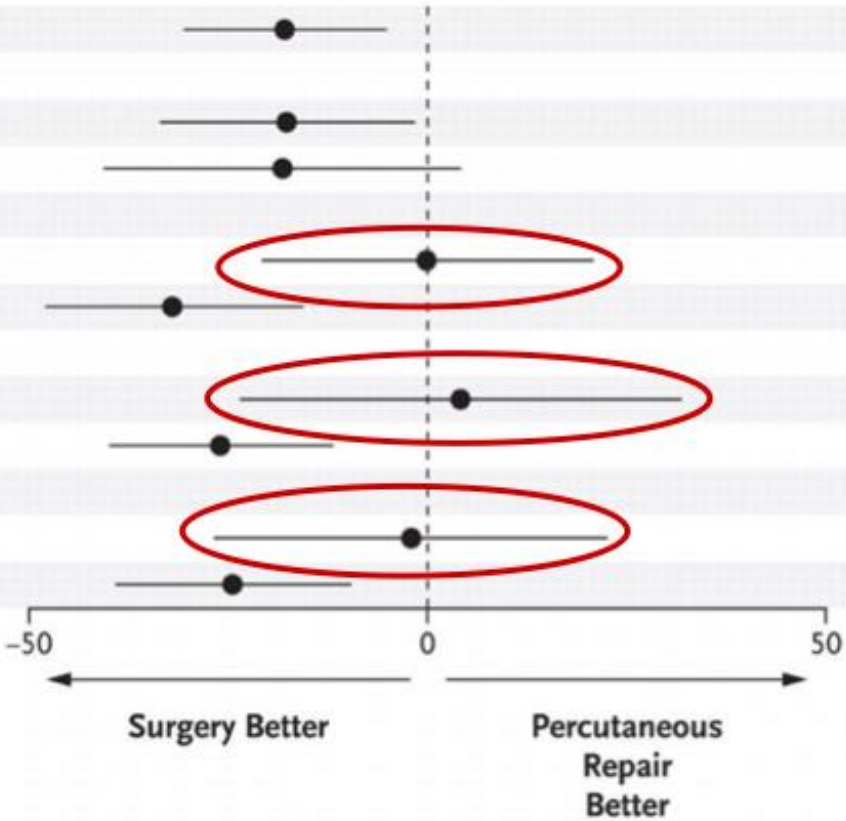
MitraClip vs Chirurgia a 5 anni
Stessa mortalità più reinterventi





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)	

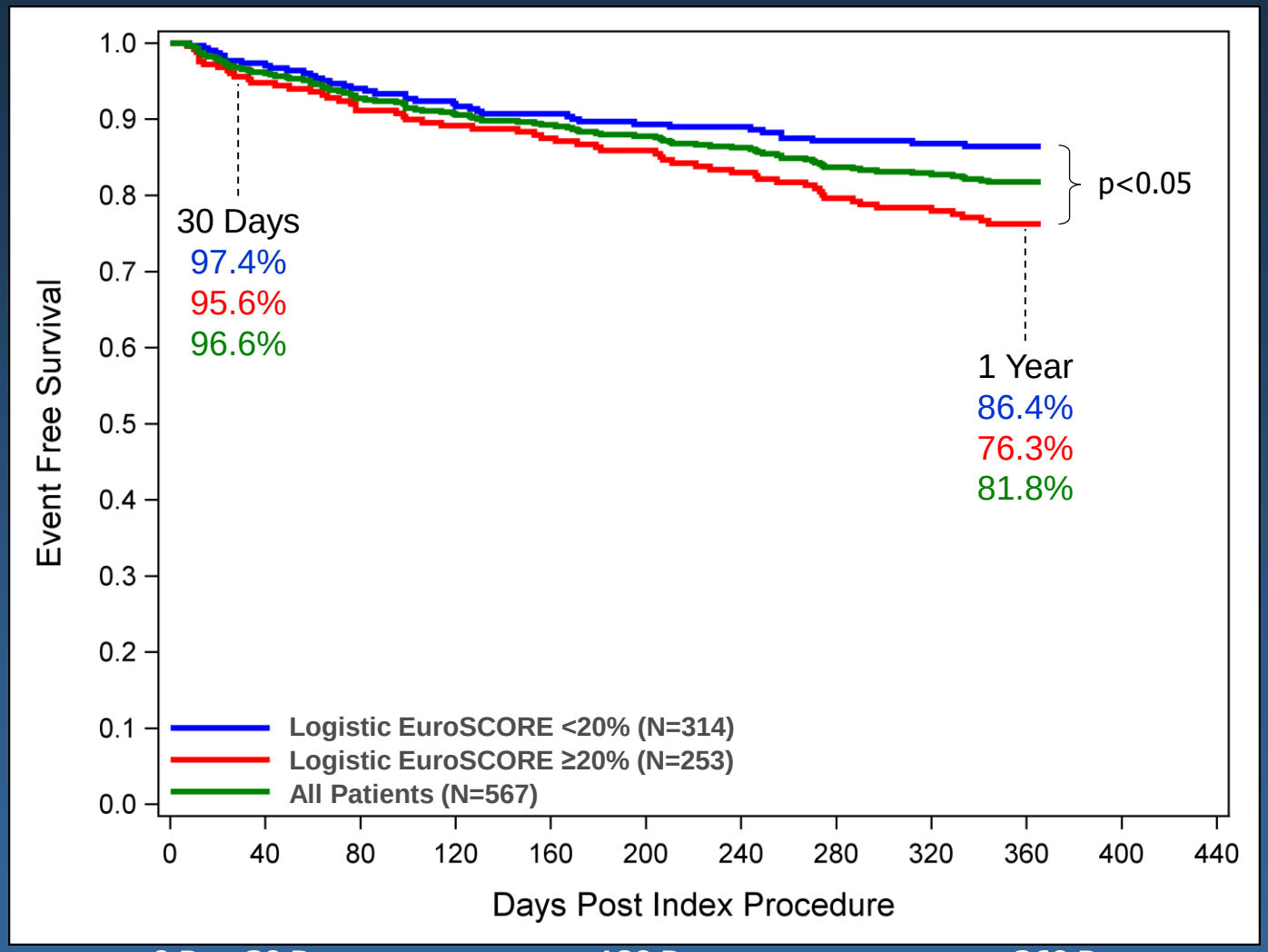


The NEW ENGLAND JOURNAL of MEDICINE

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

CARDIOVASCULAR RESEARCH FOUNDATION
A Passion for Innovation

ACCESS EU Kaplan-Meier Freedom from Death



At Risk	0 Day	30 Days	180 Days	360 Days
All Patients	567	534	475	415
Logistic EuroSCORE <20%	314	296	264	235
Logistic EuroSCORE ≥20%	253	238	211	180

Investigational Device only in the U.S. Not available for sale in the U.S.

COAPT TRIAL

COAPT: Trial design

~420 patients enrolled at up to 75 US sites

Significant FMR (≥3+ by core lab)

High risk for mitral valve surgery

Specific anatomical criteria

Randomize 1:1

MitraClip
N=210

Control group
Standard of care
N=210

Clinical and TTE follow-up:
1, 6, 12, 18, 24, 36, 48, 60 months

As of June 1st, 2012; Protocol is under reivew by FDA

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

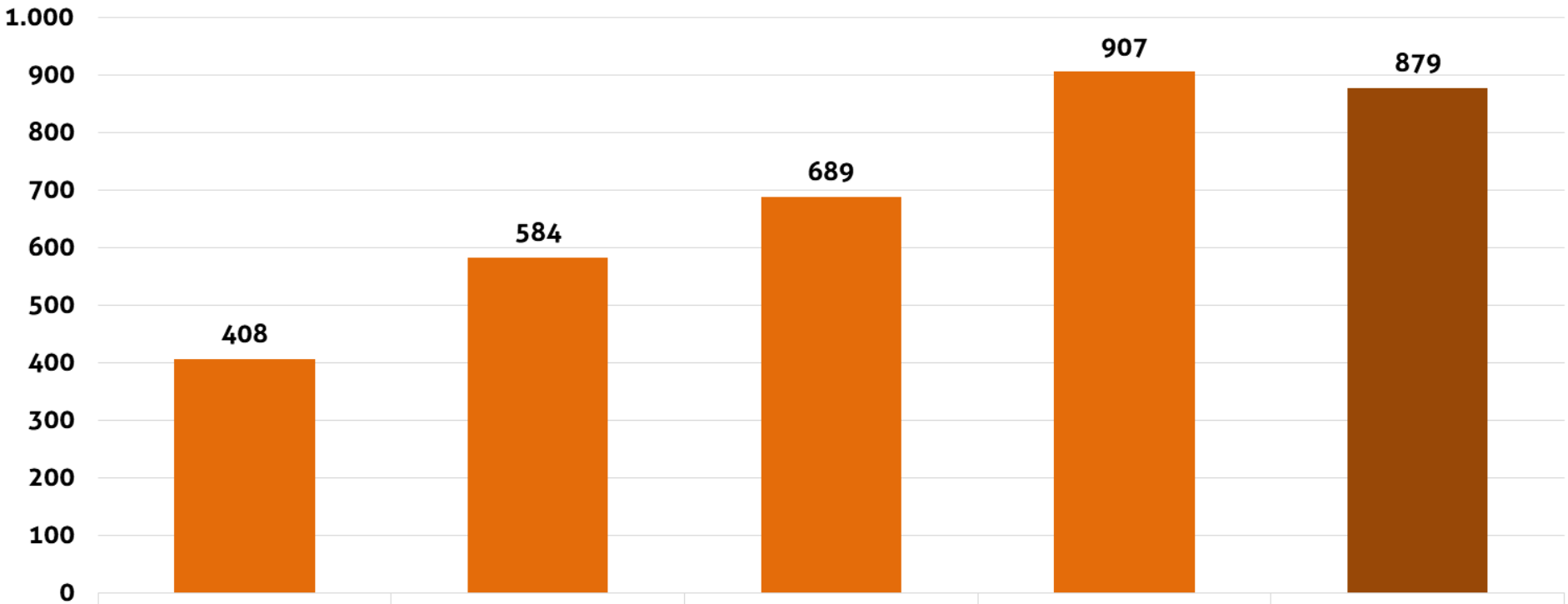
Randomize 1:1

MitraClip
N=400

Control group
Standard of care
N=400

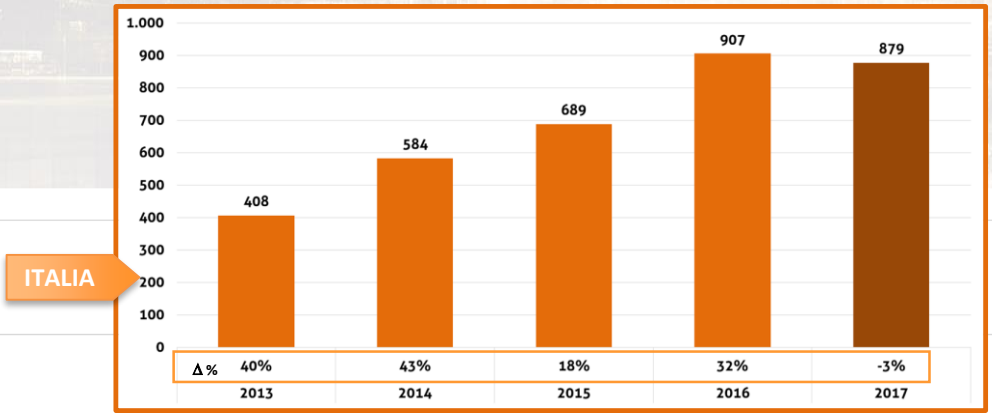
Clinical and TTE follow-up:
1, 6, 12, 18, 24 months

Clip Mitralica
Italia serie storica

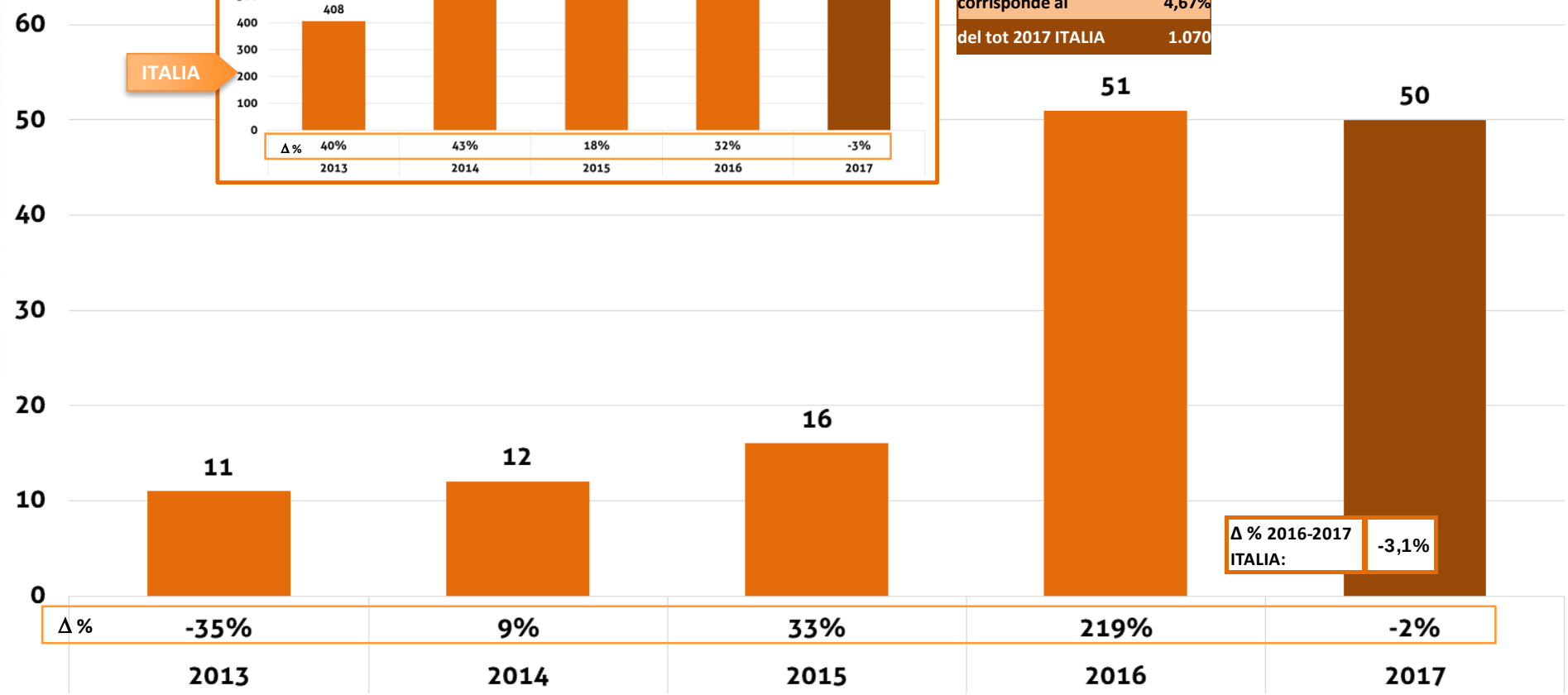


	2013	2014	2015	2016	2017
Δ %	40%	43%	18%	32%	-3%

CLIP MITRALICA SERIE STORICA

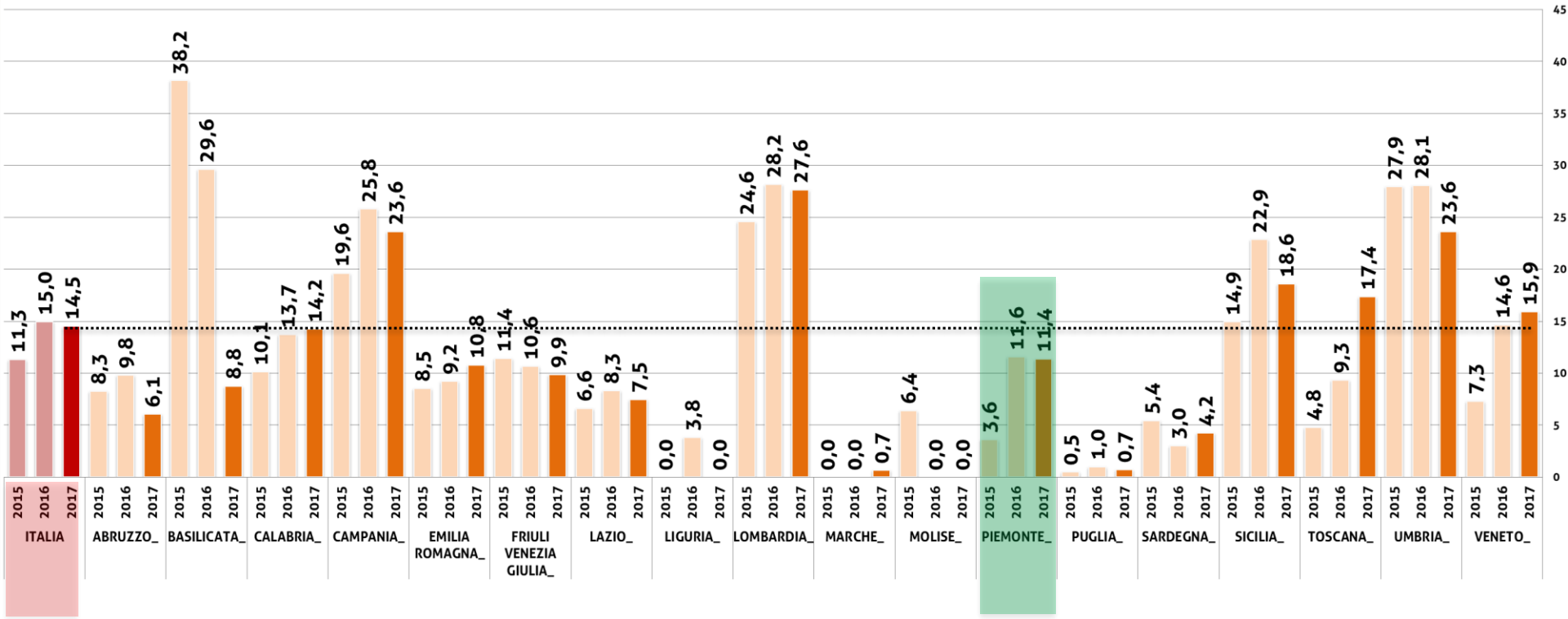


CLIP MITRALICA PIEMONTE_	50
corrisponde al	4,67%
del tot 2017 ITALIA	1.070



Clip Mitralica/1.000.000 Abitanti
Italia e Regioni 2015-2017

ALTO ADIGE
TRENTINO
VALLE D'AOSTA
non eseguono Clip Mitralica



thinkheart with GISE

Pazienti Elegibili alla riparazione percutanea[1]

80.000 nuovi pazienti all'anno con scompenso cardiaco

	82% (Ipotesi Registro italiano IN-HF)	80% (Ipotesi EuroHeart Survey)
Pazienti con insufficienza mitralica di vario grado	65.600	64.000
	13%	50%
Pazienti con insufficienza mitralica di grado moderato-severo	8.528	32.000
	50%	50%
Pazienti non eleggibili al trattamento chirurgico	4.264	16.000
	30%	30%
Pazienti non eleggibili al trattamento transcatetere	1.279	4.800
	70%	70%
Pazienti eleggibili alla riparazione transcatetere della valvola mitrale	2.985	11.200

thinkheart with GISE

L'impegno del GISE a oggi

2016
Registro GIOTTO

GIOTTO REGISTRY

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 Le 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

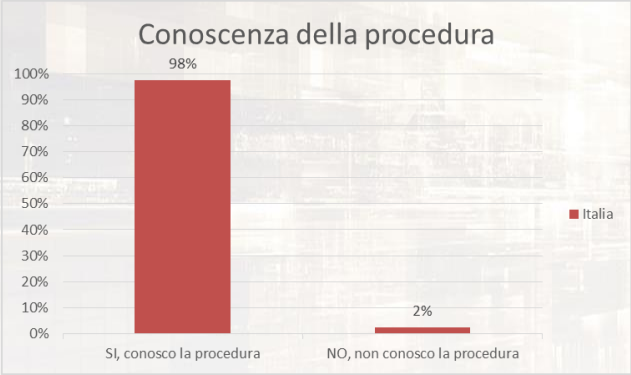
International Journal of Cardiology

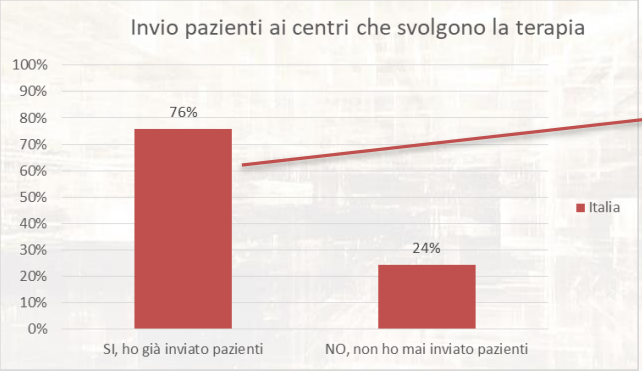
ELSEVIER

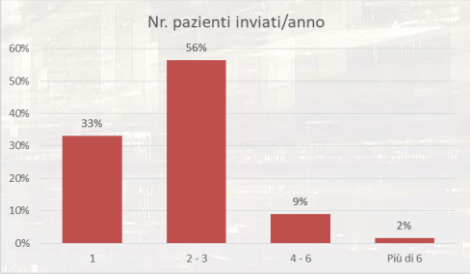
Transcatheter mitral valve interventions for mitral regurgitation, with special focus on MitraClip: The position of Spanish, Portuguese and Italian interventional societies

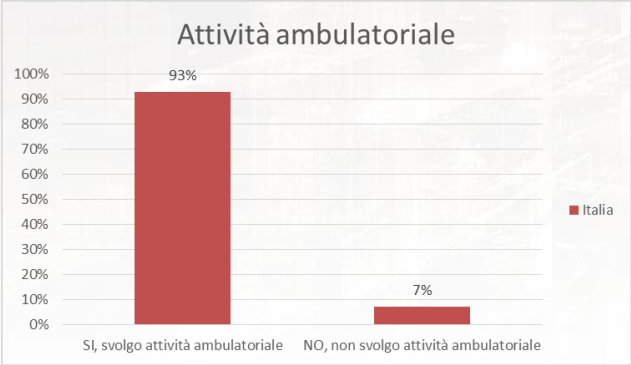
Impegno nella creazione di evidenze e *awareness* sulla terapia grazie alla condivisione dell'esperienza del Sud Europa

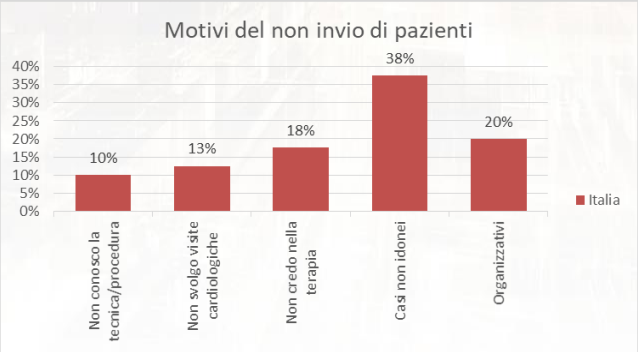
Survey GISE – Focus su Centri che non eseguono la procedura (n=165)











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

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

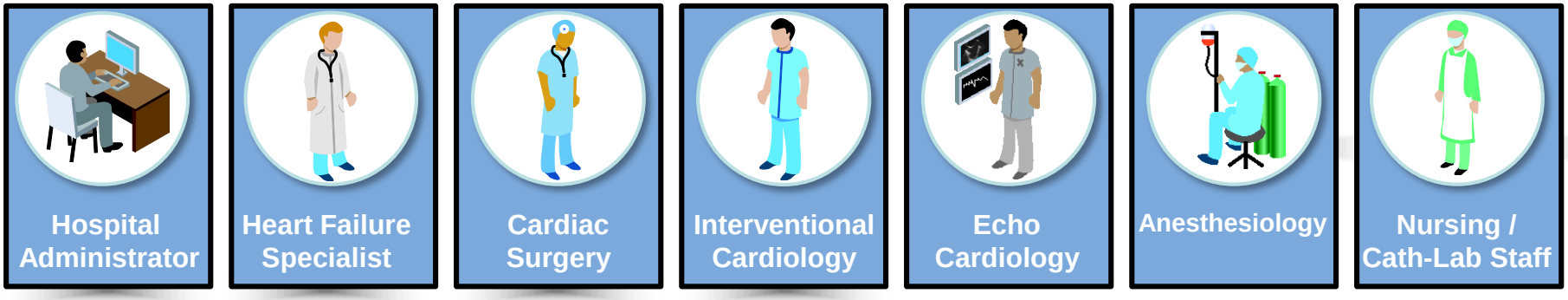
1. **Inoperable/high surgical risk pts + No CABG planned + FE>30%**
2. **Low likelyhood of durable repair**
3. **CRT non-responders**
4. **End-stage heart failure/Severe LV disfunction**
4. **Bridge to LVAD or Transplant**

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

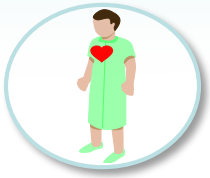
How to improve long-term outcomes?

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

Role of a multidisciplinary Heart-Team



Patient Referral | **Optimal Patient Selection** | **Plan Therapy & Resources** | **Echo Guidance & Communication** | **Post Procedure Care**



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

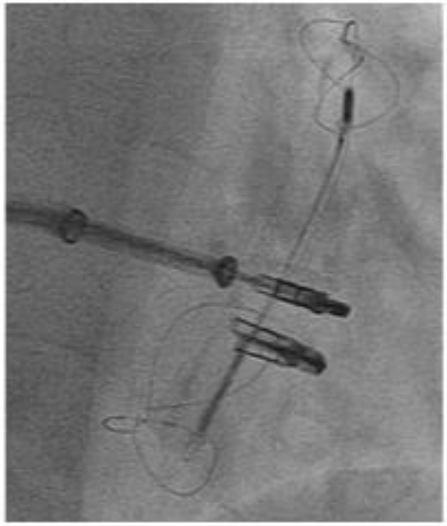
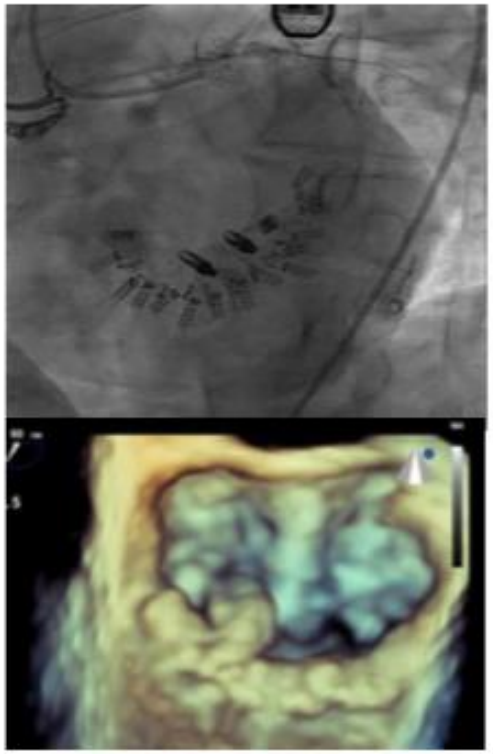


Image courtesy of R.S. von Bardeleben

EMO GVM CENTRO CUORE COLUMBUS s.r.l.

- Migliore navigabilità

Cardioband + MitraClip



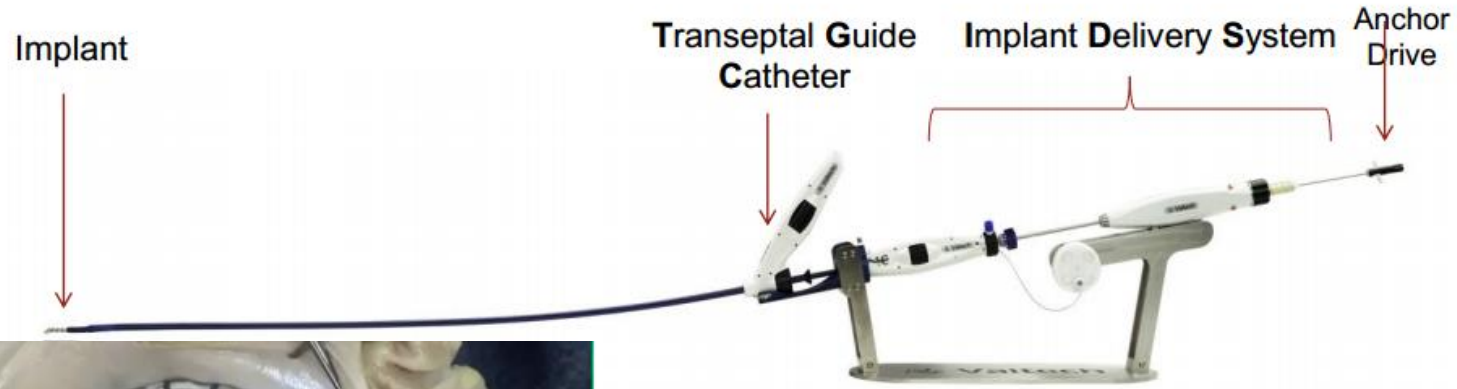
Latib - Agricola

- Migliore navigabilità

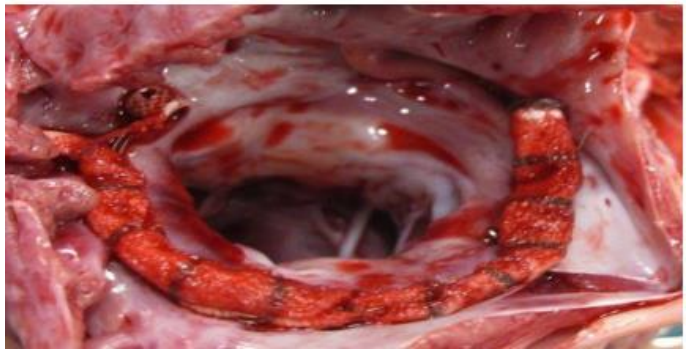
TriClip

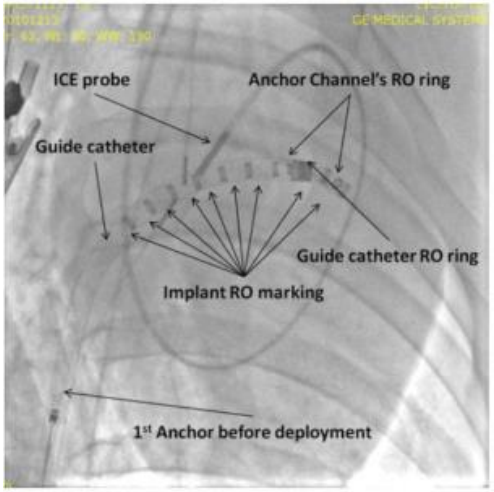
2019

Valtech Cardio: Percutaneous Annuloplasty Device Without Open-Heart Surgery



Cardioband Implant

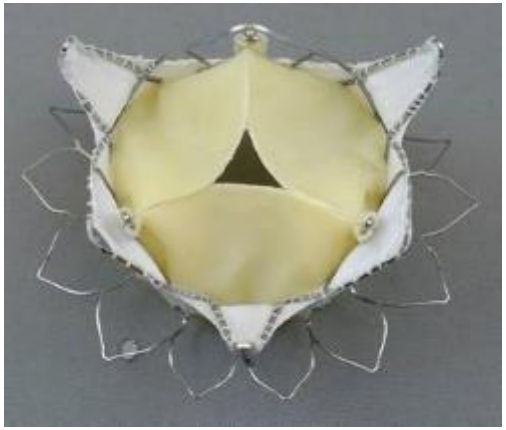




Sostituzione valvola mitrale transcatetere: dispositivi già impiantati nell'uomo

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

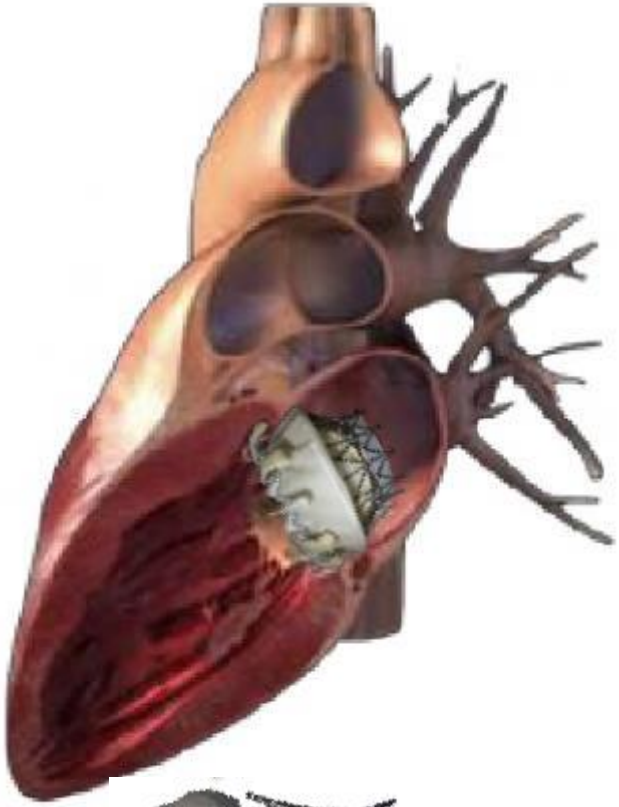
PRECISE, CONTROLLED POSITIONING

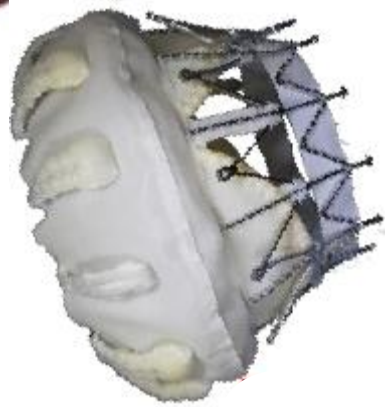
- Intra/Supra annular placement
- Multi-stage controlled deployment
- Self-positioning within native valve annulus

SECURE ANCHORING

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

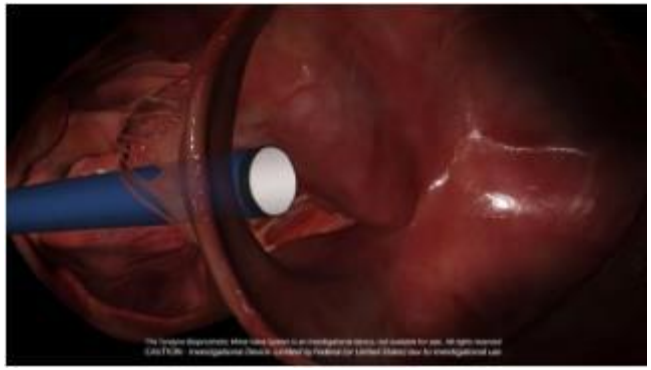
8 Human cases success in 7
In H death 4 cases

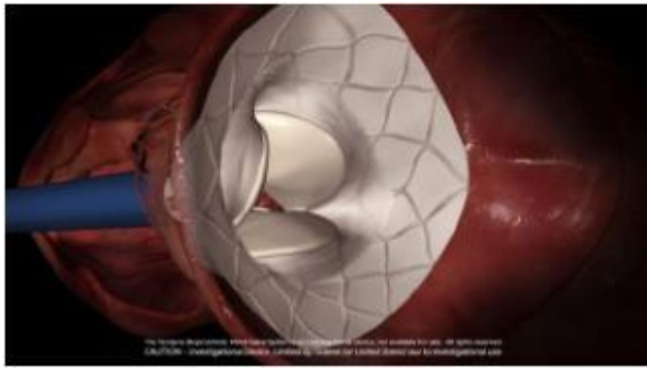


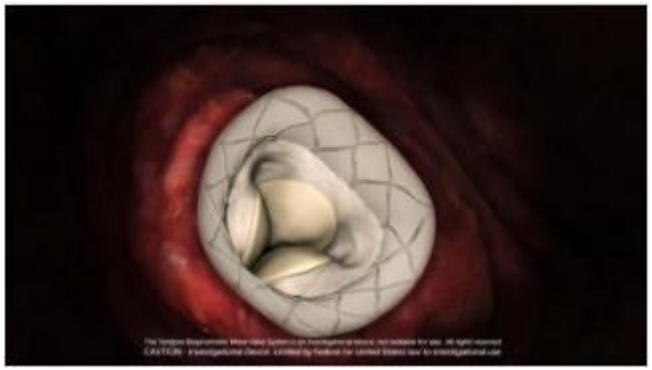


Tendyne Transcatheter Mitral Valve
(Abbott)

- ✓ 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**
- **Percoutaneous leaflet repair shows good long-term clinical results in pts with successful index procedure but long-term results still missing (Reshape, COAPT, Matterhorn, MITRA-FR). Combination therapies may achieve best long-term success rate**
- **RCT are awaited to better understand indications for percutaneous options**