



# Mitral regurgitation. Problems and solutions

**Prof. J Zamorano**

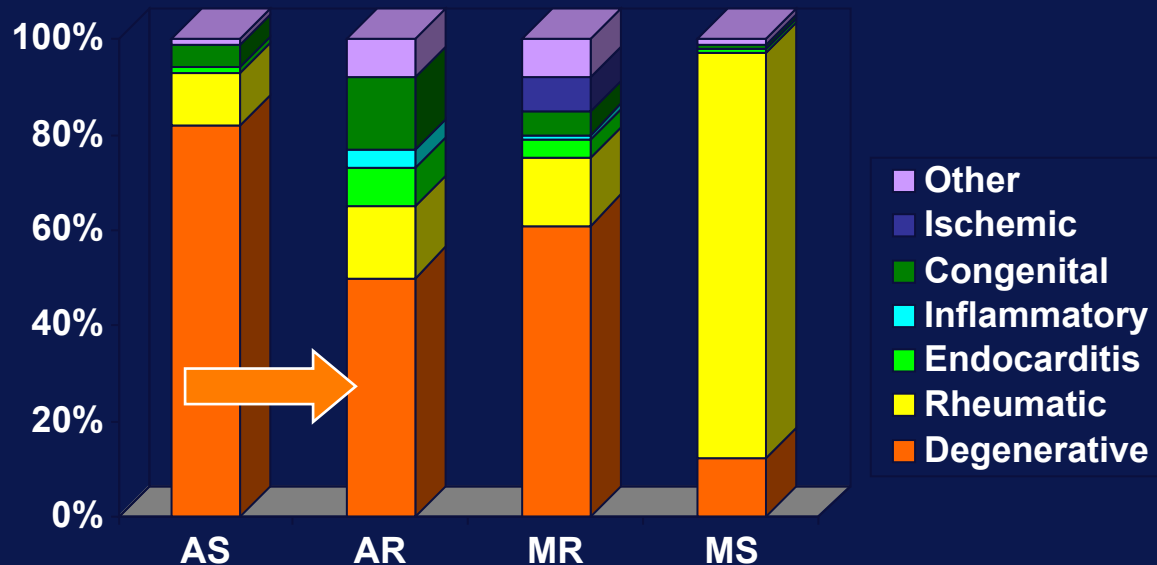


# Euro Heart Survey on Valvular Heart Disease

## Incidence and Etiology of Native VHD

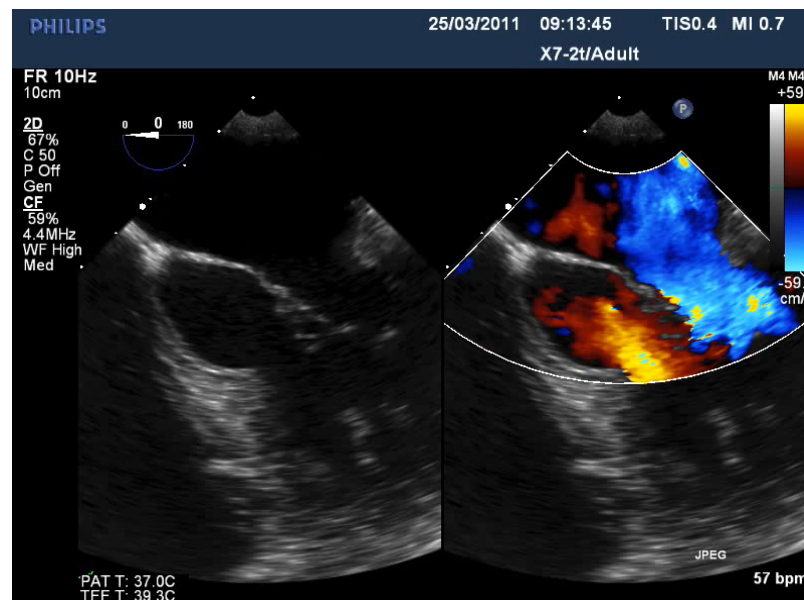
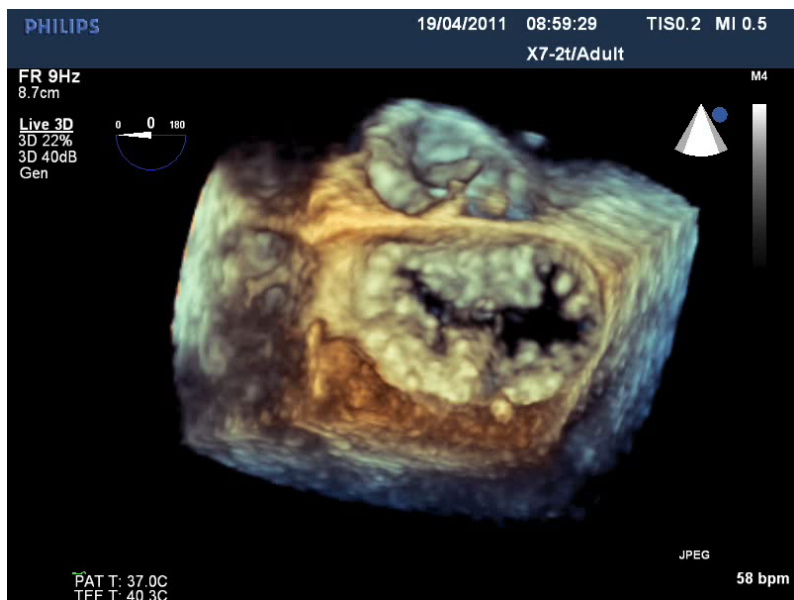
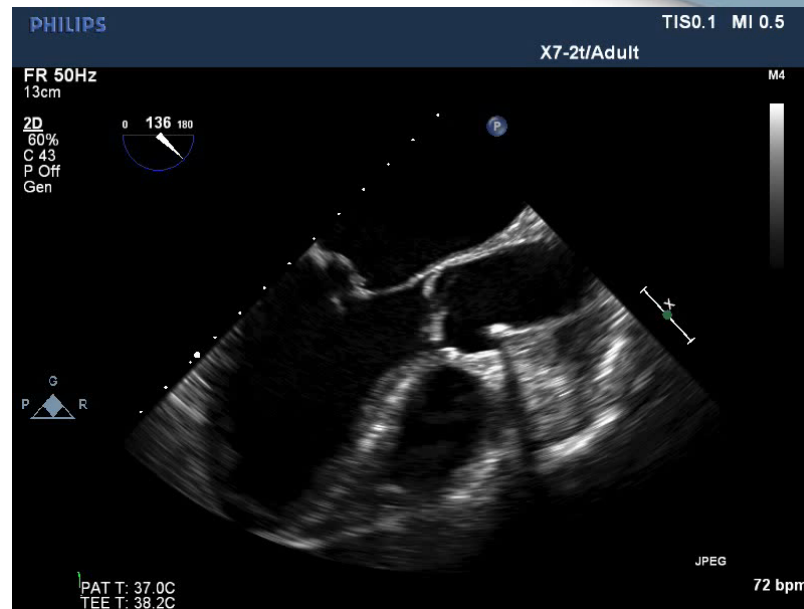
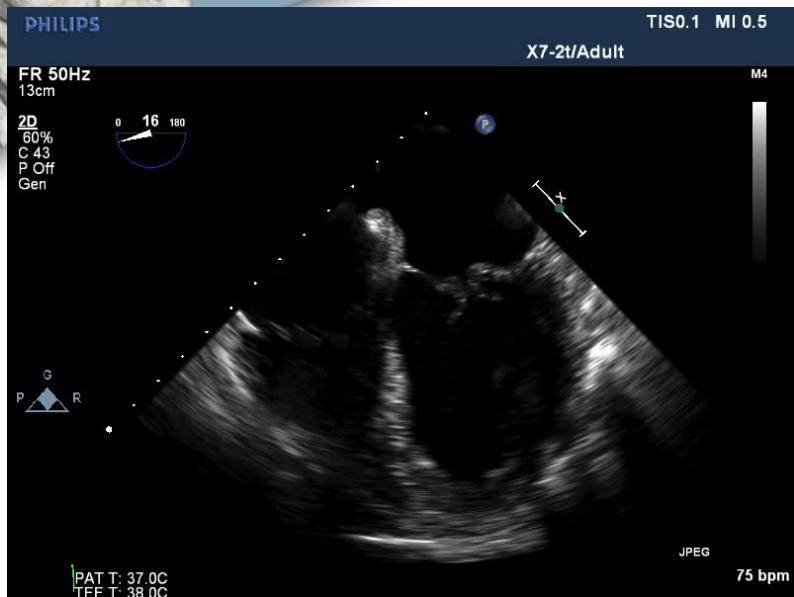


% Native VHD      44%                      13%                      31%                      12%

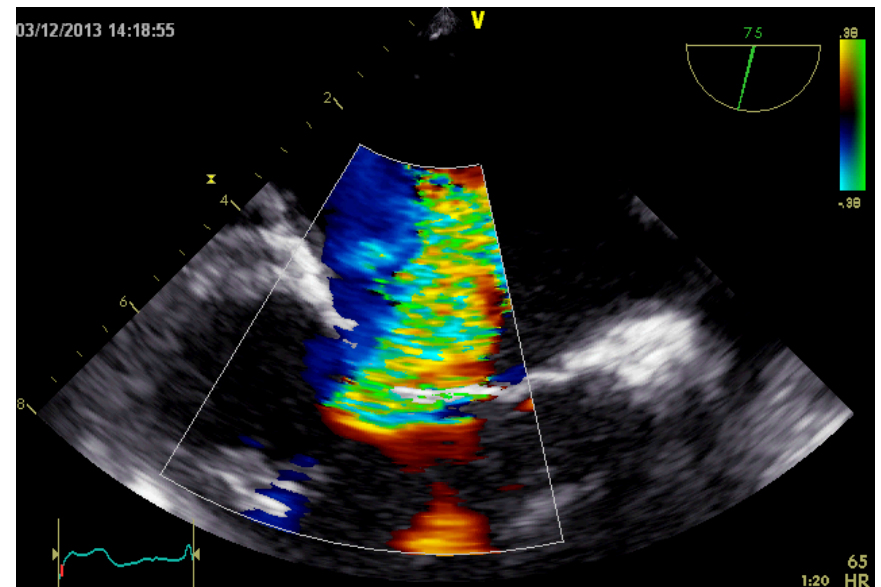
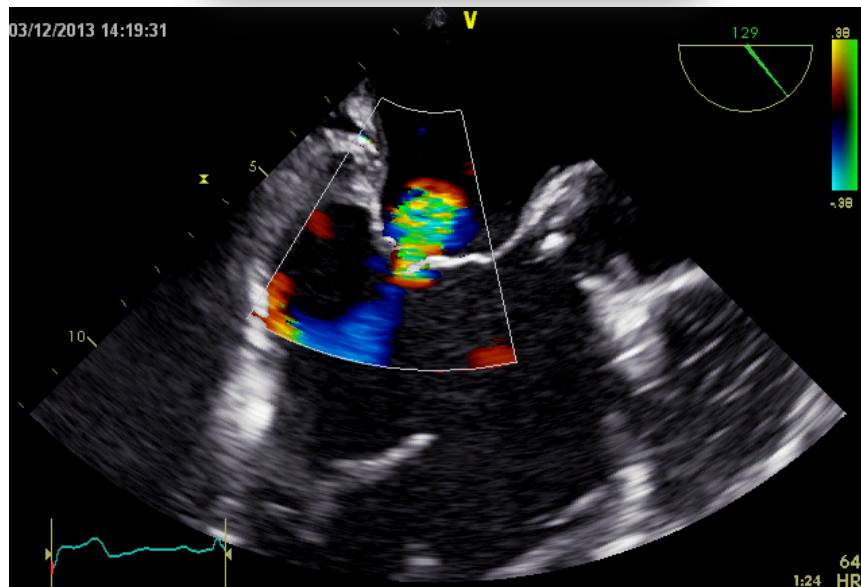
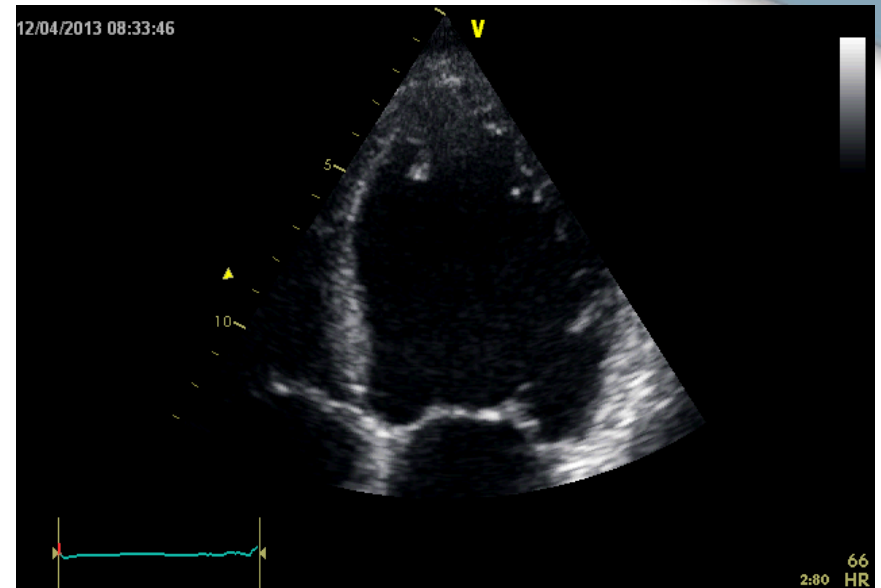
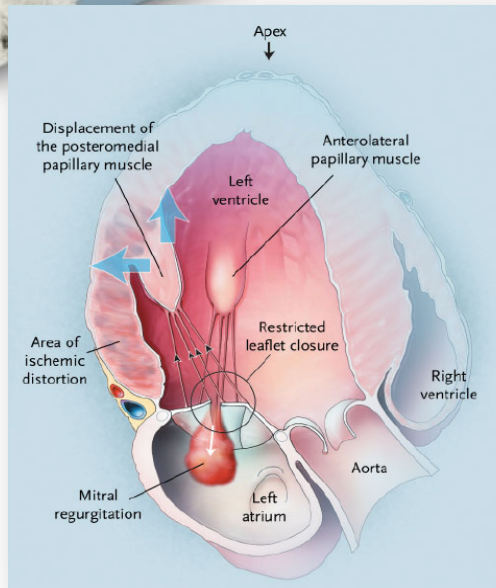


(lung, Eur Heart J 2003; 24: 1231)

# Two types of MR: DMR



# Two types of MR: FMR



# What are the goals of MR treatment?

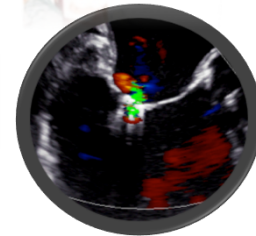
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Improve symptoms



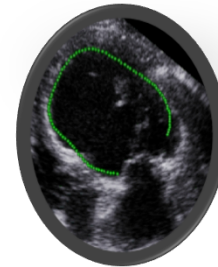
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Persistent MR reduction



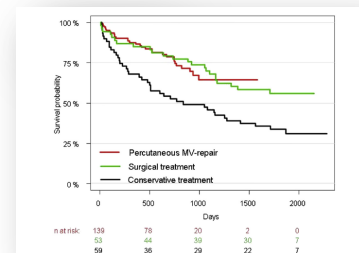
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Inverse remodeling



4

Improve survival



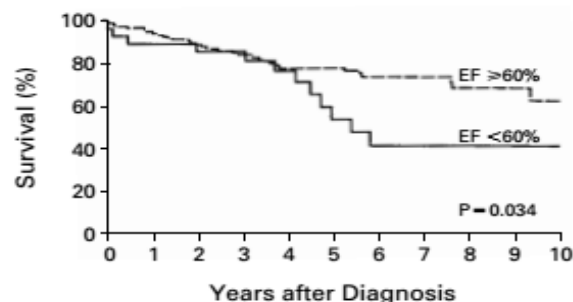
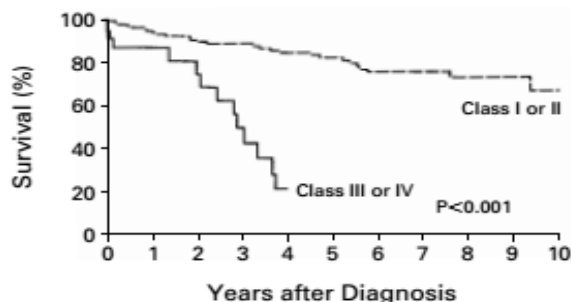


# Guidelines

# What have we learnt form surgery? DMR

## CLINICAL OUTCOME OF MITRAL REGURGITATION DUE TO FLAIL LEAFLET

LIENG H. LING, M.B., B.S., MAURICE ENRIQUEZ-SARANO, M.D., JAMES B. SEWARD, M.D., A. JAMIL TAJIK, M.D., HARTZELL V. SCHAFF, M.D., KENT R. BAILEY, PH.D., AND ROBERT L. FRYE, M.D.



Indications for intervention in DMR: symptoms or LV dysfunction

	Class	Level
Mitral valve repair should be the preferred technique when it is expected to be durable.	I	C
Surgery is indicated in symptomatic patients with LVEF > 30% and LVESD < 55 mm.	I	B
Surgery should be considered in patients with severe LV dysfunction (LVEF < 30% and/or LVESD > 55 mm) refractory to medical therapy with high likelihood of durable repair and low comorbidity.	IIa	C
Surgery may be considered in patients with severe LV dysfunction (LVEF < 30% and/or LVESD > 55 mm) refractory to medical therapy with low likelihood of durable repair and low comorbidity.	IIb	C

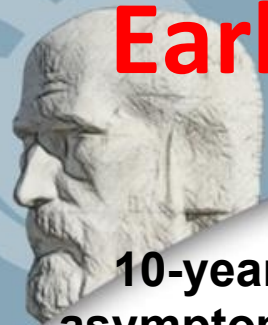
# Recognized indications for early surgery in DMR

**In order to improve prognosis and not as "rescue surgery"**

Indication	Class	Level
Surgery is indicated in asymptomatic patients with LV dysfunction (LVESD $\geq 40$ mm and/or LVEF $\leq 60\%$ ).	I	C
Surgery should be considered in asymptomatic patients with LV dysfunction and new onset of atrial fibrillation or pulmonary hypertension (pulmonary pressure at rest $> 50$ mmHg).	IIa	C
Surgery should be considered in asymptomatic patients with preserved LV function, high likelihood of durable repair, low surgical risk, and aortic regurgitation with aortic leaflet and LVESD $\geq 40$ mm.	IIa	C
Surgery may be considered in asymptomatic patients with preserved LV function, high likelihood of durable repair, low surgical risk, and: <ul style="list-style-type: none"> <li>• left atrial dilatation (LA diameter <math>\geq 40</math> mm and LA volume index <math>\geq 60</math> ml/m<sup>2</sup> BSA) and sinus rhythm, or</li> <li>• pulmonary hypertension on exercise (SPAP <math>\geq 60</math> mmHg at exercise).</li> </ul>	IIb	C

**TIMING OF INTERVENTION MATTERS**

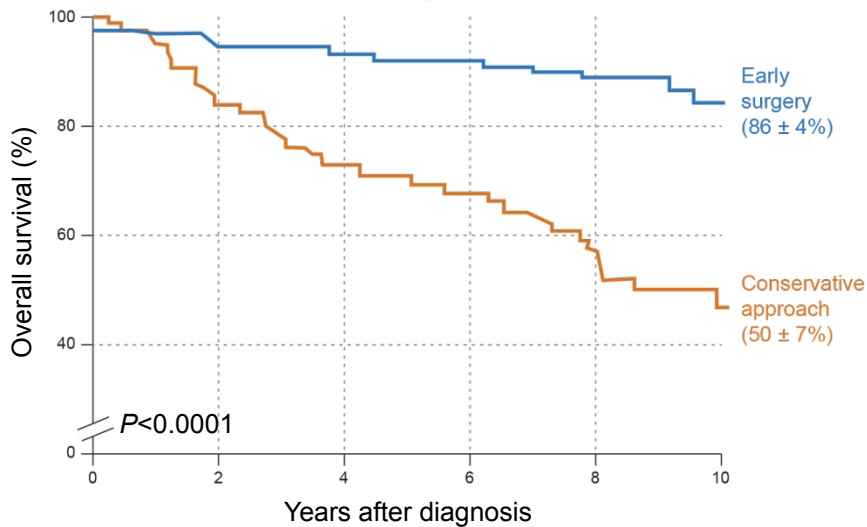




# Early surgical intervention improves outcomes

EARLIER  
TREATMENT

10-year overall survival of asymptomatic MR patients was significantly greater with early Surgery vs. medical management



Otto, C. Heart 2003

***“early intervention to prevent left ventricular systolic dysfunction or pulmonary hypertension provides optimal clinical outcomes”.***

1. Otto, C. – Timing of surgery in mitral regurgitation - Heart 2003;89:100–105

Montant P, Chenot F, Robert A, et al. Long-term survival in asymptomatic patients with severe degenerative mitral regurgitation: a propensity score-based comparison between an early surgical strategy

and a conservative treatment approach. J Thorac Cardiovasc Surg. 2009;138(6):1339-1348.

# MitraClip as Tx option for high risk surgical patients in ESC Heart Failure 2012 guidelines



## ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC.

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...“In 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.” .....

although its effect on survival is unknown. In this situation, the decision to operate should take account of response to medical therapy, co-morbidity, and the likelihood that the valve can be repaired (rather than replaced).

**Secondary mitral regurgitation**  
This occurs because LV enlargement and remodelling lead to reduced leaflet closing. Effective medical therapy leading to reverse remodelling of the LV may reduce functional mitral regurgitation, and every effort should be made to optimize medical treatment in these patients.

Ischaemic mitral regurgitation is a particular type of secondary mitral regurgitation that may be more suitable for surgical repair. As it is often a dynamic condition, stress testing is important in its evaluation. An exercise-induced increase of effective regurgitant orifice ( $\geq 13 \text{ mm}^2$ ) is associated with a worse prognosis. Combined valve and coronary surgery should be considered in symptomatic patients with LV systolic dysfunction, coronary arteries suitable for revascularization, and evidence of viability. Predictors of late failure of valve repair include large interpapillary muscle distance, severe posterior mitral leaflet tethering, and marked LV dilatation (LV end-diastolic diameter  $> 65 \text{ mm}$ ). In these patients, mitral valve replacement, rather than repair, may be advisable. In the presence of AF, atrial ablation and left atrial appendage closure may be considered at the time of mitral valve surgery.

The role of isolated mitral valve surgery in patients with severe functional mitral regurgitation and severe LV systolic dysfunction who cannot be revascularized or have non-ischaemic cardiomyopathy is questionable, and in most patients conventional medical and device therapy are preferred. In selected cases, repair may be considered in order to avoid or postpone transplantation.

In 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.<sup>150</sup>

### 13.4 Heart transplantation

Heart transplantation is an accepted treatment for end-stage HF.<sup>251,252</sup> Although controlled trials have never been conducted, there is consensus that transplantation—provided that proper selection criteria are applied—significantly increases survival, exercise capacity, quality of life, and return to work compared with conventional treatment.

Apart from the shortage of donor hearts, the main challenges in transplantation are the consequences of the limited effectiveness and complications of immunosuppressive therapy in the long term (i.e. antibody-mediated rejection, infection, hypertension, renal failure, malignancy, and coronary artery vasculopathy). The indications for and contraindications to heart transplantation are summarized in Table 23.

### 13.5 Mechanical circulatory support

MCS is an umbrella term describing a number of different technologies used to provide both short- and longer term assistance in patients with either chronic HF or AHF. A variety of terms have been used to describe the use of these technologies (Table 24).<sup>211,253</sup> The most experience is with MCS in end-stage

**Table 23 Heart transplantation: indications and contraindications**

Patients to consider	End-stage heart failure with severe symptoms, a poor prognosis, and no remaining alternative treatment options
	Motivated, well informed, and emotionally stable
	Capable of complying with the intensive treatment required post-operatively
Contraindications	Active infection
	Severe peripheral arterial or cerebrovascular disease
	Current alcohol or drug abuse
	Treated cancer in previous 5 years
	Unhealed peptic ulcer
	Recent thrombo-embolism
	Significant renal failure (e.g. creatinine clearance $< 30 \text{ mL/min}$ )
	Significant liver disease
	Systemic disease with multigorgan involvement
	Other serious co-morbidity with poor prognosis
	Emotional instability or untreated mental illness
	High fixed pulmonary vascular resistance ( $> 4\text{--}5$ Wood Units and mean transpulmonary gradient $> 15 \text{ mmHg}$ )

HF = heart failure.

**Table 24 Terms describing various uses of mechanical circulatory support (MCS)**

Bridge to decision (BTD):	Use of MCS in patients with drug-refractory acute circulatory collapse and at immediate risk of death to sustain life until a full clinical evaluation can be completed and additional therapeutic options can be evaluated.
Bridge to candidacy (BTC):	Use of MCS to improve end-organ function in order to make an ineligible patient eligible for transplantation.
Bridge to transplantation (BT):	Use of MCS to keep a patient at high risk of death before transplantation alive until a donor organ becomes available.
Bridge to recovery (BTR):	Use of MCS to keep patient alive until intrinsic cardiac function recovers sufficiently to remove MCS.
Destination therapy (DT):	Long-term use of MCS as an alternative to transplantation in patients with end-stage heart failure ineligible for transplantation.

MCS = mechanical circulatory support.

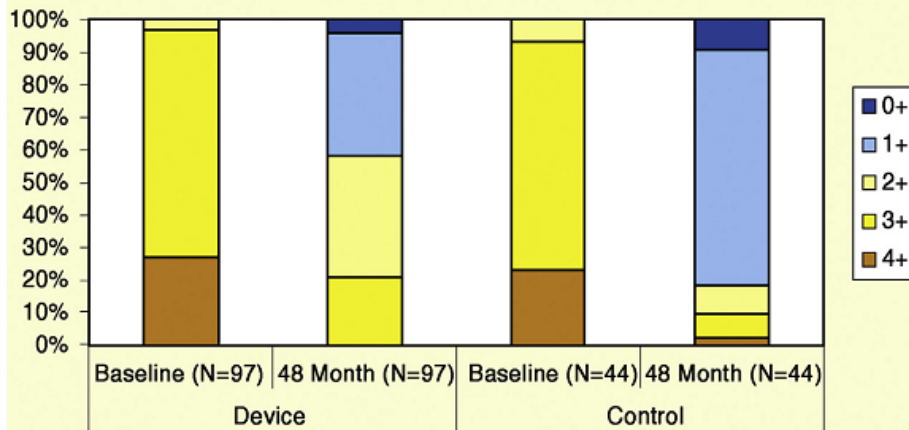


# WHAT TO EXPECT FROM MITRA CLIP

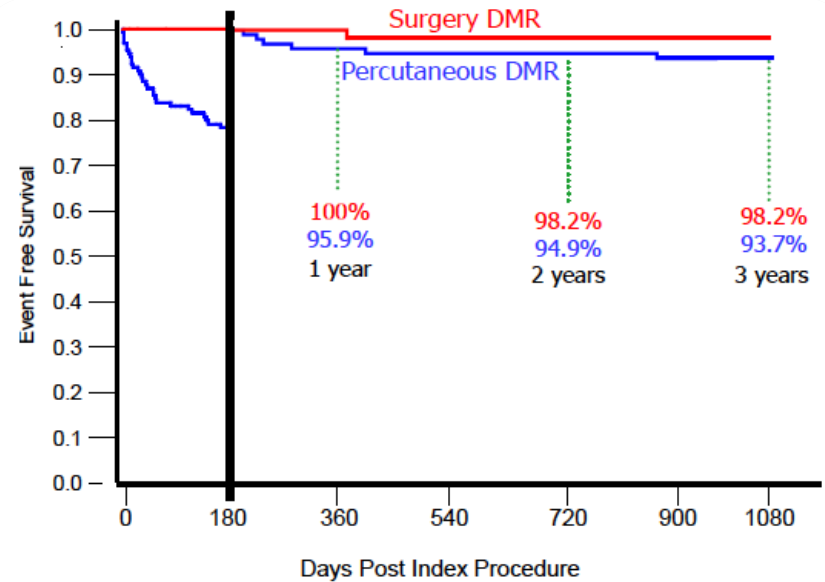
## EVEREST II

### Persistent reduction of MR

MR Severity at Baseline and 48 Months



### No more re-do after 6 months

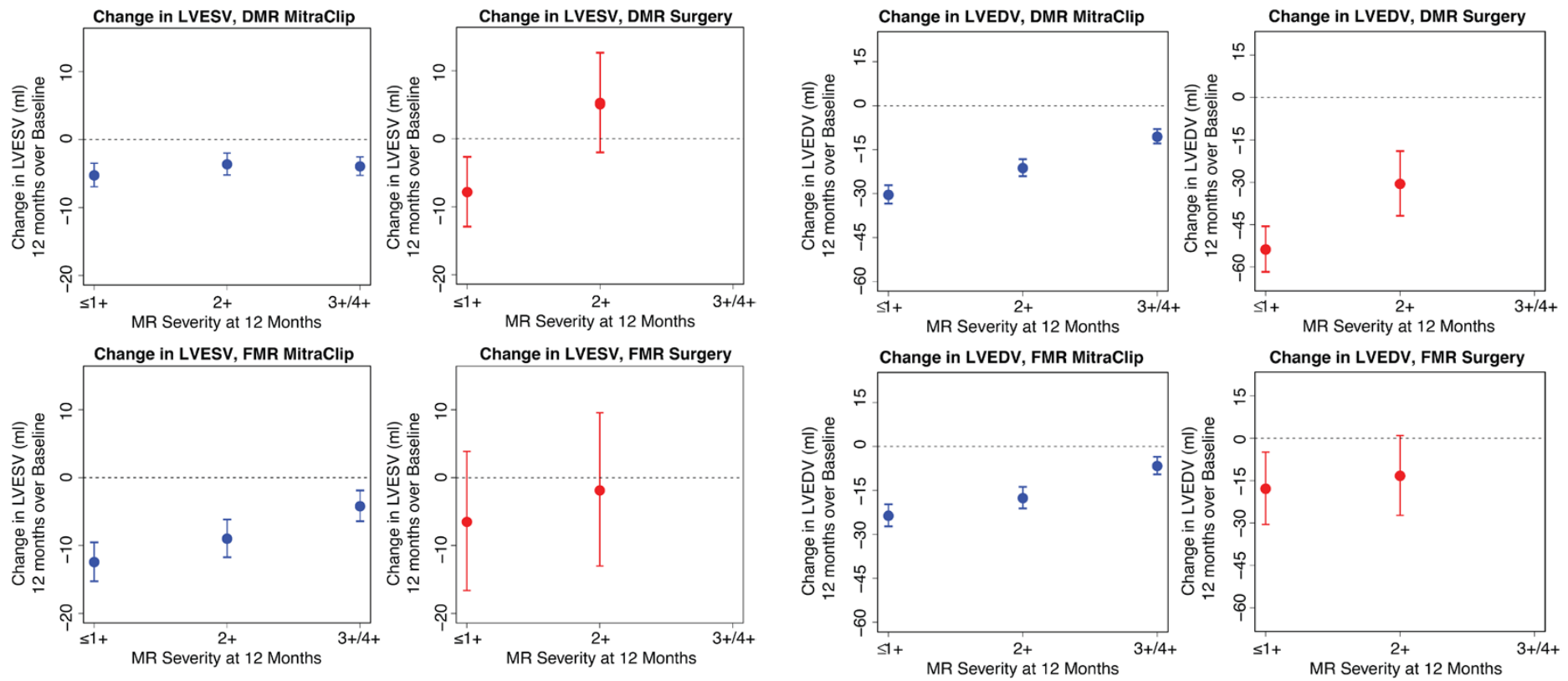




# WHAT TO EXPECT FROM MITRACLIP

## EVEREST II

### POSITIVE EFFECT IN LV REMODELING

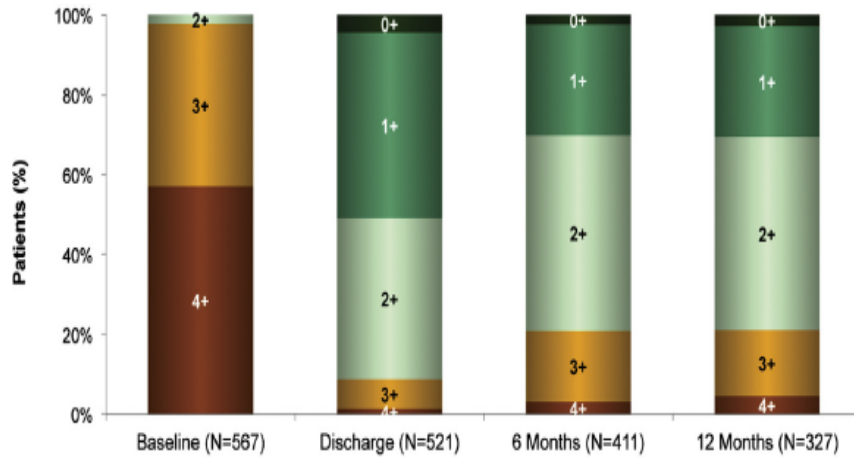




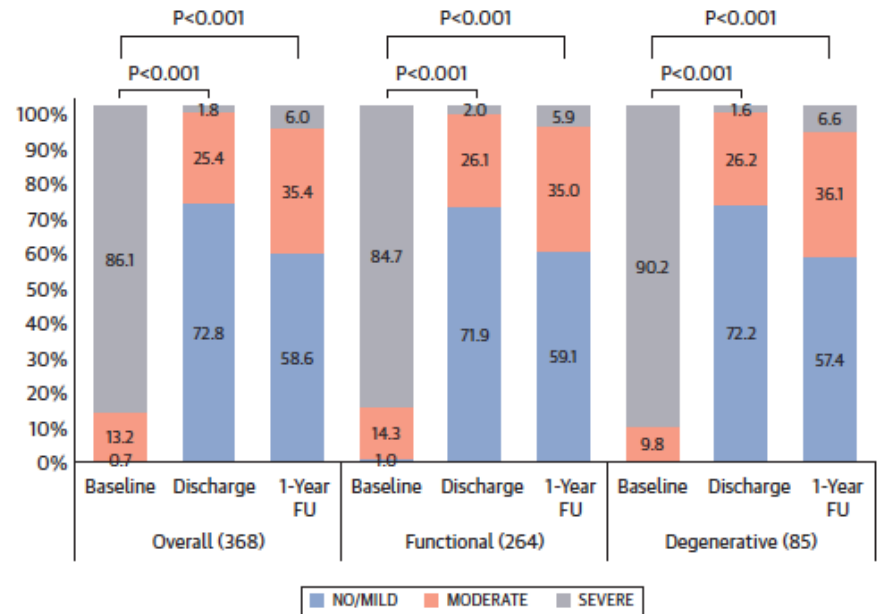
# WHAT WE KNOW FROM REAL WORLD

REAL WORLD

## Persistent reduction MR@ 1 year



**ACCESS EU**



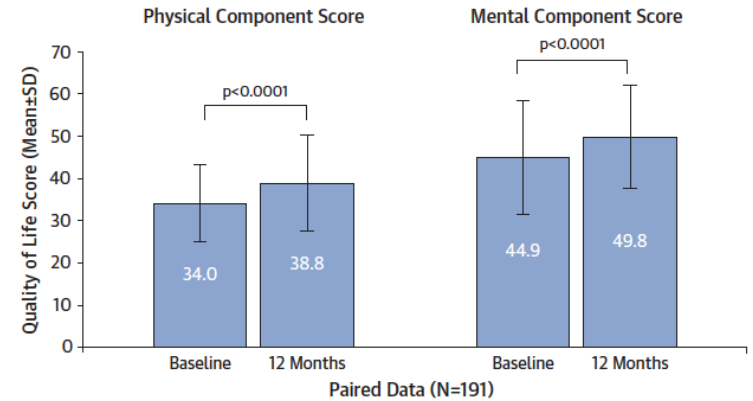
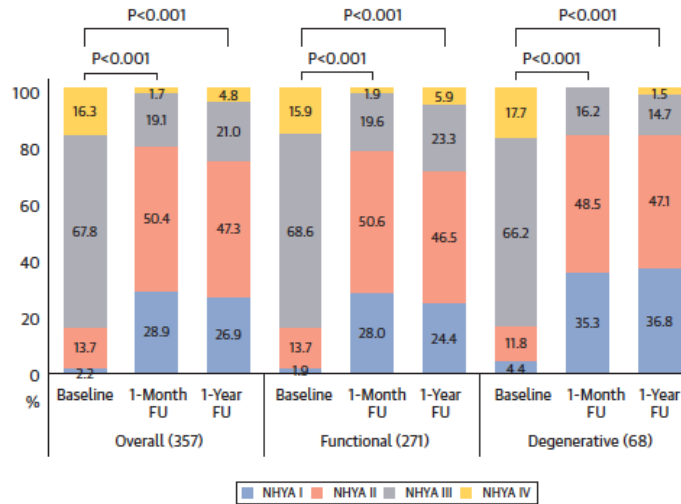
**ESC SENTINEL**



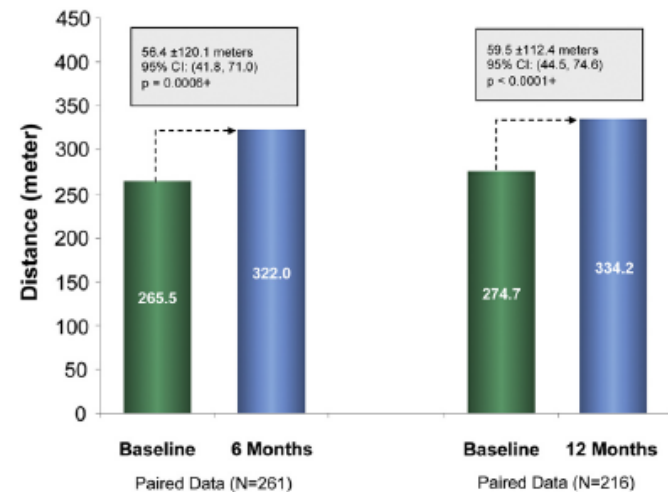
# FUNCTIONAL IMPROVEMENT

**REGISTRIES**

## NYHA CLASS IMPROVEMENT *ESC SENTINEL*



## 6MWT *ACCESS EU*

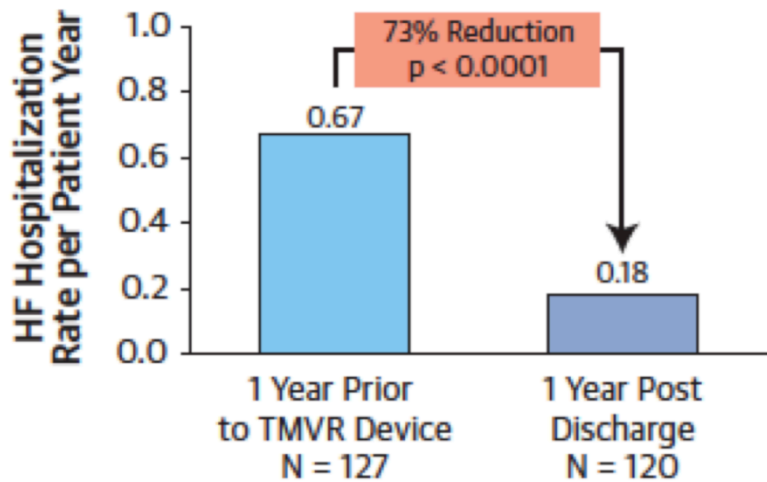


## QOL *EVEREST HIGH RISK*

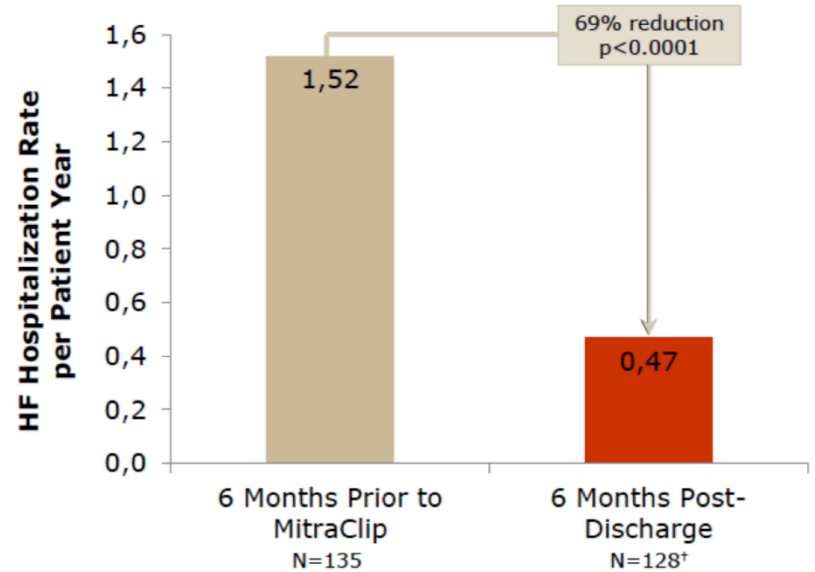
Maisano F, J Am Coll Cardiol 2013; 62:1051  
 Nickenig G, Estevez-Loureiro R, J Am Coll Cardiol 2014;64:875  
 Glower D, J Am Coll Cardiol 2014;64:172

# REDUCTION IN REHOSPITALIZATIONS

## REGISTRIES



**EVEREST II  
DMR**

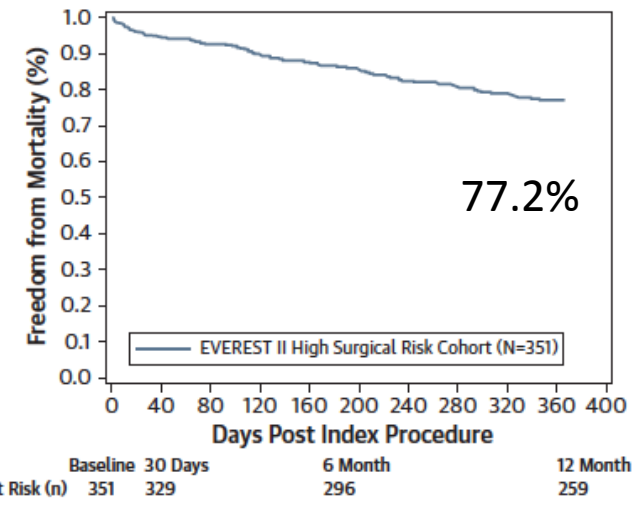
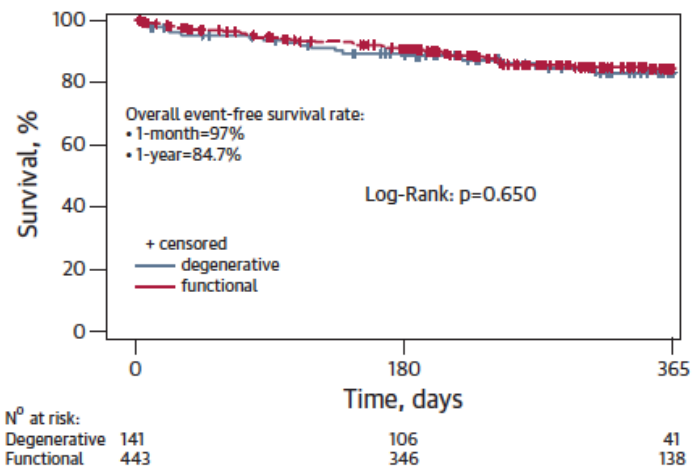


**ACCESS EU  
FMR**

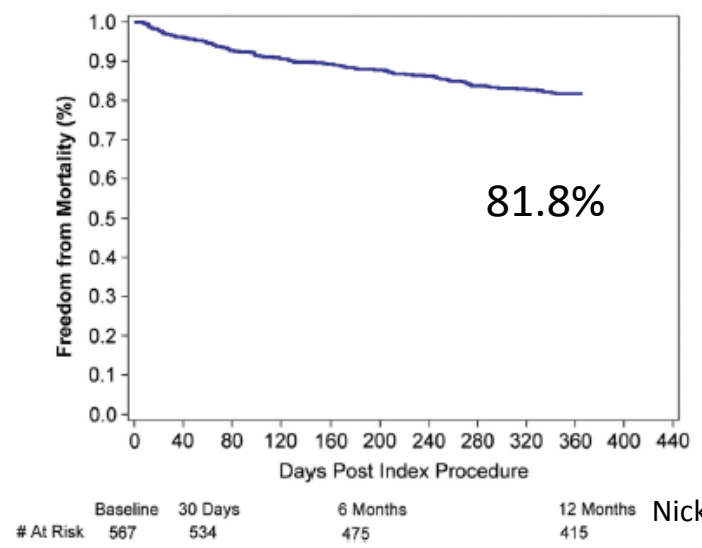


# REGISTROS

# SURVIVAL



## ESC SENTINEL



## EVEREST HRR

Maisano F, J Am Coll Cardiol 2013; 62:1051  
 Nickenig G, Estevez R, J Am Coll Cardiol 2014;64:875  
 Glower D, J Am Coll Cardiol 2014;64:172-81

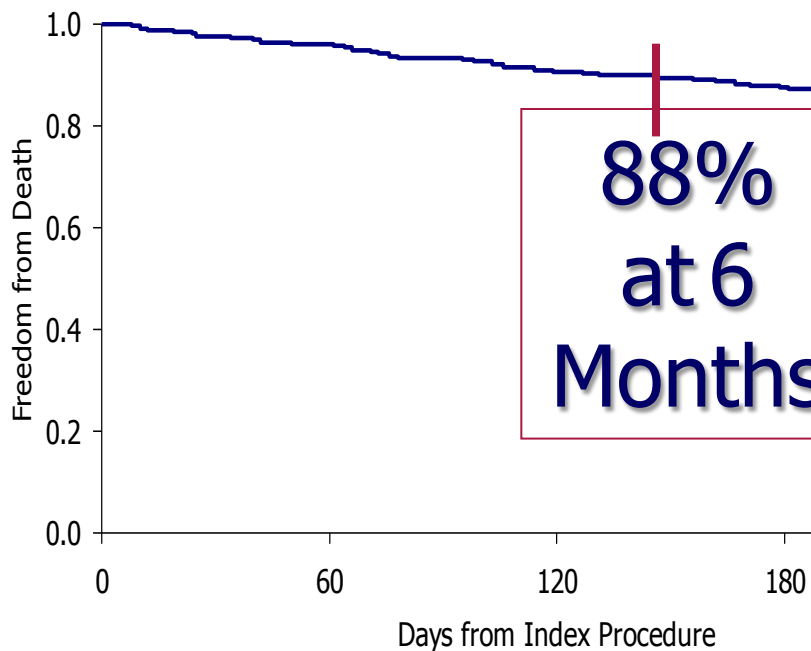
## ACCESS EU



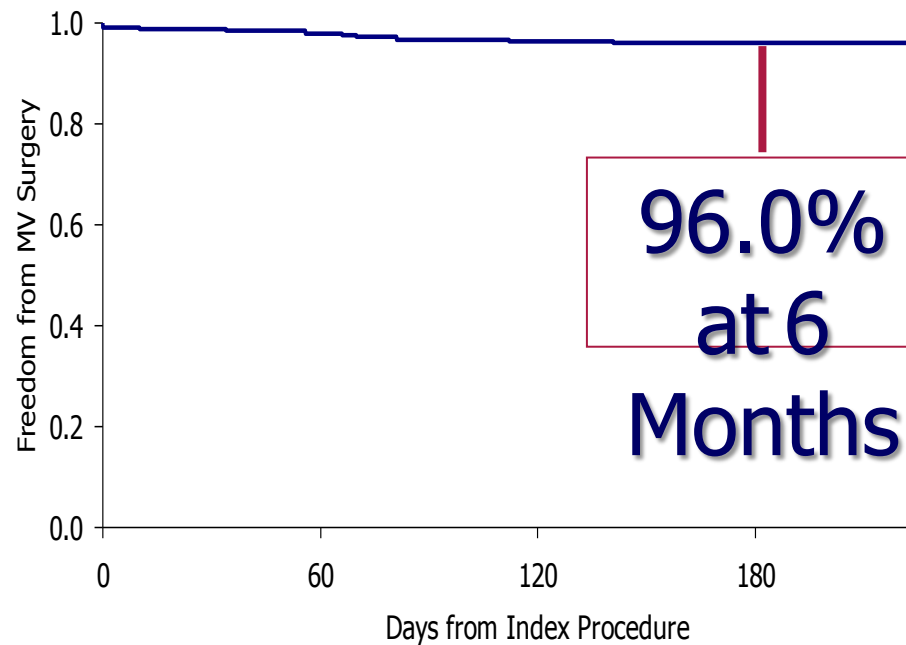


# Outcomes in ACCESS EU

## Freedom from death



## Freedom from MV Surgery



# Safety of PMVR (German TRAMI registry; n=486)

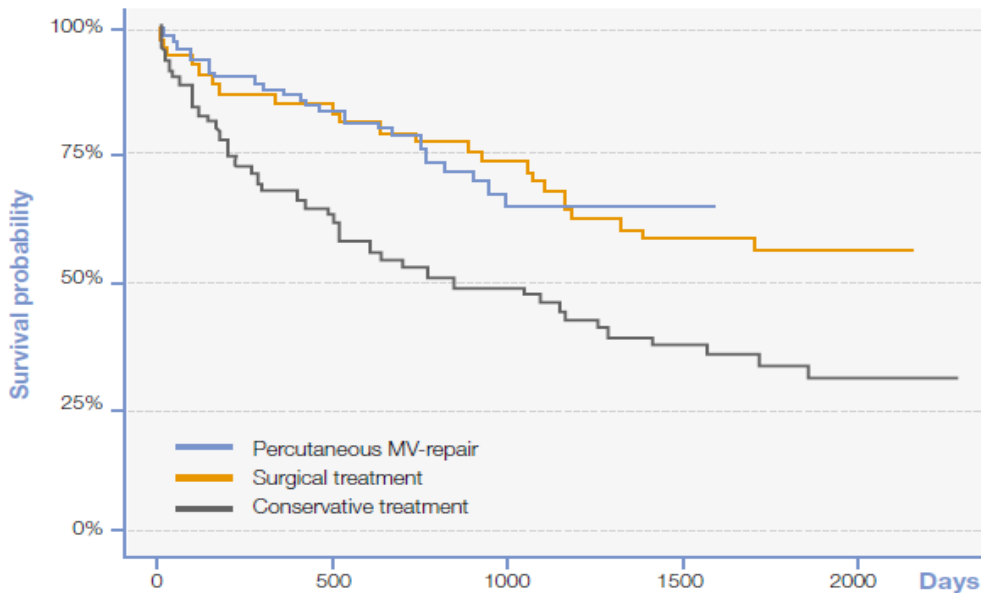


**Table 2 Major adverse events at follow-up**

	<i>n/N (%)</i>
.....	
Pre-discharge complications	
Death	12/479 (2.5)
Stroke	2/462 (0.4)
Repeat percutaneous intervention	8/463 (1.7)
Surgery for failed percutaneous intervention	16/463 (3.5)
Severe bleeding (haemodynamic instability, intracranial, transfusion)	18/461 (3.9)
Transfusion	48/462 (10.4)
Pericardial effusion	4/461 (0.9)
Major vascular complication (requiring surgery or transfusion)	13/461 (2.8)
Minor vascular complication (bleeding, ischaemia)	20/461 (4.3)
Partial clip detachment	1/461 (0.2)
Post-discharge complications	
Death	34/272 (12.5)
Surgery for failed percutaneous intervention	2/111 (1.8)

# MitraClip intervention improves survival

## Kaplan-Meier Survival Curves



n at risk	0	500	1000	1500	2000
Percutaneous MV-repair	139	78	20	2	0
Surgical treatment	53	44	39	30	7
Conservative treatment	59	36	29	22	7

**MitraClip therapy\* is superior to conservative treatment and survival rates are comparable to surgery in high-surgical-risk patients with symptomatic MR (DMR and FMR)**

\*Swaans - Survival of Transcatheter Mitral Valve Repair Compared With Surgical and Conservative Treatment in High-Surgical-Risk Patients – JACC, 2014( 7); 8 : 875-881

# MitraClip intervention improves survival



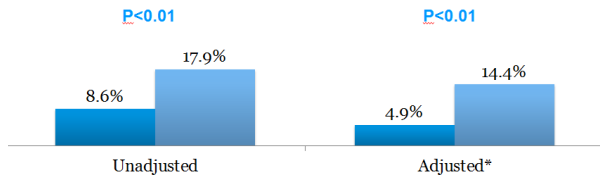
MitraClip therapy\* is superior to conservative treatment and survival rates are comparable to surgery in high-surgical-risk patients with symptomatic MR (DMR and FMR)

## MITRACLIP VS MT IN PATIENTS WITH HF

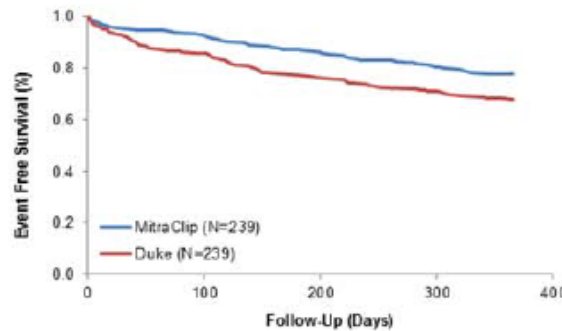
REGISTRY OF 493 PATIENTS WITH HF AND MODERATE-TO-SEVERE MR

12-month all-cause death

■ Mitraclip ■ Conservative



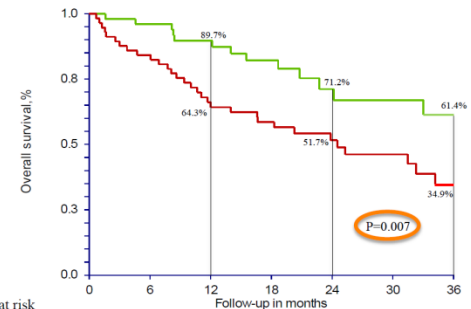
Adjusted by a propensity score model including age, hypertension, diabetes mellitus, dyslipidemia, MR etiology [i.e., ischemic or non-ischemic], number of prior hospitalizations for HF, prior myocardial infarction, prior revascularization, prior cancer, prior pacemaker implantation, chronic obstructive pulmonary disease, NYHA class, chronic kidney disease, gender, prior intra-cardiac device implantation, atrial fibrillation, left ventricle ejection fraction and body mass index



No. at risk	Day 0	Day 30	Day 180	Day 365
MitraClip	239	226	202	175
Duke	239	219	178	147

PCR 2015

Overall Survival



N <sub>0</sub> at risk	Day 0	Day 12	Day 24	Day 36
PMVR group	60	43	18	10
OMT group	60	35	21	10

Armeni - Real-world cost effectiveness of MitraClip combined with Medical Therapy Versus Medical therapy alone in patients with moderate or severe mitral regurgitation – International Journal of Cardiology 209 (2016) 153–160; The MitraClip and survival in patients with mitral regurgitation at high risk for surgery: A propensity-matched comparison Eric J. Velazquez, MD, American Heart Journal; Transcatheter mitral valve repair VS conservative treatment in severe functional mitral regurgitation: a single-centre experience Francesca Fiorelli, MD, PCR Valve, Berlin, 2015



# Experience

# WORLDWIDE EXPERIENCE



Study	Population	Status	N
EVEREST I (Feasibility)	Feasibility patients	Closed	55
EVEREST II (Pivotal)	Pre-randomized patients	Closed	60
EVEREST II (Pivotal)	Non-randomized patients (High Risk Study)	Closed	78
EVEREST II (Pivotal)	Randomized patients (2:1 Clip to Surgery)	Closed	279 184 Clip 95 Surgery
REALISM (Continued Access)	Non-randomized patients	Enrollment Complete. Follow-up ongoing	899
Compassionate/Emergency Use	Non-randomized patients	Enrollment Complete. Follow-up ongoing	66
ACCESS Europe Phase I	Non-randomized patients	Closed	567
ACCESS Europe Phase II	Non-randomized patients	Closed	286
Post-Approval Study 1 (PAS1)	Commercial patients	Enrolling	1583 <sup>§</sup>
Post-Approval Study 2 (PAS2)	Commercial patients	Enrollment to start Q1'16	n/a
COAPT Trial	Randomized patients (1:1 Clip to Medical Therapy)	Enrolling	47 Roll-Ins* 317 Randomized*
MitraClip Japan	Non-randomized patients	Enrolling	10
Commercial Use	Commercial patients	Ongoing	Over 25000*
<b>Total</b>			<b>Over 28000 +95 surgery</b>

Data as of : <sup>§</sup>March 2015 , <sup>\*</sup>December 10, 2015  
Source: Abbott Vascular



# Growing body of clinical evidence – over 25.000 patients treated



**Overall clinical feasibility & safety**



**Efficacy & safety in clinical practice**



**Address specific patient populations**



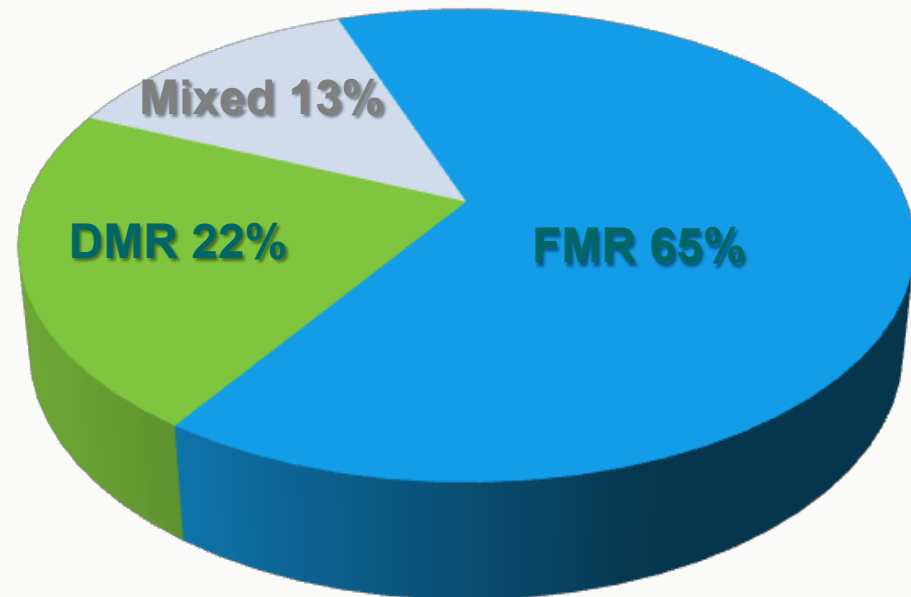
# WORLDWIDE COMMERCIAL IMPLANT EXPERIENCE

JL  
N

**>25,000 Patients**

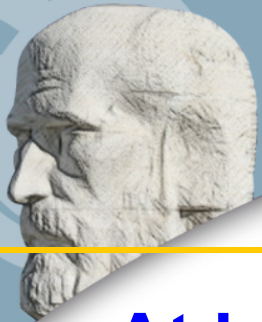
**Implant Rate: 96%**

## Etiology



Data as of Sept 2015. Source: Abbott Vascular





# PMVR in specific patients populations



- **At high risk for surgery**
  - Pledger et al. AJC 2011; Rudolph et al. JACC 2011; Treede et al. JTCVS 2011; Baldus et al. EJHF 2012; Van den Branden et al. JACC 2012
- **Prior cardiac surgery**
  - Ussia et al., J Card Surg 2012
- **With Atrial fibrillation**
  - Herrmann et al. JACC 2012
- **CRT non-responders**
  - Auricchio et al. JACC 2011
- **Severe HF**
  - Tamburino EHJ 2010; Franzen et al. EJHF 2011; van den Branden JACC
- **Waiting for heart Tx**
  - Brescia, ongoing

# Reimbursement and Funding overview

Sweden: Reimbursement limited to research purpose only.

Denmark: DRG for percutaneous, transseptal insertion of mitralclip

Netherlands: DRG for MitraClip per procedure

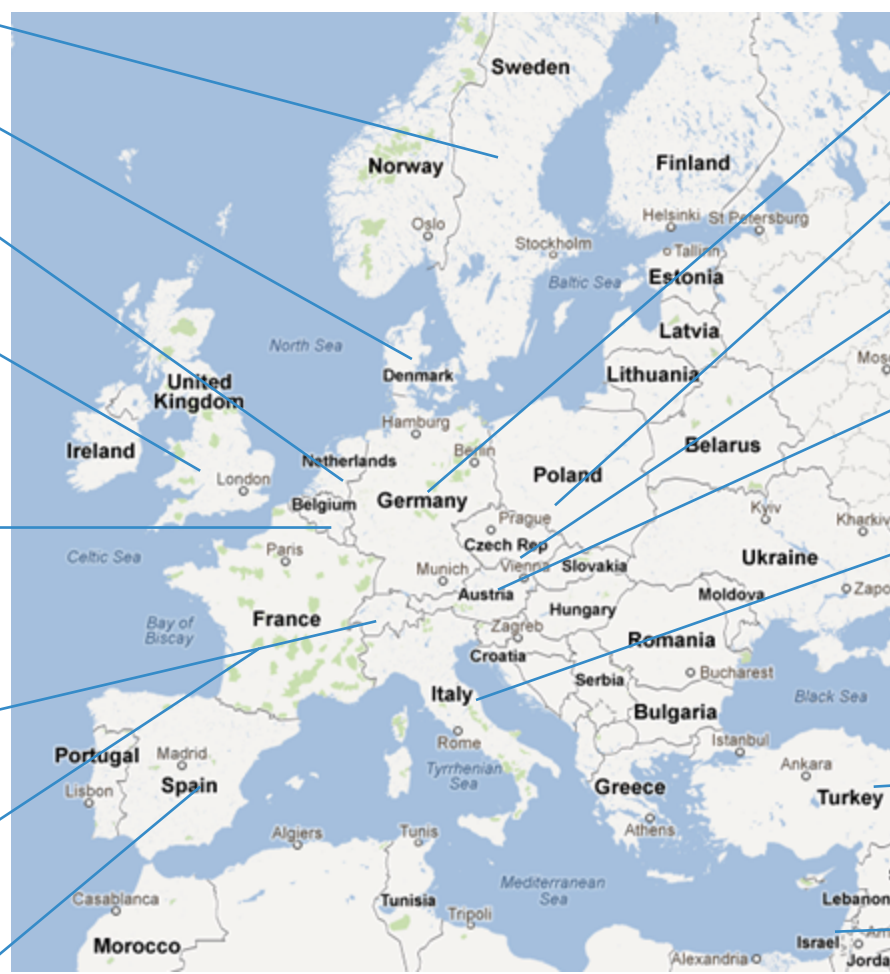
UK: Commissioning through Evaluation granted until March 2018

**Belgium: Reimbursement is granted from March 2016 under a new national framework of "Coverage with Evidence Development".**

Switzerland: DRG for endovascular mitral valve reconstruction, transvenous

France: Decision expected in Q1 2016

Spain: MitraClip is part of the National Health Basket; reimbursement is negotiated per region.



Germany: DRG for for transvenous clip-reconstruction of mitral valve

Poland: Decision expected in Q1 2016

Czech Republic: 2 Private insurances agreement

Austria: Procedure code for implantation of mitral valve clip-percutaneous

Italy: Regional or innovation funding ongoing  
Device reimbursed on top of DRG in Lombardy (80%)

Turkey: SGK coverage in public hospitals\*

Israel: Reimbursement as of Jan 2014

In place    Partial/restricted    Expected

\*conditions apply

# Transcatheter MV Repair: **Device Landscape**

## Edge-to-edge

- MitraClip\*
- MitraFlex

## Direct annuloplasty and basal ventriculoplasty

- Mitralign Bident\*
- GDS Accucinch\*
- Valtech Cardioband\*
- Quantum Cor (RF)
- Micardia enCor

\*In patients

## Coronary sinus annuloplasty

- Cardiac Dimensions Carillon\*
- Cerclage annuloplasty

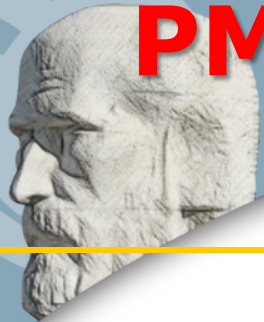
## MV replacement

- CardiAQ\*
- Neovasc\*
- Edwards Fortis\*
- Micro Interventional
- Valtech Cardiovalve
- ValveXchange
- Lutter Valve
- Medtronic
- Tendyne\*
- MitrAssist
- MVAlve

## Other approaches

- MitraSpacer\*
- St. Jude leaflet plication\*
- Cardiac Implant perc ring
  - NeoChord\*
  - Babic chords
- Valtech Vchordal
- Middle Peak Medical
  - Mardil BACE
  - Mitralis
  - Millipede





# PMVR: Conclusions after the first 30.000 patients



- Data from RCT, registries and cohorts indicate MitraClip as a safe and effective option
- Efficacy & safety confirmed in
  - Patients at high risk for surgery
  - CRT non-responders
  - Patients with severe heart failure
- The Heart Team approach can maximize patients' referral and treatment