

Michigan ACC 2010

Timing of Surgery for Primary Mitral Regurgitation: Early Intervention or Watchful Waiting

George S. Hanzel, MD, FACC, FSCAI
Director, Structural Heart Disease
Beaumont Hospital
Royal Oak, MI

9 October 2010



Disclosures

No Relevant Disclosures

Outline

- Adherence to guidelines
- Review study data supporting current guidelines
- Review four observational studies of management of severe asymptomatic MR patients without accepted indications for surgery
- Risk stratification with exercise and B-Type Natriuretic Peptide

LV Response to Severe MR

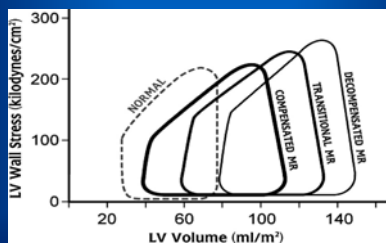
Table. LV Structure and Function in the 3 Stages of Chronic MR

Stage 1	Chronic compensated MR with LV enlargement, eccentric hypertrophy, and normal systolic function
Stage 2	Transitional phase with mild LV dysfunction that is reversible after surgical correction of the regurgitant lesion
Stage 3	Decompensated MR with progressive and irreversible structural and functional changes in the ventricle

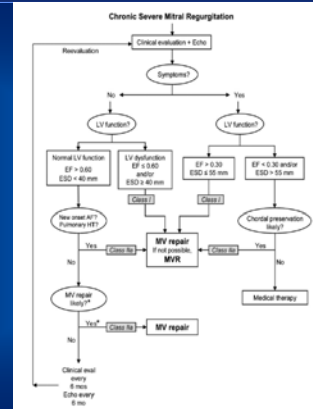
Gaasch and Meyer. *Circulation*. 2008;118:2298-2303

Complications Related to Severe MR

- Occult LV Dysfunction
- Sudden Cardiac Death
- Atrial Fibrillation

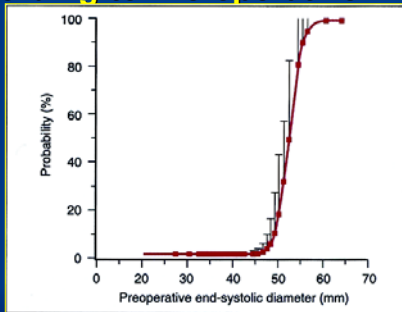


Gaasch and Meyer. *Circulation*. 2008;118:2298-2303



ACC/AHA 2006 Practice Guidelines JACC 2006;48:598-675

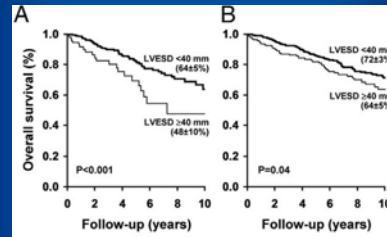
Post-operative Death or CHF According to Pre-operative LVESD



Adapted From: Wisenbaugh et al. *Circ* 1994;89:191

Survival According to LVESD

MIDA Registry: 739 patients with flail leaflets

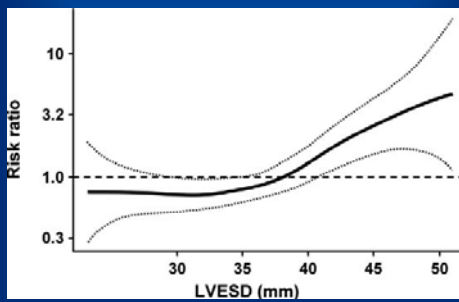


Patients at risk

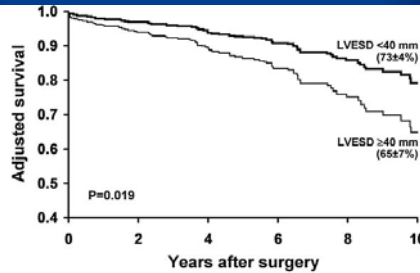
Follow-up (years)	0	2	4	6	8	10
<40mm	545	206	140	88	50	21
>40mm	194	44	29	13	8	4

Tribouilloy et al. *JACC* 2009;54:1961-1968

Association of LVESD and Mortality in Conservative Management



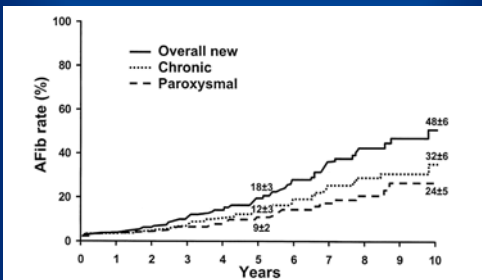
Tribouilloy et al. *JACC* 2009;54:1961-1968



Patients at risk

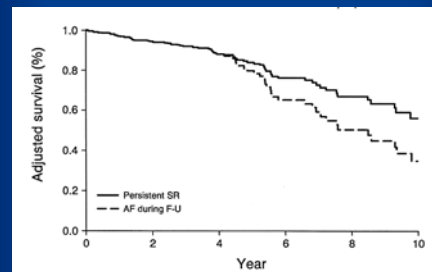
Years after surgery	0	2	4	6	8	10
<40mm	393	303	230	149	86	38
>40mm	159	128	92	70	32	13

Incidence of AF in Conservatively Managed Flail Leaflet



Grigioni et al. *JACC* 2002;40:84-92

Survival According to SR vs AF



RR 3.42, 95% CI 1.7-6.7

Grigioni et al. *JACC* 2002;40:84-92

Pulmonary Hypertension

- Has not been adequately studied
- RV dysfunction due to pulmonary hypertension in severe MR associated with sudden death
 - 50% mortality at 2 years
- Mild pulmonary hypertension may predict development of CHF or indications for surgery
 - < 40 mmHg, 40-45 mmHg, 46-50 mmHg
 - Hazard Ratio 1.87 (95% CI 1.22-2.87, p=0.003)

Hochreiter et al. *Circulation* 1986;73:900-912
Kang et al. *Circulation* 2009;119:797-804

Surgery for All Asymptomatic Severe MR Patients?

- Volume overload will ultimately cause LV dysfunction and CHF
 - Will we miss the golden window during "watchful waiting"?
- Postponing surgery may result in sudden death
- High rate of atrial fibrillation
- Low operative mortality
 - Asymptomatic patient <1%
- Low rate of reoperation
- Minimally invasive approaches



Mitral Repair vs Replacement

- Repair rate in United States = 69%
- Repair rate in Europe = 46.5%

Advantages of Repair

- Maintenance of LV function and geometry
- Low rates of thromboembolism
- Resistance to endocarditis
- Durability
- No need for anticoagulation
- Lower operative mortality

Reoperation rate 7-11% at 10 years

Perioperative Stroke ~1.5%

Gammie et al. *Ann Thorac Surg* 2009;87:1431-1439
Iung et al. *Eur Heart J* 2003;24:1231-1243

Surgery for Asymptomatic Severe MR without Accepted Indications?

- What is the annual risk of death?
- What is the annual risk of occult LV dysfunction and CHF?
- What is the repair rate at your institution?
- What is the predicted operative mortality for any individual patient?
- Can patients be further risk stratified?

Study	Number of patients	Symptoms	MR cause	MR severity	Age (years)	LV diameter (mm)	Study specifics	Yearly mortality	Yearly cardiac events	Relative risk (95% CI) with surgery
Enriquez-Sarano, et al. ¹¹	129	0	Organic	Moderate (ERO area 20-30 mm ²)	65	58	Quantitative, prospective	3%	6%	-
Bowdler, et al. ¹²	332	0	Degenerative	Moderate to severe	55	58	Bedside cardiac, prospective	6%	6%	-
Avolio, et al. ¹³	253	0	MFP	Moderate to severe	60	58	Community based	6%	14%	-
Iung, et al. ¹⁴	279	0%	Flail leaflets	Severe	66	64	Case specific, 6-7% reop, 4-5% without symptoms	10-12%	0.29 (0.15-0.58)	-
Grigori, et al. ¹⁵	360	0%	Degenerative in MR	Severe	65	66	Case specific	6%	10-12%	-
Roos, et al. ¹⁶	33	0	Organic	Severe	52	65	Prospective, with exercise	-	10%	-
Enriquez-Sarano, et al. ¹¹	198	0	Organic	Severe (ERO area >40 mm ²)	61	61	Quantitative, prospective	9%	15%	0.28 (0.14-0.55)

ERO=effective regurgitant orifice; LV=left ventricle; MR=mitral regurgitation; MFP=mitral valve prolapse; M=mitral; D=diastolic; ERO=effective regurgitant orifice. *Data for patients with exclusively or mostly moderate MR (as shown by slight mitral valve enlargement or quantitative measures), showing average yearly mortality of about 2%. *Mortality compared during the first 2 years of follow-up. †Part of the same study of 408 asymptomatic patients with quantified MR. ‡Data for patients with exclusively or mostly severe mitral regurgitation (as shown by substantial mitral valve enlargement or quantitative measures), showing average yearly mortality of about 6%. ‡Data for patients with moderate to severe mitral regurgitation, mortality decreased by about 70%.

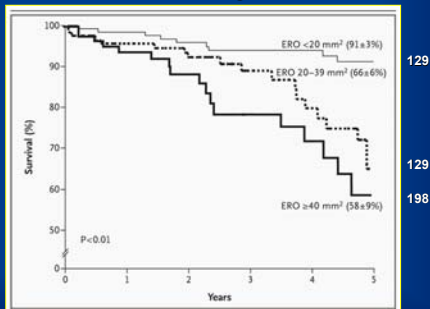
Table 3. Clinical outcomes of organic mitral regurgitation under medical management

Natural History: Mayo Clinic

- 456 patients with asymptomatic primary MR
- Prospectively enrolled
- MR measured quantitatively
- Clinical management according to personal physician recommendations
- Follow-up and treatment not pre-specified
- Outcomes collected retrospectively

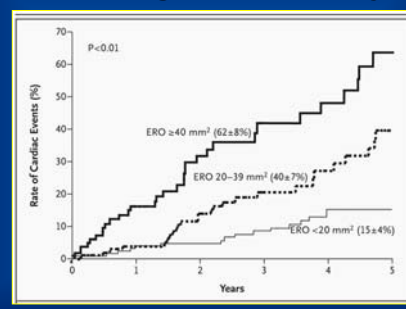
Enriquez-Sarano M et al. *NEJM* 2005;352:875

Mayo Clinic: Survival According to MR Severity



Enriquez-Sarano M et al. NEJM 2005;352:875

Mayo Clinic: Cardiac Event Rate According to MR Severity



Enriquez-Sarano M et al. NEJM 2005;352:875

Natural History: Mayo Clinic

- 232 patients underwent surgery
 - 94 = symptoms
 - 91 = echo parameters
 - 47 = patient or physician discretion
- Decreased subsequent risk of death on multivariate analysis (RR 0.28)

Conclusion: patients with ERO > 40mm² should be considered for early surgery

Enriquez-Sarano M et al. NEJM 2005;352:875

Asan Registry: Event Free Survival

- 447 consecutive patients with severe asymptomatic MR
- PISA radius ≥ 8mm and no classic indications for surgery
- 1998 ACC/AHA guidelines
- 161 early surgery, 286 conventional rx
- End Point: Operative death, cardiac death, repeat surgery, CHF

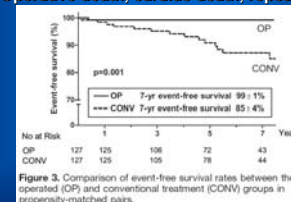


Figure 3. Comparison of event-free survival rates between the operated (OP) and conventional treatment (CONV) groups in propensity-matched pairs.

Seven Year Cardiac Mortality Rate: 0% vs 5% (p=0.008)

Kang et al. Circulation 2009;119:797-804

Table 4. Comparison of Echocardiographic Results Between the Early Surgery Group and Those Who Had Late Surgery

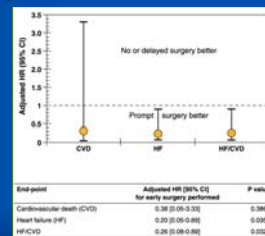
	Early Surgery Group (n=161)			Late Surgery Group (n=53)		
	Preop	Postop	Follow-Up	Baseline	Postop	Follow-Up
LVEDD, mm	36±5	34±6†	31±5*	37±4	37±6	33±5
LVEDV, mm	59±6	49±7*	49±5	60±5	51±6	50±6
LVESV, mL	45±16	38±17†	36±74*	47±14	48±19	42±12
LVEDV, mL	130±40	85±28†	90±28*	136±37	105±33	102±25
EF	0.66±0.05	0.56±0.09	0.60±0.06	0.65±0.05	0.55±0.08	0.59±0.05

Preop indicates before surgery; Postop, after surgery; LVEDD, LV end-systolic dimension; LVEDV, LV end-diastolic dimension; LVESV, LV end-systolic volume; and LVEDV, LV end-diastolic volume.
*P<0.05, †P<0.01 vs late surgery group.

Kang et al. Circulation 2009;119:797-804

European MIDA Sites: Early vs Delayed Surgery

102 asymptomatic flail leaflets; 70 underwent surgery



Five Year Mortality Rate: 0% MV surgery within 12 months vs 4% initial conservative rx

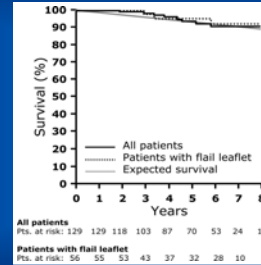
Grigioni F et al. JACC Img 2008;1:133

Natural History: Vienna Study

- 132 consecutive asymptomatic patients with severe MR
- Followed prospectively for 62 months
- MR evaluated quantitatively
 - Vena contracta >6mm and flow convergence radius >7mm
- 12 month follow-up for stable patients with prior echo
- 3-6 month follow-up
 - New patient without prior echo
 - Change from prior echo
 - Echo measurements near prespecified cut-point
- Surgery
 - Symptoms
 - EF <60%, LVESD ≥45mm, RVSP >50mmHg, atrial fibrillation

Rosenhek R et al. Circ 2006;113:2238

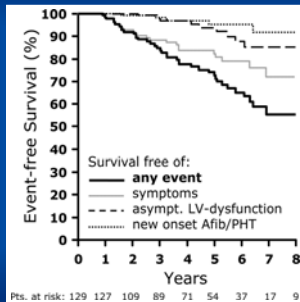
Survival with "Watchful Waiting"



No significant difference from expected survival (p=0.34)

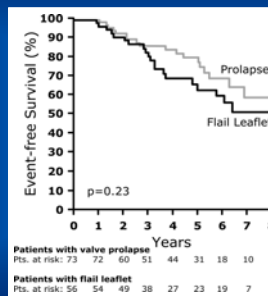
Rosenhek R et al. Circ 2006;113:2238

Event-Free Survival



Rosenhek R et al. Circ 2006;113:2238

Event-Free Survival: Prolapse vs Flail



p=0.23

Rosenhek R et al. Circ 2006;113:2238

Natural History: Vienna Study

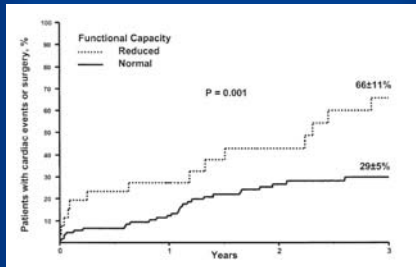
- 35 patients underwent surgery
 - Repair 82.9%
 - Concomitant CABG 22.9%
- No perioperative deaths
- Functional status
 - 23 asymptomatic
 - 4 NYHA I
 - 8 NYHA II
- Post-operative LV dysfunction in 4 patients (2 MVR and 2 with CAD who underwent CABG)

"Watchful waiting" with close follow-up is safe in patients with severe asymptomatic MR

Rosenhek R et al. Circ 2006;113:2238

Risk Stratification

Functional Capacity in "Asymptomatic" Mitral Regurgitation

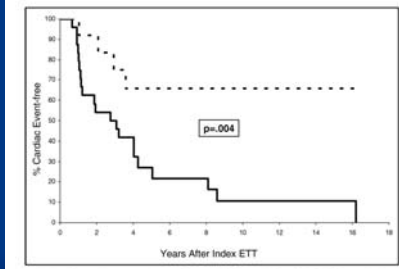


1. Reduced FC defined as < 84% of expected Vo_2 max
2. Death, CHF, new AF 36% vs 13%, p=0.02

Messika Zeitoun et al. JACC 2006;47:2521-2527

Exercise Testing in Asymptomatic MR

Modified Bruce: ≥ 15 min vs < 15 min (10 METS)
Events = SCD, CHF, AF, EF < 60%, LVESD ≥ 45 mm



Supino et al. AJC 2007;100:1274-1281

Predictive Value of Contractile Reserve in Predicting Post-Operative LV Function

Table 4. Sensitivity and Specificity of Diagnostic Cutoff Values of Preoperative Rest and Exercise Indexes of Left Ventricular Function (as determined by receiver operating characteristic curves) in Predicting Early Postoperative Left Ventricular Dysfunction

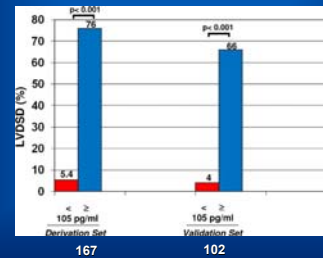
Variable	Optimal Diagnostic Cutoff Value	Specificity	Sensitivity
ESVI _{EXE}	25 cm ³ /m ²	83%	83%
EF _{EXE}	68%	80%	81%
Δ EF _{EXE}	4%	75%	79%
LV dP/dt	1,000 mm Hg/s	73%	65%
ESWS _{REST}	52.4 $\times 10^3$ dynes/cm ²	65%	64%
ESVI _{REST}	29 cm ³ /m ²	63%	66%
EF _{REST}	66%	51%	67%

Abbreviations as in Tables 1 and 2.

Leung et al. JACC 1996;28:1198-1205

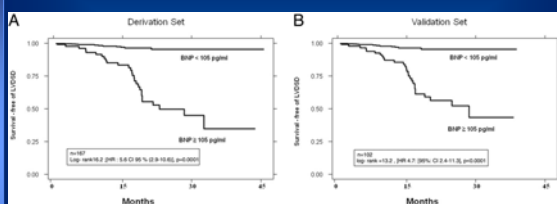
BNP: CHF, LV Dysfunction, and Death

- 269 severe asymptomatic MR patients with EF >60%
- EROA ≥ 40 mm² and RV ≥ 60 mL; FC ≥ 7 METS
- Mean FU 36 months



Pizarro et al. JACC 2009;54:1099-1106

BNP: CHF, LV Dysfunction, and Death



	OR (95% CI)	p Value
BNP ≥ 105 pg/ml	4.6 (2.7-11.6)	0.0001
End-systolic diameter/BSA > 22 mm/m ²	3.4 (1.6-10.7)	0.01
EROA > 55 mm ²	4.2 (2.1-11.4)	0.001

Pizarro et al. JACC 2009;54:1099-1106

	Mild	Moderate	Severe
Specific signs	Small central jet < 4 cm ² or $< 10\%$ of LA, vena contracta width < 0.3 cm, no or minimal flow convergence	MR more than mild, without any criteria for severe MR	Vena contracta width ≥ 0.7 cm with large central MR jet (area $> 40\%$ of LA) or with a small impinging jet of any size, large flow convergence, systolic reversal in pulmonary veins, prominent flail leaflet or ruptured papillary muscle
Supportive signs	Systolic dominant flow in pulmonary veins, A-wave dominant mitral inflow, low-density diastolic MR signal, normal LV size	MR more than mild, but no criteria for severe MR	Dense, triangular diastolic MR signal, E-wave dominant mitral inflow (≥ 2 m/s), enlarged LV and LA, (particularly with normal LV function)
Quantitative variables			
RVAI (ml per beat)	< 30	30-44, 45-50	≥ 60
RI	$\geq 20\%$	$\geq 10\%$, $\geq 10-20\%$	$> 50\%$
EROA (cm ²)	< 20	20-29, 30-39	≥ 40

Modified from Zoghbi and colleagues. *ERO=effective regurgitant orifice area. LA=left atrium. LV=left ventricle. MR=mitral regurgitation. RI=regurgitant fraction. RVAI=regurgitant volume.

Table 2. Gradation of mitral regurgitation by doppler echocardiography

Conclusions

- No randomized trial data to guide decision making
- Adherence to guidelines: Are we as good as we think?
- Compelling observational data for:
 - EF \leq 50%
 - LVESD \geq 40 mm
- Reasonable observational data for:
 - New AF
 - Pulmonary Hypertension
- Asymptomatic severe MR without accepted indications for surgery:
 - Is MR truly severe?
 - Is the patient truly asymptomatic?
 - Can the patient be further stratified?
 - Exercise testing
 - B-Type Natriuretic Peptide
 - What is the likelihood of repair?
 - What is the patient's predicted operative risk?

THANK YOU