When to treat or refer for PMVR and survival after PMVR

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

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• Grant/Research Support	• None
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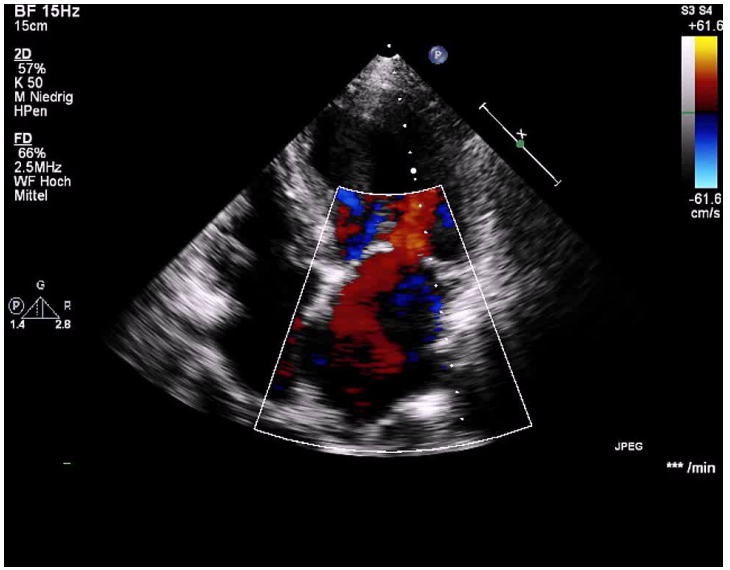
• Major Stock Shareholder/Equity	• None
• Royalty Income	• None
• Ownership/Founder	• None
• Intellectual Property Rights	• None
• Other Financial Benefit	• None

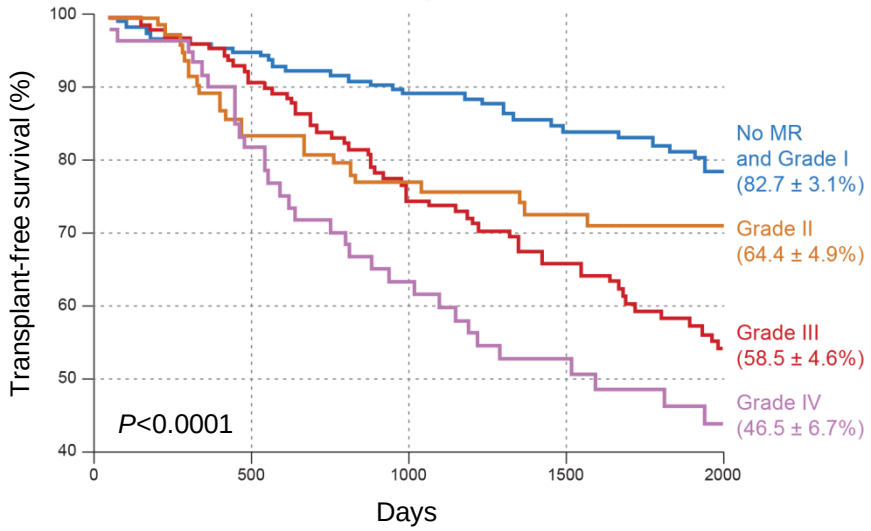
Mitral Regurgitation



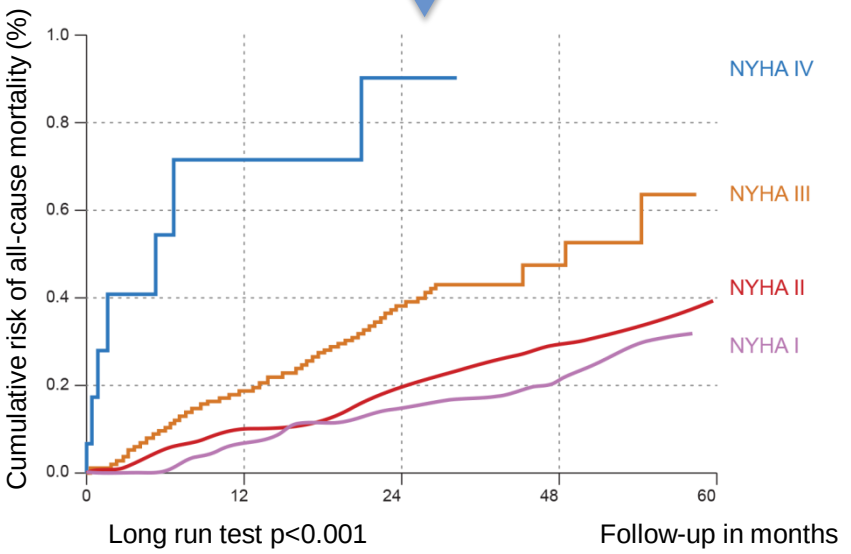
- Mitral regurgitation (MR) is the second most common type of heart valve disease needing surgery in Europe
- Controversy regarding optimal timing of intervention in asymptomatic patients with severe MR, consensus in symptomatic patients
- Poor prognosis in absence of surgery
- Even with optimal medical therapy (OMT)

As mitral regurgitation becomes more severe, morbidity and mortality risk increases

Event – free survival decreases with increasing MR severity



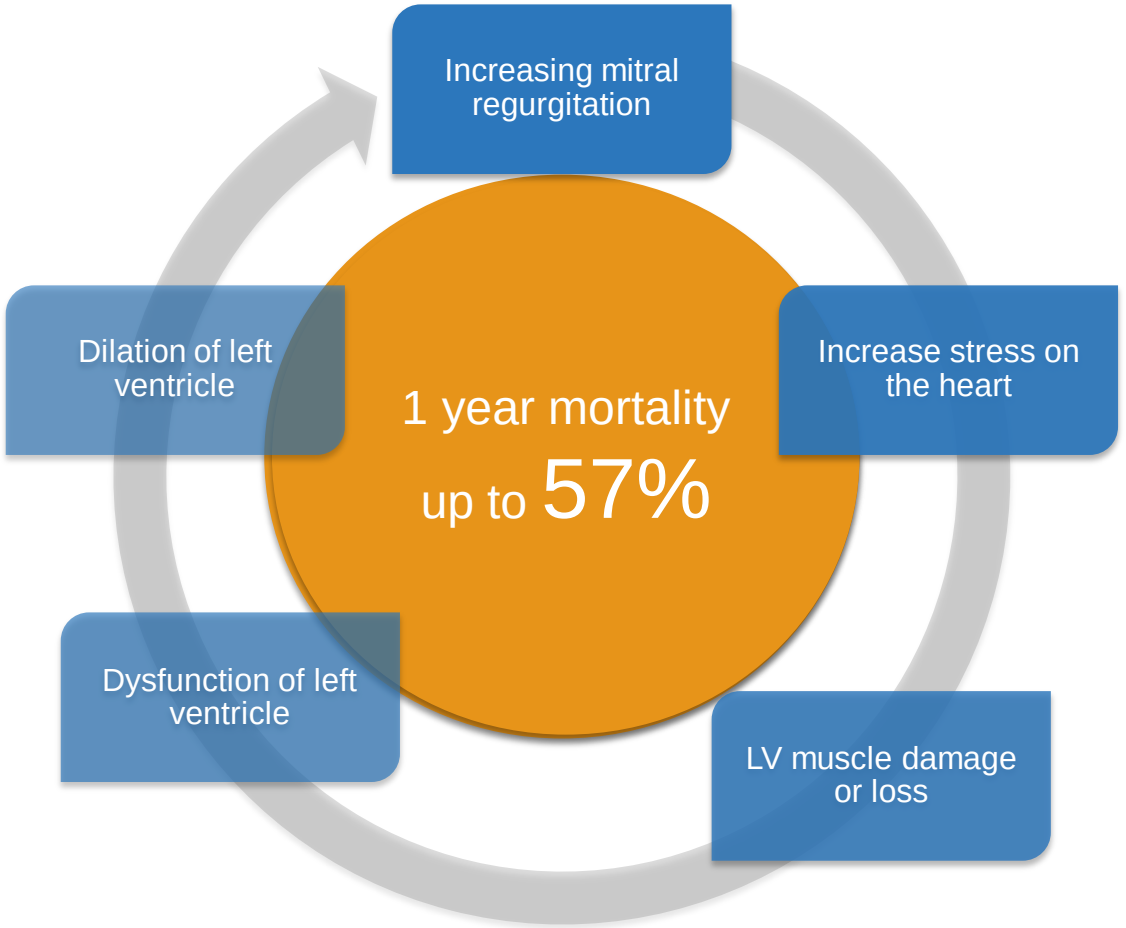
Risk of mortality increases with increasing NYHA class



- Poor quality of life
- Repeat hospitalisations

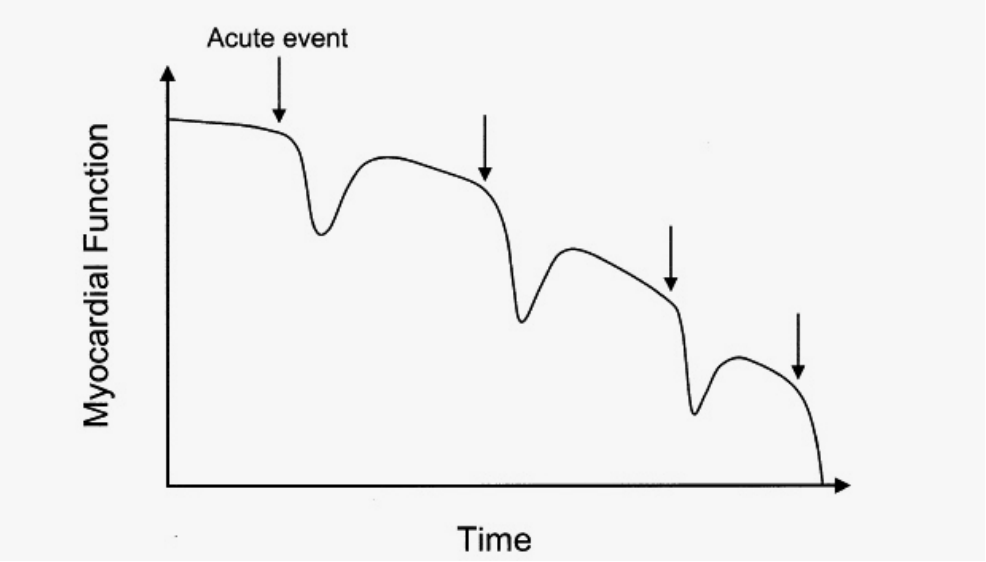
Agricola E et al. Eur J Heart Fail 2009;11:581–7.

Mitral regurgitation (MR) progresses to Heart Failure

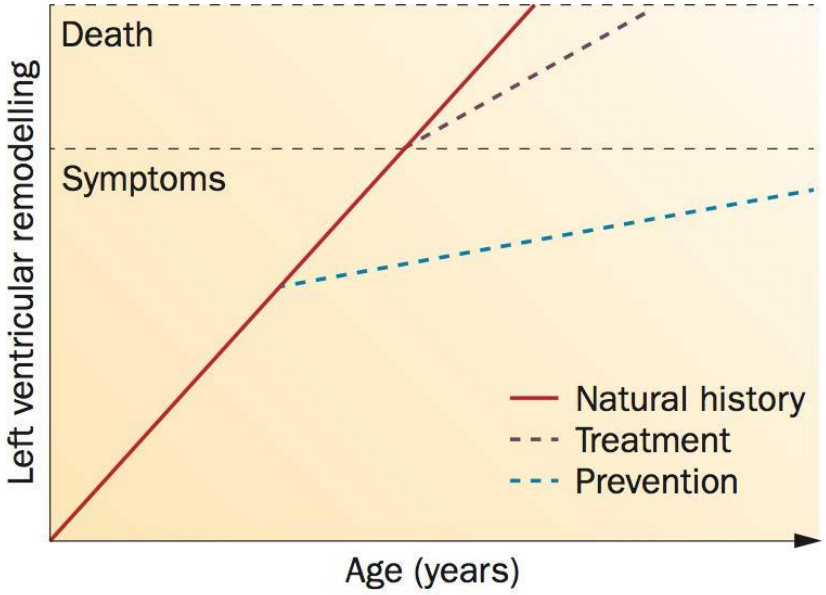


Cioffi G et al. European Journal of Heart Failure 2005

MR and heart failure



Gheorghiade M et al. Am J Cardiol. 2005;96[suppl]:11G-17G.



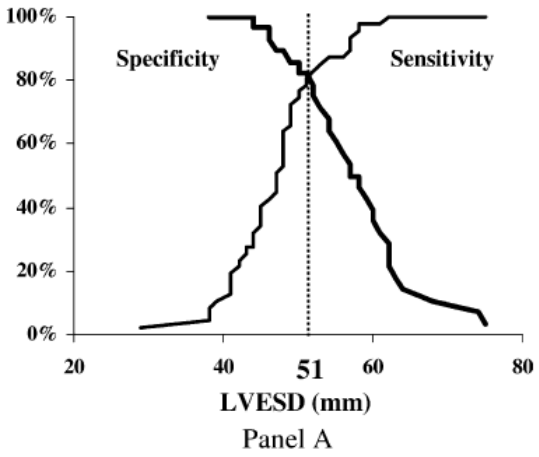
Cohn, J. N. Nat .Rev. Cardiol. 11, 69–70 (2014)

LV reverse remodeling after MVA

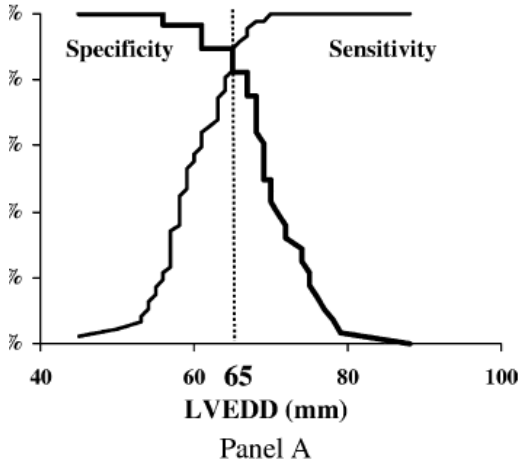
- Late reverse remodeling after MVA is influenced by pre-operative LV-size
- Smaller LV retains the ability to reverse remodel
- Cutoff:
  - LVESD 51 mm
  - LVEDD 65 mm

Table 4. Predictors of Reverse Left Ventricular Remodeling

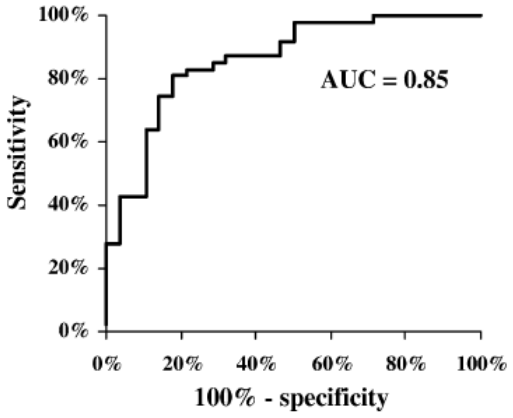
Variable	Odds Ratio	*p* (univariate)	*p* (multivariable)
Age	0.9	0.7	
Duration of CHF	0.6	0.06	0.05
Ischemic etiology	1.5	0.04	0.9
Associated CABG	1.4	0.02	0.9
Successful ablation of AF	3.7	0.05	0.2
EF	0.9	0.3	
SPAP	0.9	0.4	
LVEDD	0.9	0.2	
LVEDVI	1	0.7	
LVESVI	1	0.3	
Tenting area	0.8	0.5	
Coaptation depth	1.8	0.2	
Use of edge-to-edge	2.1	0.08	0.09
Ring number	0.8	0.2	
Ring type	1.2	0.8	

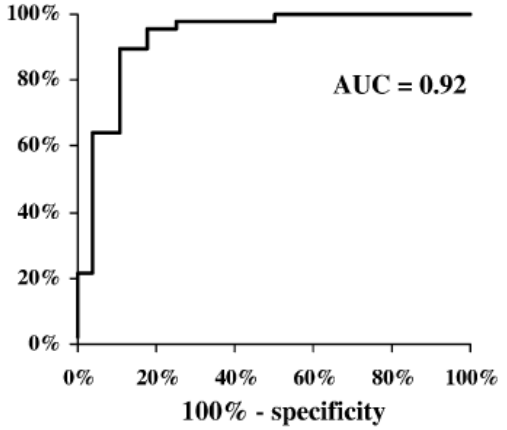


Panel A



Panel A





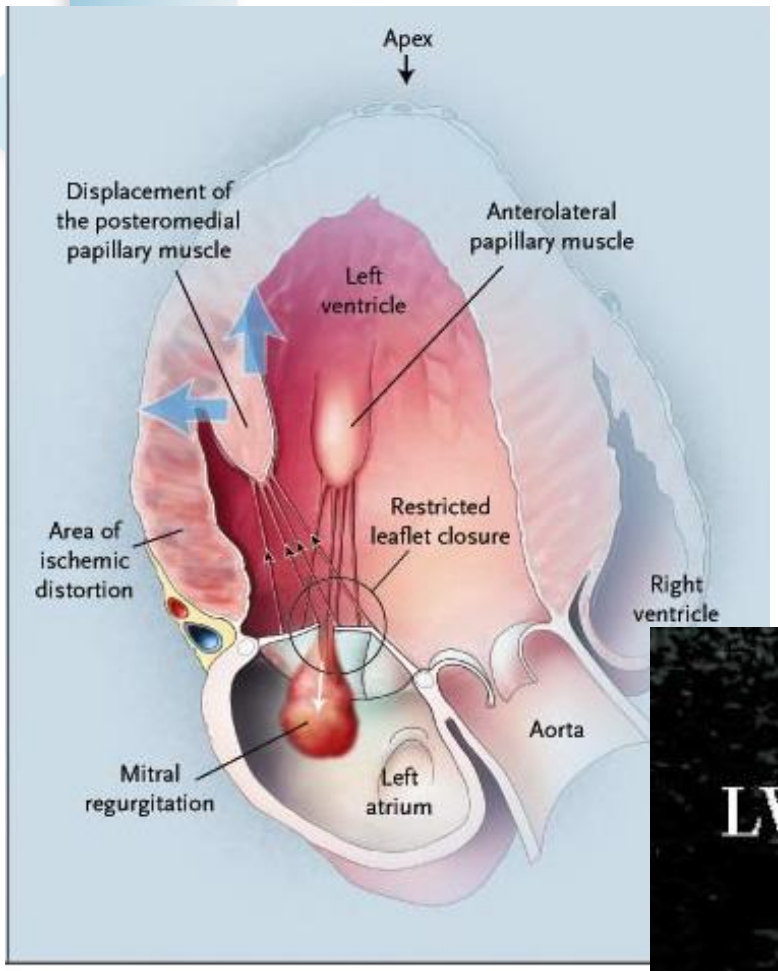
Braun J et al. Eur J of Cardio-thoracic Surg 2005; 27:847–853

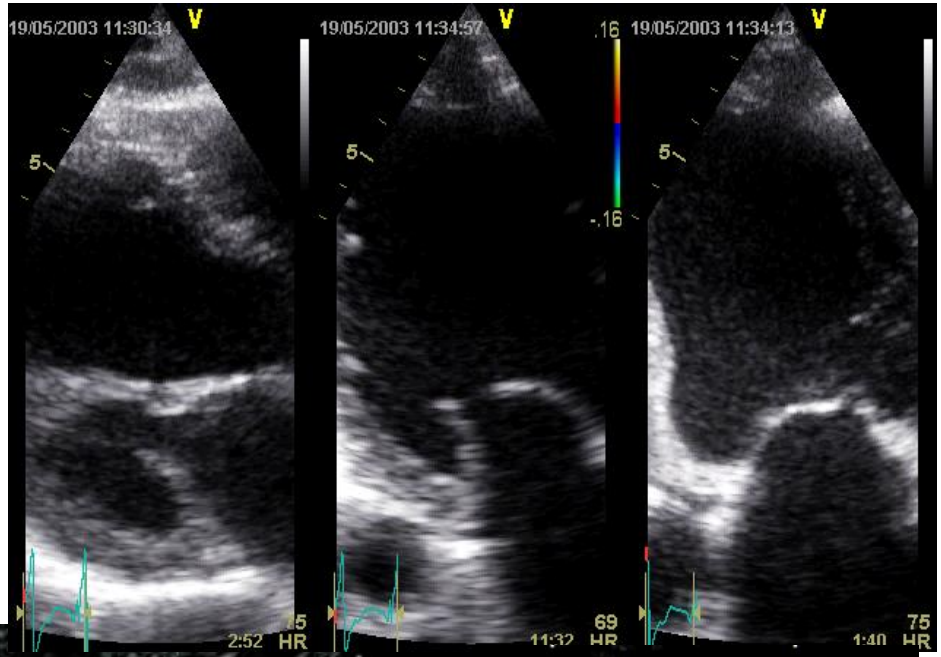
Diagnosis of MR

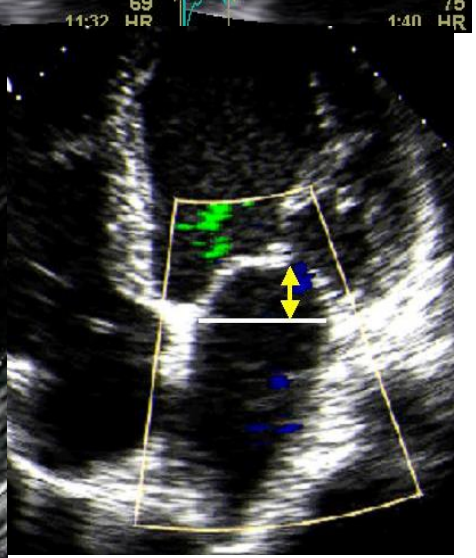
- Earlier diagnosis and treatment of SMR is crucial!
  - Poor prognosis on OMT
  - Break the vicious circle
  - Avoiding extensive LV-remodeling / LV-dysfunction
  - Higher chance of LV reverse remodeling

- Low-threshold for TTE
- SMR can be dynamic!
- Consider stress echo
  - to identify/provoke dyspnea
  - increase in severity of MR and SPAP
  - High risk patients

Secondary MR

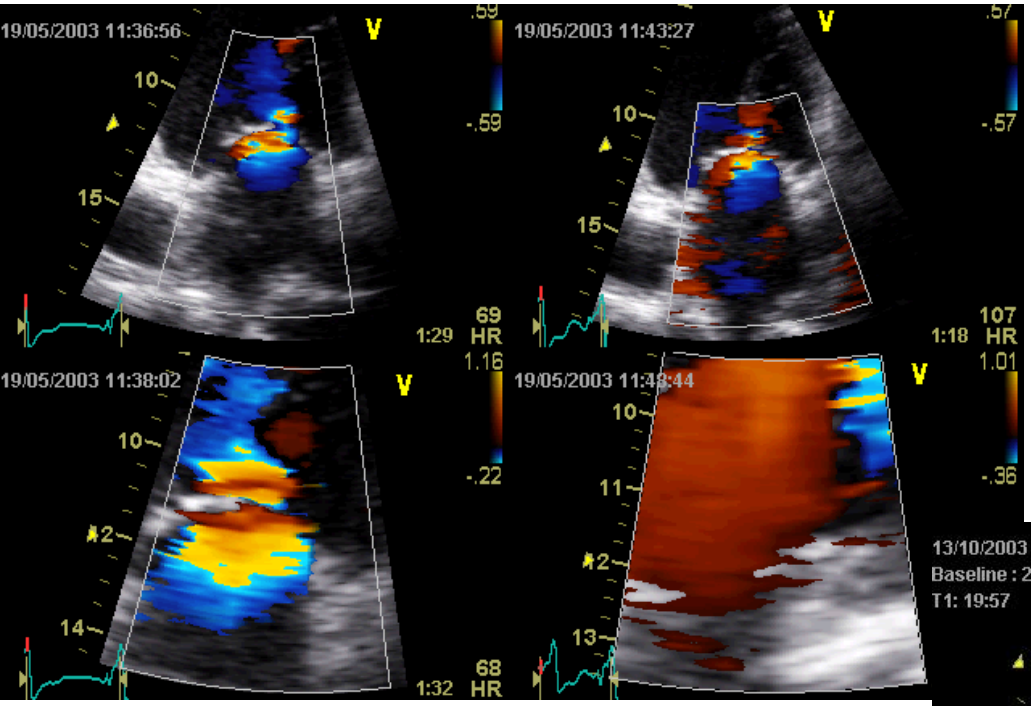




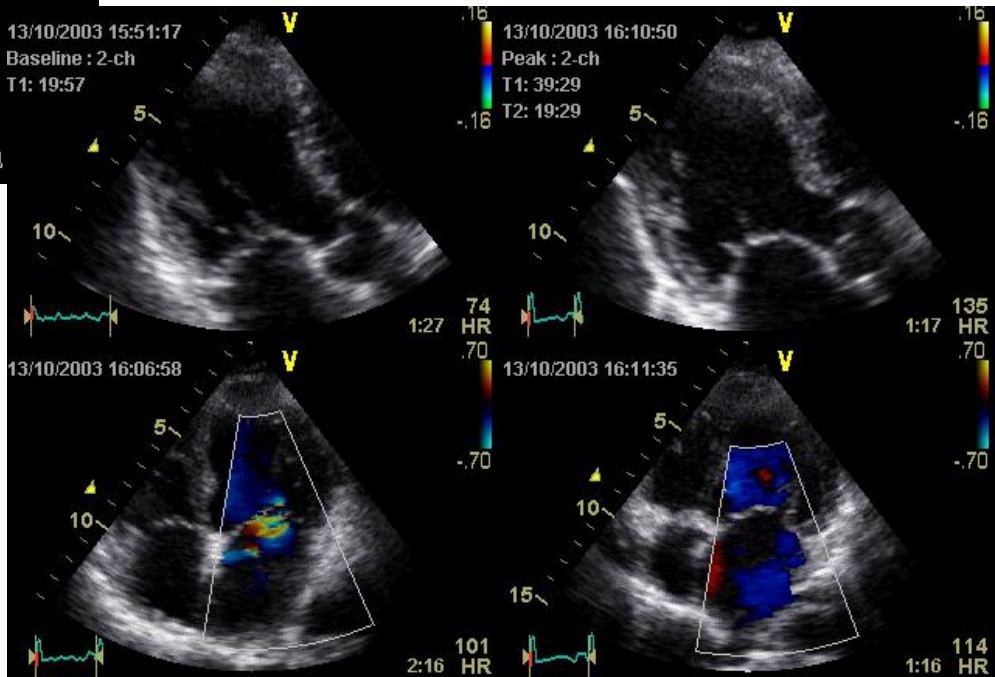


Exercise-induced changes in tethering force

Rest Exercise



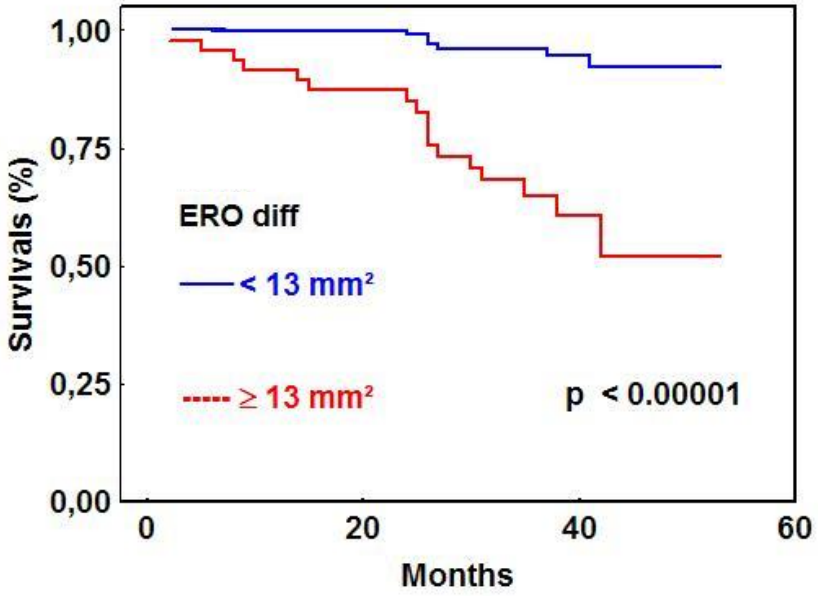
Rest Exercise



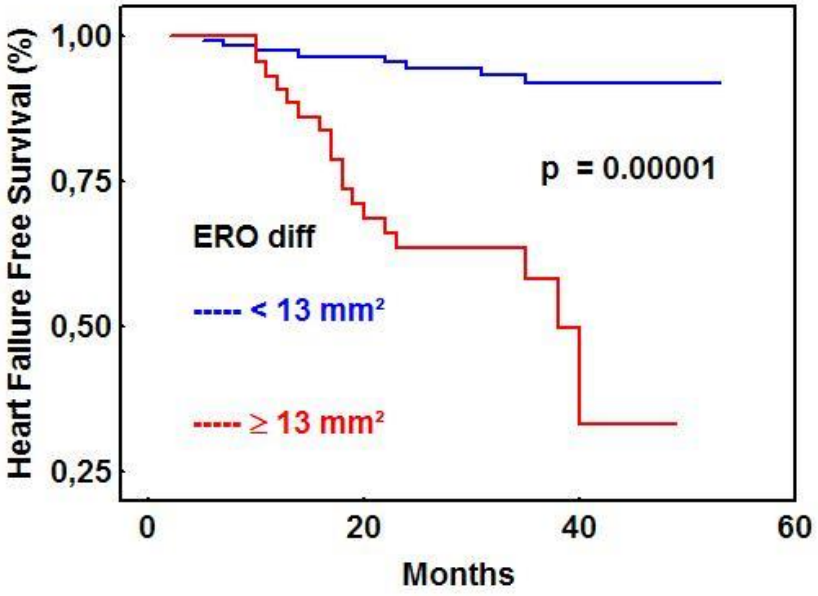
Lancellotti, Lebrun, Piérard JACC 2003, 42,1921-28

Prognosis of dynamic SMR

Survival

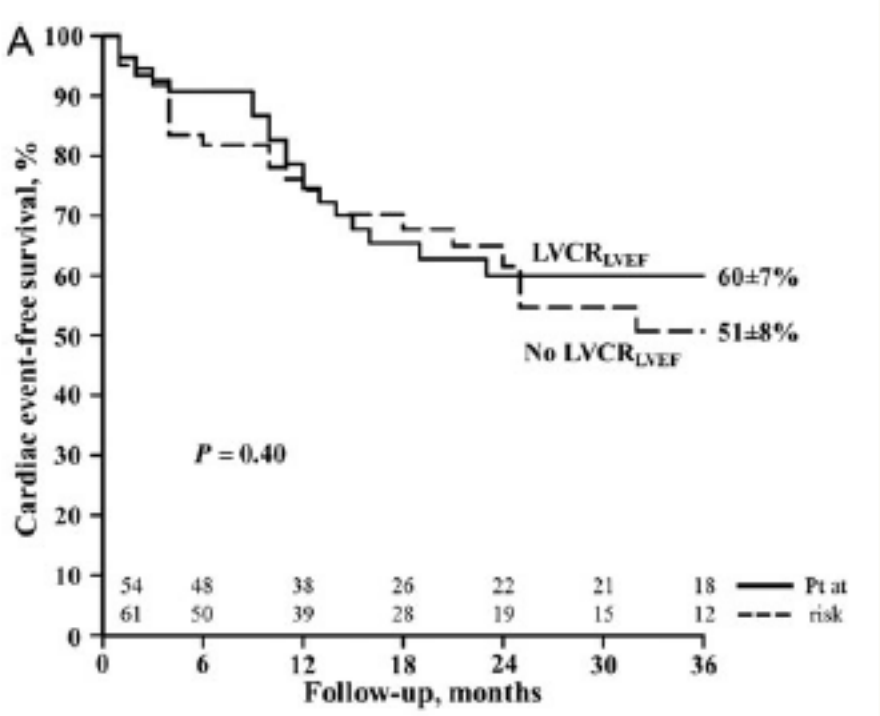


Heart failure

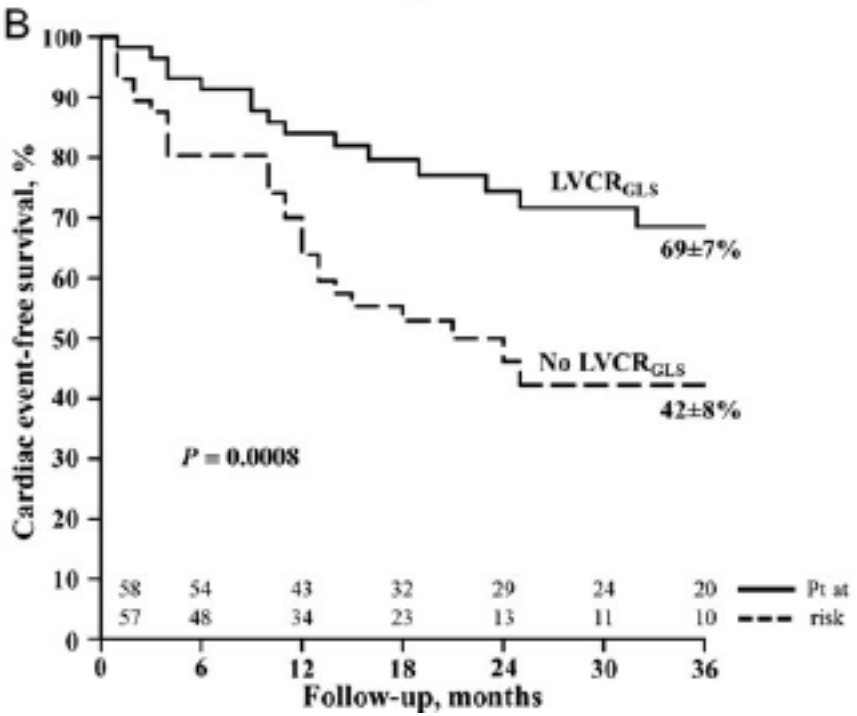


Lancellotti, Gérard, Piérard. Eur Heart J 2005;26:1528-32

Contractile reserve



LVEF



GLS

Magne et al. EHJ 2014

MV-surgery in MR

High-risk MV-surgery

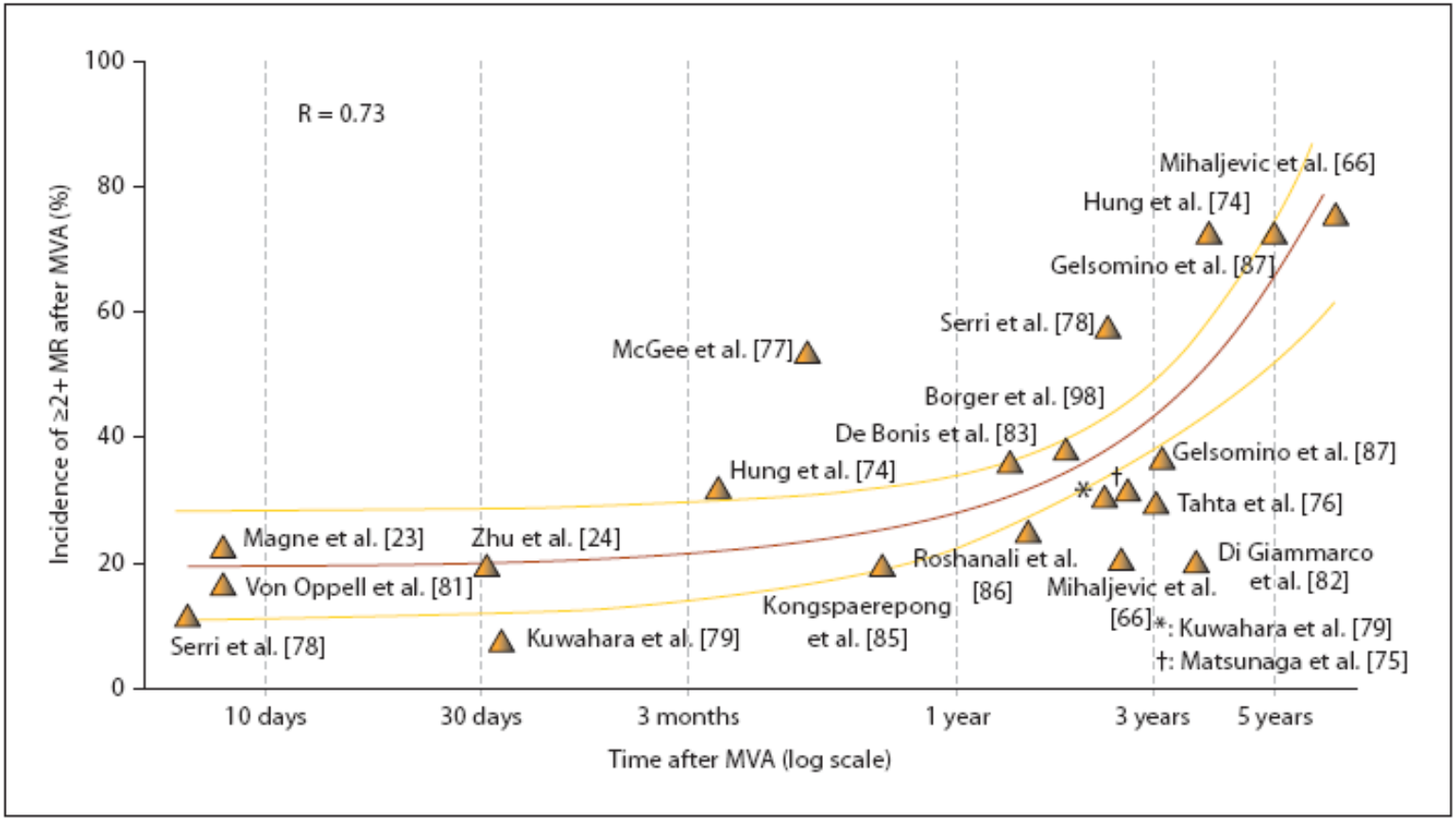
- Symptomatic patients with a severe MR have a class I recommendation for surgery
- Up to 50% of patients are not referred to surgery
- Even higher when accompanied by heart failure

- Operative risk not negligible in SMR!
- In-hospital mortality ranges between 5-10%, up to 25% in high risk patients

- High rates of residual or recurrent MR

Iung B et al. The Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231–43.
Goel SS et al. J Am Coll Cardiol 2014;63:185-6

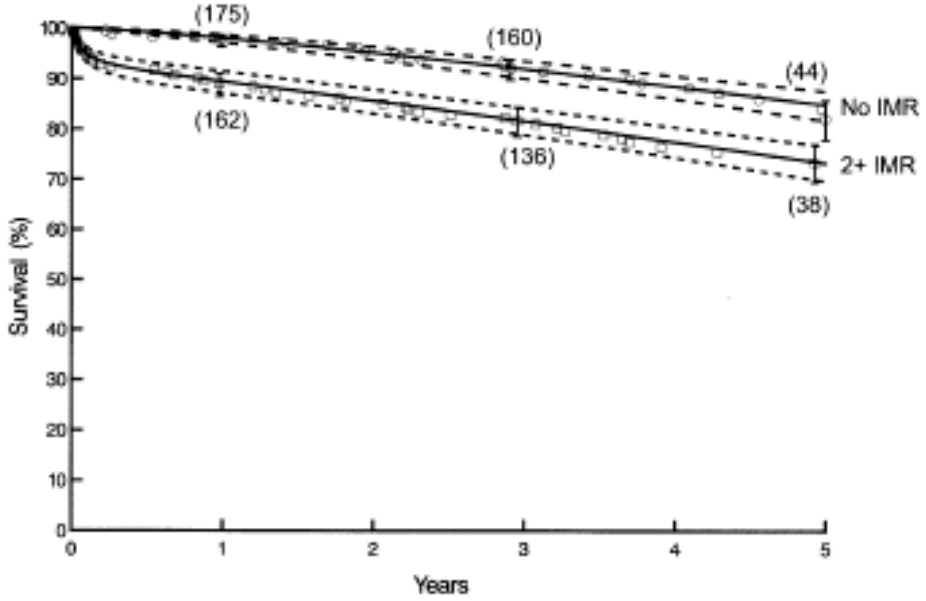
Residual / recurrent MR > 2+ after undersized annuloplasty

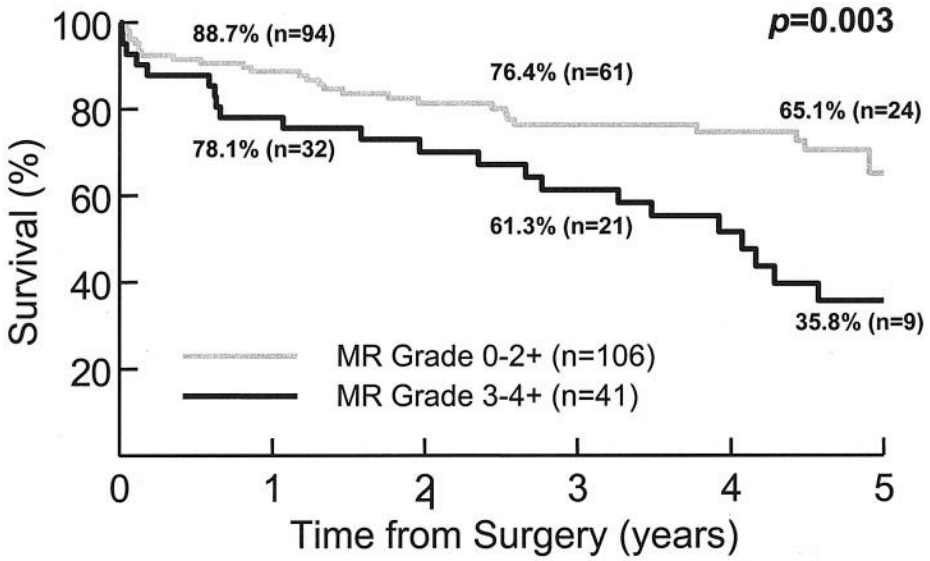


Magne et al. Cardiology 2009;112:244.

Residual or recurrent MR worsens prognosis

- Recurrence of MR also parallels the absence of LV-remodeling

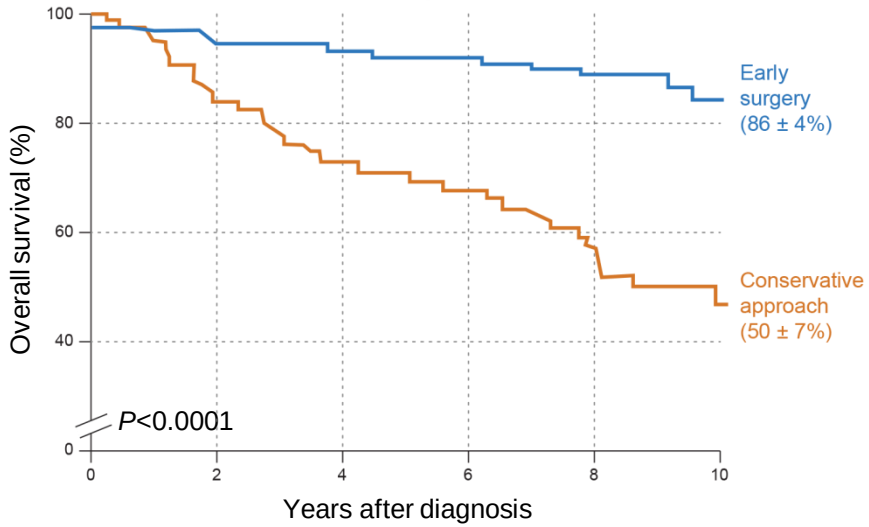




De Bonis M et al. Ann Thorac Surg 2008;85:932-9
McGee EC et al. JTCVS 2004;128:916-24
Mihaljevic et al. J Am Coll Cardiol 2007;49:2191-201
Crabtree TD et al. Ann Thorac Surg 2008;85:1537-43

Early surgical intervention improves outcomes

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



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

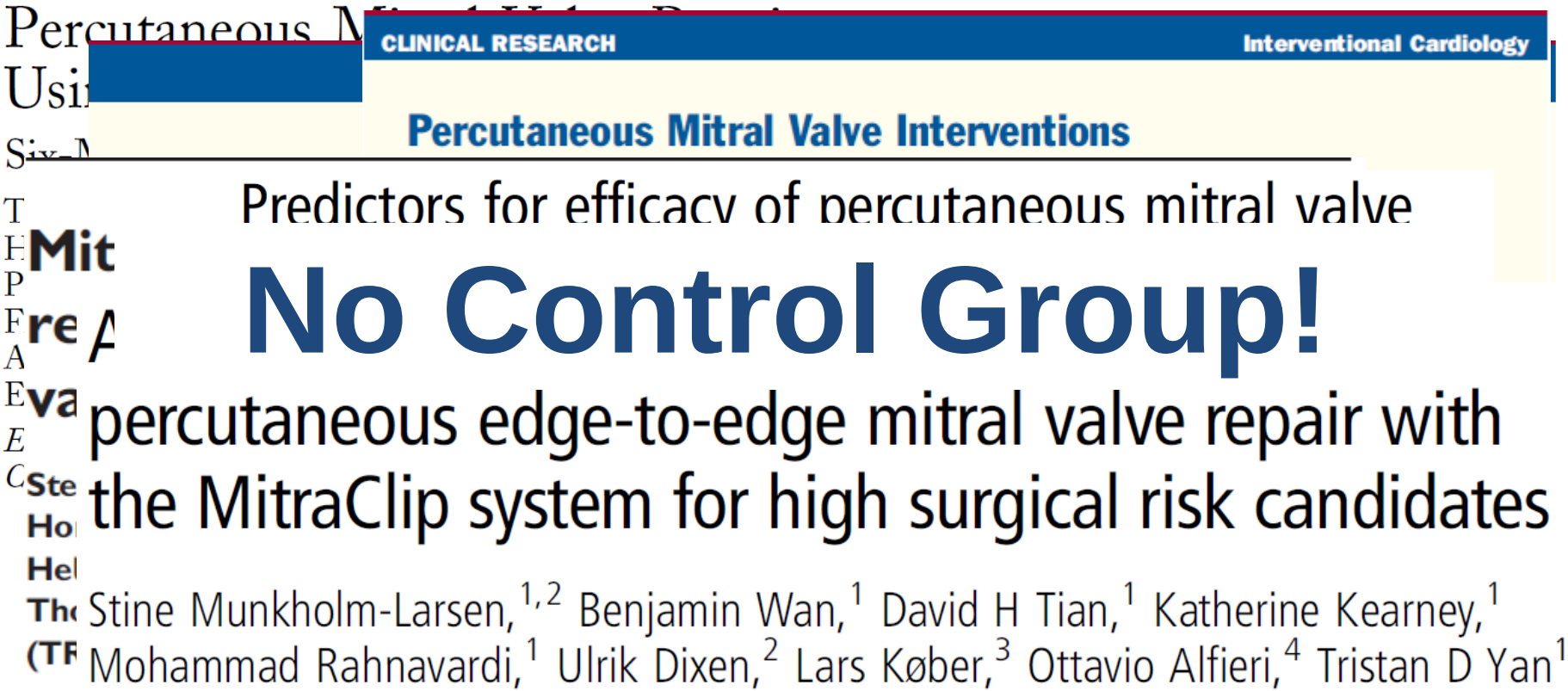
Otto, C. Heart 2003

Montant et al. J Thorac Cardiovasc Surg 2009

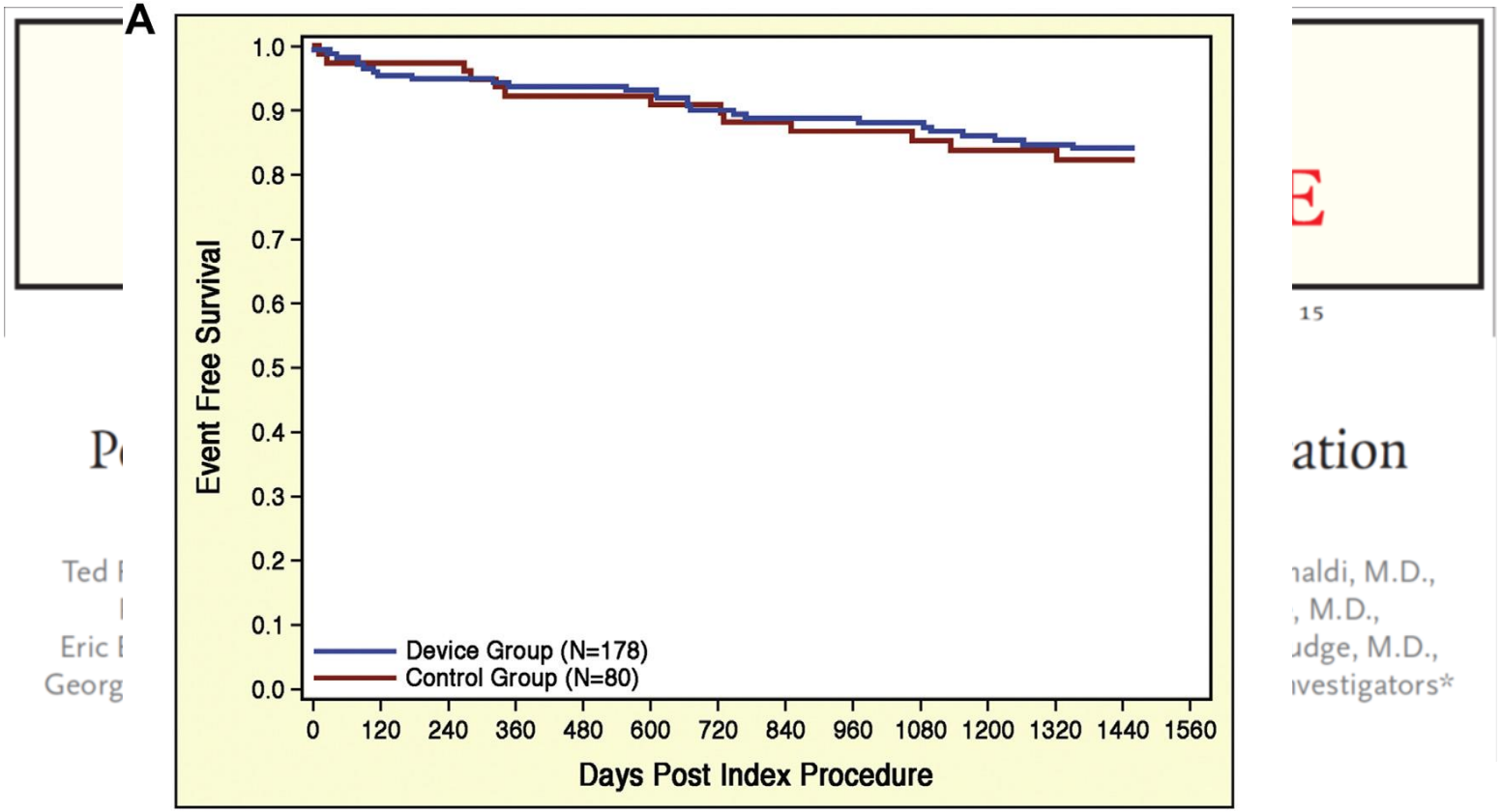
MitraClip a solution?

Introduction

Multiple studies shown feasibility and efficacy of MitraClip



EVEREST II



- Not high risk patients! All surgical candidates!
- Only 27% with FMR
- No data comparing MitraClip vs surgery vs conservative treatmen in high surgical risk patients

ZIEKENHUIS ST ANTONIUS

Survival of transcatheter mitral valve repair compared to surgical and conservative treatment in high risk patients

MJ Swaans, ALM Bakker, A Alipour, MC Post, JC Kelder, TL de Kroon, FD Eefting, BJWM Rensing,

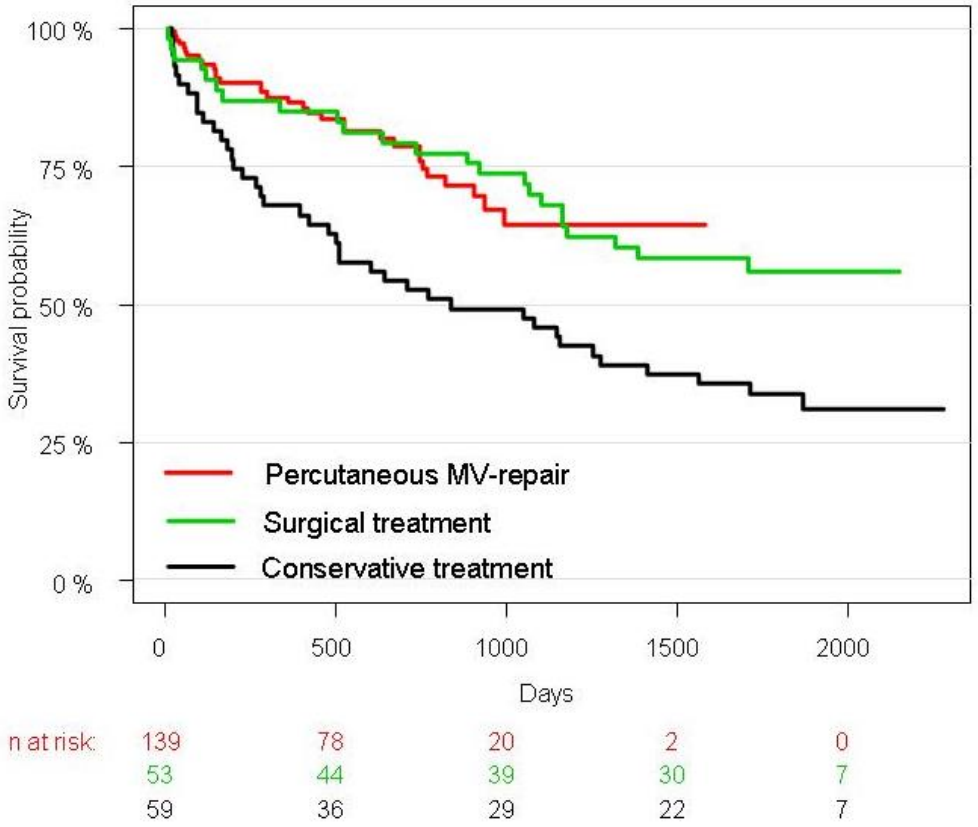
JAS Van der Heyden

JACC Cardiovasc Interv. 2014 Aug;7(8):875-81.

St Antonius Hospital, Nieuwegein, The Netherlands

MitraClip intervention improves survival

Kaplan-Meier Survival Curves



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 et al. JACC Cardiovasc interventions 2014

Results

- After weighting for propensity score MitraClip as well as MV-surgery showed superior survival rates compared to the conservative group

- MitraClip vs. conservative treatment

  HR=0.41 95%CI [0.22 - 0.78], p=0.006

- Surgical treatment vs. conservative treatment

  HR=0.52 95%CI [0.30 - 0.88], p=0.014

- Both treatment groups did not differ statistically significantly: surgical treatment vs. MitraClip

  HR=1.25 95%CI [0.72 – 2.16], p=0.43

Is MitraClip the first choice for FMR?

- Surgical treatment of FMR is associated with
  - High hospital mortality (up to 25%)
  - High recurrence rate
  - Long hospital stay
  - Unproven survival benefit

- Mitraclip for FMR
  - Procedure more simple than for DMR
  - Improvement of symptoms at low risk
  - Failure does not modify the surgical option

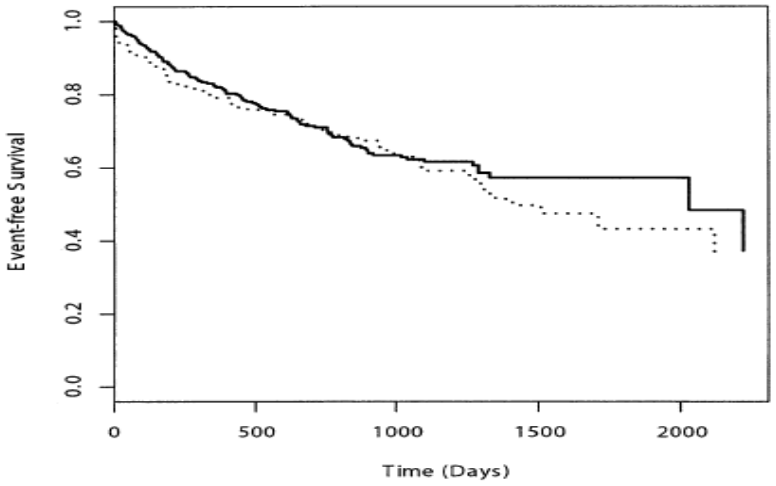


Figure 1. Event-free survival for non-mitral-valve annuloplasty (MVA) group **(solid line)** and MVA group **(dotted line)**.

Results - FMR

- Same trend was observed if only FMR patients were considered

- MitraClip vs. conservative treatment
  HR=0.46 95%CI [0.23 - 0.93], p=0.03
- Surgical treatment vs. conservative treatment
  HR=0.54 95%CI [0.29 – 1.02], p=0.057

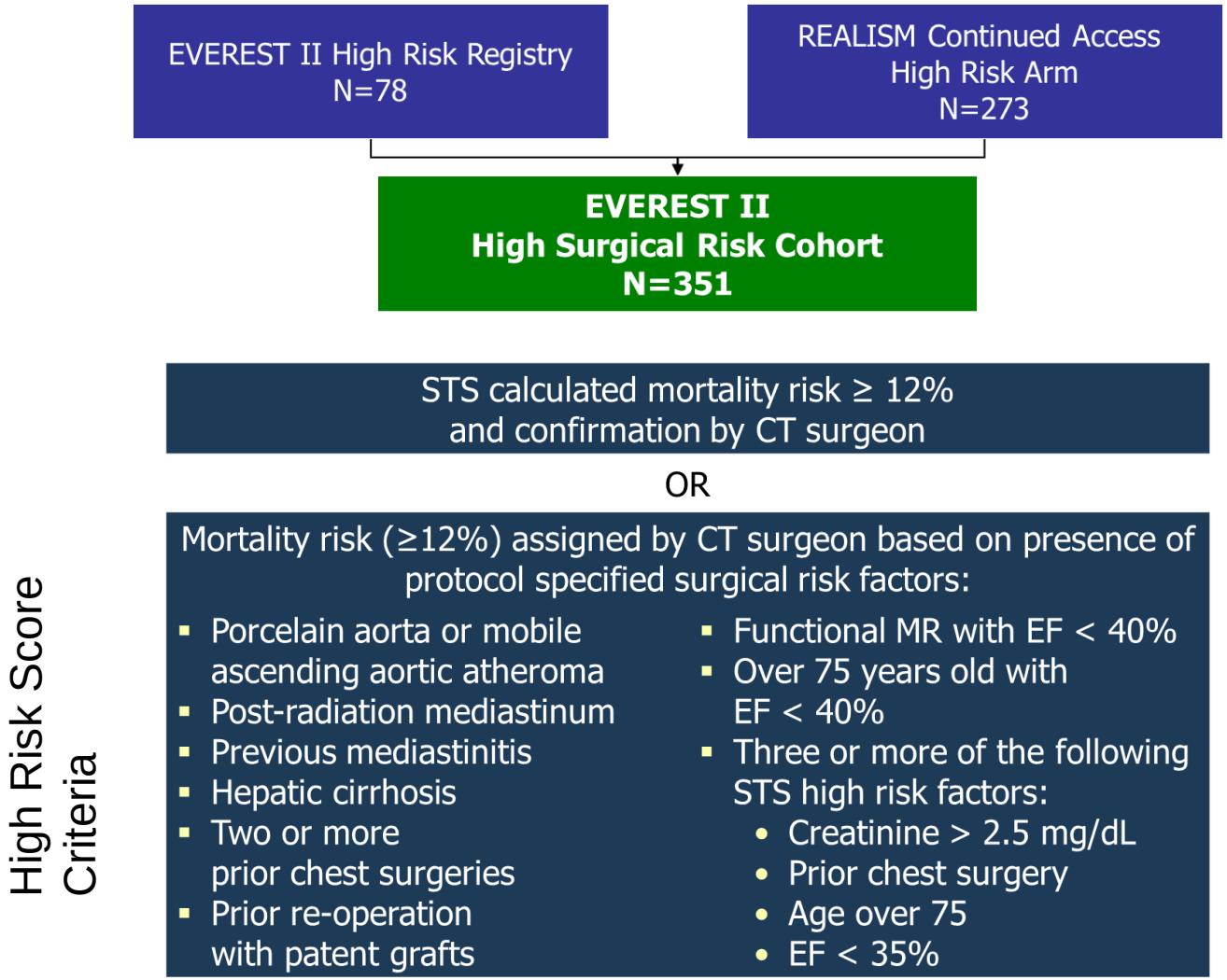
- Both treatment groups did not differ statistically significant: surgical treatment vs. MitraClip
  HR=0.84 95%CI [0.45 – 1.59], p=0.60.

The MitraClip and Survival in Patients with Mitral Regurgitation at High Risk for Surgery: A Propensity-Matched Comparison

Eric J. Velazquez MD, Zainab Samad MD, MHS, Hussein R. Al-Khalidi PhD, Chithra Sangli MA, Paul A. Grayburn MD, Joseph M. Massaro PhD, Susanna R. Stevens MS, Ted E. Feldman MD, Mitchell W. Krucoff MD

The American Journal of Cardiology

Selection of patients



Duke database served as a foundation for this analysis

Duke Echocardiography Laboratory Database (DELD)

Comprehensive digital archive of all clinically performed echocardiograms linked to a searchable reporting database.

Duke Databank for Cardiovascular Diseases (DDCD)

Ongoing clinical follow up on patients referred for cardiac catheterization since 1969 at 6 months, 1 year and then annually thereafter to obtain vital status, hospitalizations and medication usage.

Duke High-Risk Cohort

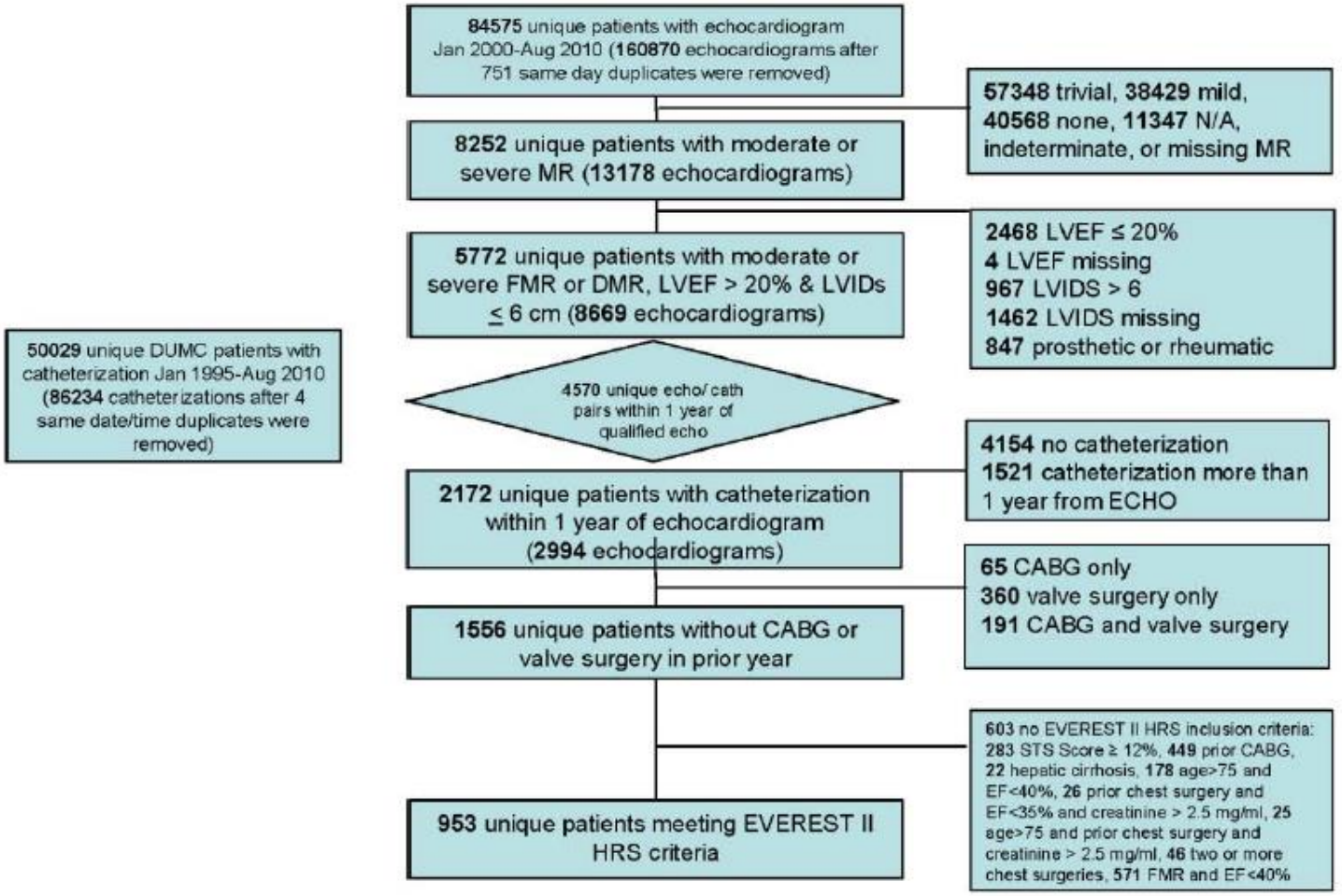
DELD and DDCD databases merged for patients treated between **January 2000 and August 2010**. MR severity was obtained from DELD clinical report and visually estimated. Baseline data for event reporting was the date of the first transthoracic echo that reported moderate-to-severe MR. Key inclusion criteria includes:

- Moderate-to-severe MR
- 3+/4+ DMR or FMR on angiography
- LVEF > 20%
- LVID ≤ 6 cm
- No mitral valve surgery within first year of echo
- High risk status as defined for MitraClip patients

953 Patients

Duke researchers identified high risk patients by using several screening criteria.

Figure 1: Flow chart for extracting Duke MT cohort (N=953 Patients) from Duke database (DELD)



Velazquez E J., et al. *American Heart Journal* 2015

Difference in demographics, creating the need for propensity matching

Table I. Demographic and baseline characteristics of Duke and MitraClip high-risk cohorts

Characteristic	MitraClip high-risk patients (N = 351)	Duke high-risk patients (N = 953)	P
Age, mean±SD, y	75.7±10.5	68.5±13.2	<.0001
Age >75 y	58.1 (204)	36.1 (344)	<.0001
Male sex	61.0 (214)	48.9 (466)	.0001
BMI, mean±SD, kg/m^2	26.9±11.6	27.1±6.18	.0082
Previous cardiac surgery	59.8 (210)	49.9 (476)	.0018
MI	50.7 (177)	42.8 (408)	.0119
NYHA class III/IV	84.9 (298)	46.6 (440)	<.0001
COPD*	11.1 (39)	7.1 (68)	.0230
Stroke	12.8 (45)	14.7 (140)	.4214
Diabetes	39.4 (138)	35.5 (338)	.1946
Hypertension	89.5 (314)	71.5 (681)	<.0001
Renal disease	30.5 (107)	18.5 (176)	<.0001
Atrial fibrillation	68.5 (217)	51.7 (493)	<.0001
MR etiology			<.0001
Functional	70.1 (246)	93.2 (888)	
Degenerative	29.9 (105)	6.8 (65)	
LVEF, mean±SD, %	47.5±14.2	36.7±10.9	<.0001
LVID, mean±SD, systole (cm)	4.36±1.11	4.18±0.95	.0249
STS valve replacement score, mean±SD	11.3±7.70	9.66±8.83	<.0001

Values are presented as percent (number), unless otherwise indicated.
*COPD was defined as dyspneic with the use of home oxygen.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVID, left ventricular internal dimension; MI, myocardial infarction.

Propensity matching addressed certain variables such as age, gender, history of MI, stroke, NYHA status and LVEF at baseline

Velazquez E J., et al. *American Heart Journal* 2015

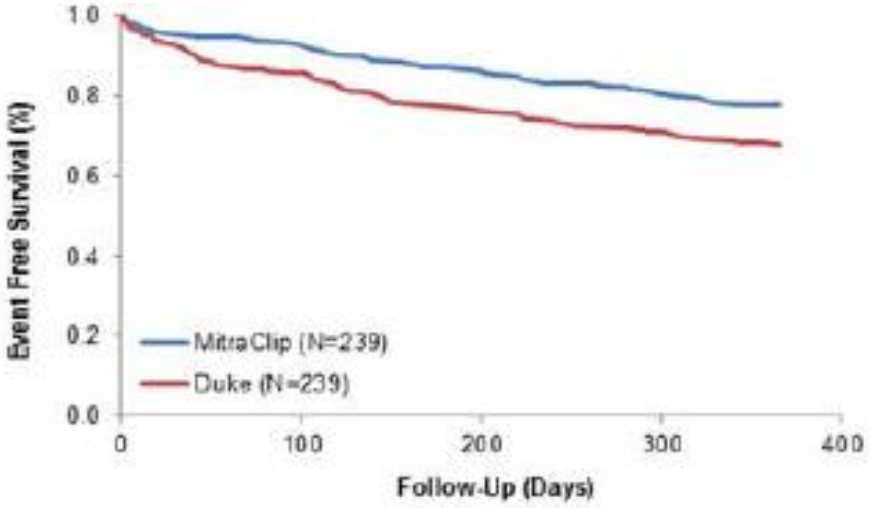
Optimally matched patients

Table II. Demographic and baseline characteristics of propensity-matched patients

Characteristic	MitraClip high-risk patients (N=239)	Duke high-risk patients (N=239)	*P*
Age, mean±SD, y	73.7±10.5	73.7±11.0	.8734
Age >75 y	51.0 (122)	53.6 (128)	.6471
Male sex	59.8 (143)	54.4 (130)	.2674
BMI, mean±SD, kg/m^2	27.3±13.3	27.0±5.48	.1438
Previous cardiac surgery	60.3 (144)	55.2 (132)	.3084
MI	52.1 (124)	45.6 (109)	.1699
NYHA class III/IV	78.2 (187)	79.8 (190)	.7360
COPD*	9.2 (22)	9.6 (23)	1.0000
Stroke	14.2 (34)	15.1 (36)	.8972
Diabetes	39.5 (94)	43.9 (105)	.3535
Hypertension	87.9 (210)	81.6 (195)	.0745
Renal disease	26.8 (64)	25.9 (62)	.9173
Atrial fibrillation	64.9 (137)	58.2 (139)	.1469
MR etiology			.0144
Functional	82.8 (198)	90.8 (217)	
Degenerative	17.2 (41)	9.2 (22)	
LVEF, mean±SD, %	41.5±12.0	42.0±10.7	.3073
LVID, mean±SD, systole (cm)	4.71±1.00	3.91±0.97	<.0001
STS valve replacement score, mean±SD	9.93±7.00	13.8±10.9	.0001

Values are presented as percent (number), unless otherwise indicated.
*COPD was defined as dyspneic with the use of home oxygen.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVID, left ventricular internal dimension; MI, myocardial infarction.

MitraClip intervention improves survival



No. at risk	Day 0	Day 30	Day 180	Day 365
MitraClip	239	226	202	175
Duke	239	219	179	142

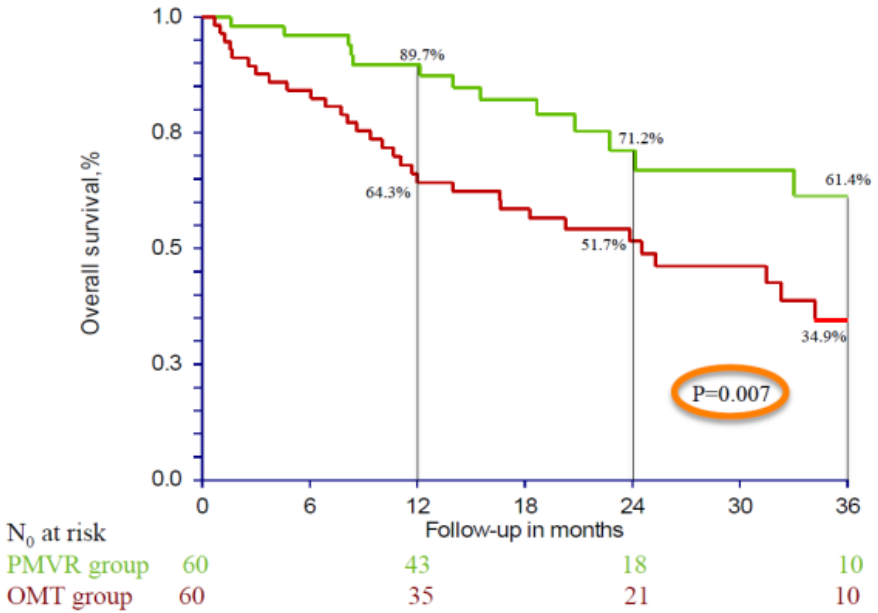
- 351 MitraClip patients vs propensity matched patients on OMT
- OMT patients from the DUKE Echo Laboratory Database (85.000)
- 239 optimally matched patients with identical baseline characteristics
- 1 year mortality rates wre 22.4% for MitrClip vs 32.0% for OMT

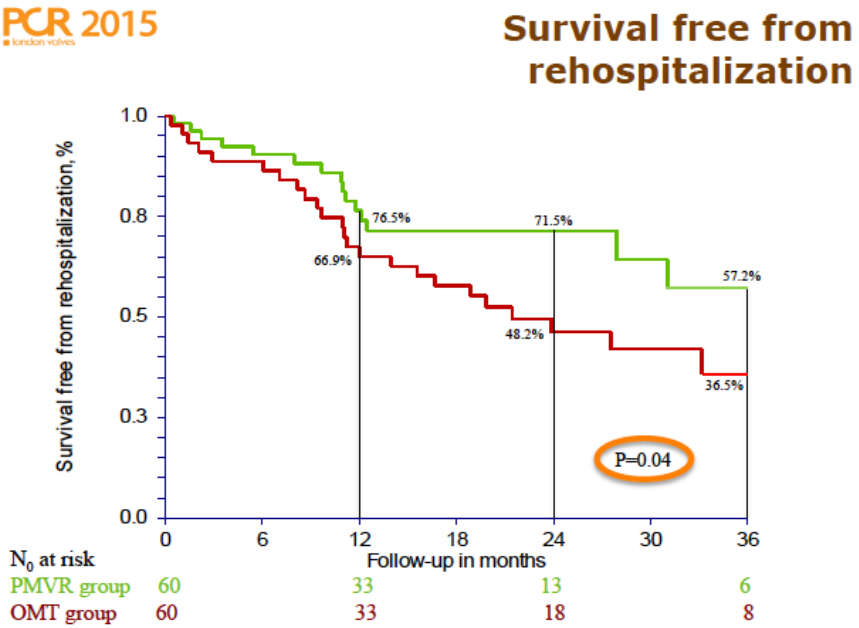
Velazquez et al. JACC Cardiovasc interventions 2014

Comparison of Percutaneous Mitral Valve Repair Versus Conservative Treatment in Severe Functional Mitral Regurgitation

Cristina Giannini, MD, PhD, Francesca Fiorelli, MD, Marco De Carlo, MD, PhD, Fabio Guarracino, MD, Michela Faggioni, MD, Paolo Giordano, MD, Paolo Spontoni, MD, Andrea Pieroni, MD, Anna Sonia Petronio, MD

MitraClip intervention improves survival





- 70 Mitraclip patients compared to 90 OMT patients, only FMR
- 60 optimally matched patients
- Overall survivalrates after 1 year: 89.7% vs 64.3%
- 3 year survival was 61.4% vs 34.9%
- Significanlty lower rehospitalization rates

Giannini C et al. Am J Cardiol. 2016

Conclusions

- ***Poor prognosis*** in absence of surgery
- Even with optimal medical therapy

- Break the vicious circle of MR

- ***Early*** diagnosis and treatment is crucial

- Up to 50% of patients are not referred to surgery

- Already 3 studies have shown that 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)

‘***move the timing of intervention earlier in the disease course*** *with the goal of preventing irreversible LV dysfunction, arrhythmias and pulmonary hypertension due to longstanding LV volume overload****.’***

Nishimura RA, et al. Heart 2014